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EXPERT REVIEWS

Currently available combined oral contraception

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Combined oral contraceptives (COCs) are amongst the most popular means to prevent unwanted pregnancy. Since their introduction to the US market in 1960, the variety and the accessibility of COCs has increased significantly. Their popularity is due to the fact that they are an effective, safe and reversible option for most women throughout the reproductive years. The popularity of COCs has increased over the past several decades. However, there are risks associated with COC use, including cardiovascular and thromboembolic events. Over time, the concentrations of both the estrogen and progestin components have undergone significant reductions and various new progestins have been developed in order to increase acceptability and safety.

Keywords: combined oral contraceptives • estrogen • progesterone

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Learning objectives

Upon completion of this activity, participants will be able to:

- Assess the physiologic actions and efficacy of different COCs
- Evaluate how to prescribe COCs effectively
- Distinguish major contraindications to COCs
- Analyze health risks associated with COCs

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Oral contraceptives are the most commonly used contraception in the USA with 28% of contraceptors aged 15–44 years reporting current use in 2006–2008 according to data from the most recent National Survey of Family Growth [1]. In addition to contraception, they provide menstrually-related benefits including decreased dysmenorrhea, premenstrual syndrome and blood loss and predictable withdrawal bleeding. Other general health benefits include ovarian and endometrial cancer risk reduction, decreased risk of benign breast conditions and improvement of acne and hirsutism.

Combined formulations of oral contraceptives contain two synthetic steroid hormones, an estrogen and a progestin. Estrogen and progesterone act at the level of the hypothalamus and the pituitary gland by blocking gonadotropin-releasing hormone and gonadotropin release [2]. Progesterone suppresses luteinizing hormone (LH) secretion, thereby blocking ovulation [3]. Progesterone's other actions include mucus hostility, endometrial changes and alteration in the motility of the Fallopian tube [4]. These secondary mechanisms play an important role as ovulation is not always inhibited by progestins. Previous studies by Rice *et al.* have shown that desogestrel administered at a dose of 60–75 µg/day inhibits ovulation completely. However, levonorgestrel 30 µg/day prevents ovulation in only 40% of cycles [5].

Estrogen suppresses follicle stimulating hormone and inhibits folliculogenesis. The progestin effect exceeds estrogen's effect at the level of the endometrium and cervix, leading to endometrial atrophy and thickened cervical mucus [4].

In a normal cycle, a cohort of follicles enters the antral growth phase synchronously. All follicles in the cohort continue to grow until one is selected as the dominant follicle. The dominant follicle continues its development while the remaining immature follicles undergo atresia and degenerate. Once the appropriate hormone signals (i.e., mid-cycle LH surge) are provided, the dominant follicle will ovulate [6]. If the hormone signals that trigger ovulation are not provided, the dominant follicle enters a static phase and remains approximately the same diameter until it undergoes regression. Dominant follicles often still develop in oral contraceptive users [7]. In combined formulations, the growth of the dominant follicle is thought to initiate during the hormone-free interval. However, the follicle that develops often has an atypical appearance. The dominant ovarian follicle during the final stages of an oral contraceptive cycle has a more irregular and atretic appearance than those of a natural cycle [8].

Progestogens

The term 'progesterone' is derived from progestational steroidal ketone. This word was coined by Willard Myron Allen and George Washington Corner at the University of Rochester Medical School (NY, USA) in 1933 [9,10].

Secretion of progesterone from the ovary starts just prior to ovulation in the dominant follicle. LH stimulates progesterone synthesis and secretion by the corpus luteum, which is formed at the site of the ruptured dominant follicle. Progesterone is secreted at a rate of 1 mg/day during the follicular phase, 20–30 mg/day during the luteal phase and several hundred mg in late pregnancy [11,12]. Progesterone stimulates development of the secretory endometrium through progesterone receptors, whose expression is upregulated by estradiol (E2) secreted during the follicular phase. Progesterone inhibits its own receptor and impedes resynthesis of E2 receptors. The abrupt drop in progesterone secretion at the end of the cycle is the main determinant for menstruation.

Progesterone acts primarily via its receptors, which are intracellular. The receptor has two main isoforms; A and B [13]. The progesterone receptor is present in tissues of other systems, including: brain (hypothalamus and pituitary) [14], thymus [15], cardiovascular system [16], mammary glands [14], bones [17], pancreas [18], gastrointestinal tract [19], bladder and urethra [20].

The ubiquity of these receptors in many organ systems help to explain the potential nonreproductive roles of progesterone in: modulation of sleep [21]; facilitation of myelinization in the CNS and peripheral nervous system [22]; affect on sexual behavior,

memory, appetite, weight gain and respiratory control in the CNS; modulation of tumorigenesis in the CNS; involvement in pathogenesis of affective disorders; and involvement in epilepsy.

There are two classification systems for synthetic progesterone or progestins. They can be classified by chemical structure (e.g., progesterone, retroprogesterone, 17α-hydroxyprogesterone derivatives, 19-nortestosterone derivatives, spironolactone derivatives, and so on) [23,24]. The timing of their introduction to the market is a common way that the synthetic progestins are classified (e.g., first generation, second generation, third generation) [24]. Most progestins used in original oral contraceptives were similar in structure to androgens, such as testosterone (Figure 1), except they lacked a methyl (CH_3) group at the 19 position.

In order to increase the activity when taken orally, first-generation progestins have an ethinyl group added to the 17 position. Norethynodrel was the progestin used in Enovid, the first oral contraceptive [25].

Norethindrone

Second-generation progestins were estrane derivatives of testosterone. They had acetate groups added at the three and 17 positions. Norethindrone (Figure 2) has an acetate at the 17 position, which increased androgen activity. In ethynodiol diacetate, the acetate at the three position decreases androgen activity [26].

Norgestrel

Later second-generation 19-norprogesterone derivatives had a methyl group attached at the C-18 methyl group to create an ethyl group at C-13. This created the gonane group of progestins (e.g., Norgestrel; Figure 3). These compounds are more androgenic [27,28].

Later progestins

Third-generation progestins were further modified by adding a methylene group at the 11 position (desogestrel) or an acetate group at the 17 position (gestodene).

Pregnane progestins are structurally similar to progesterone. These include medroxyprogesterone acetate [23,29].

There are several new progestins that have been recently introduced. Dienogest was initially produced in 1979. It is a very potent progestin that also has antiandrogenic activity [30,31]. Chlormadinone acetate is a derivative of 17α-hydroxyprogesterone. It also has antiandrogenic activity [23]. Nomogestrol acetate (NOMAC) is a new derivative of 19-norprogesterone. It has a particularly high affinity for the progesterone receptor. It has strong antiestrogenic activity and moderate antiandrogenic activity [32]. There is one combined pill containing dienogest on the US market. Chlormadinone acetate and NOMAC are approved for use in Europe and we anticipate approval for the use of NOMAC in the USA in early 2012.

Spironolactone & drospirenone

Drospirenone is the only progestin currently used in US combined oral contraceptives (COCs) that is not derived from 19-nortestosterone. Drospirenone is derived from 17α-spirolactone, making it unique among progestins (Figure 4) [33]. Spironolactone and drospirenone both exhibit antiandrogenic and antimineralocorticoid activity, but only drospirenone has progestogenic activity [34].

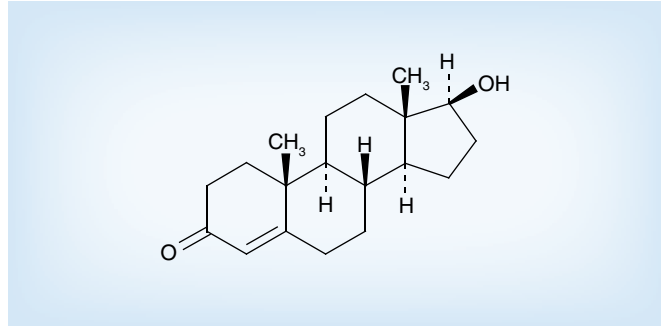

Figure 1. Testosterone.
Reproduced from [101].

In addition to synthetic progestin, progesterone is commercially available as natural and micronized natural progesterone. These progesterone products are very similar to ovarian progesterone. They are synthesized from a precursor extracted from Mexican yams, soybeans and, sometimes, animal sources. Micronization of natural progesterone increases the absorption and bioavailability.

The micronized progesterone has fewer metabolic and vascular side effects than the synthetic progestins [35,36]. Micronized progesterone overcomes the poor absorption of oral preparations of natural progesterone and has similar activity to natural progesterone in the uterus. Synthetic progestins are structurally different from natural progesterone, and therefore some are associated with side effects, including alterations in lipid levels (decreased high-density lipoprotein in postmenopausal women), glucose metabolism, vasomotility, dizziness and sedation. No COC on the US market contains micronized progesterone at this time.

Synthetic progestins are the most common progestin in oral contraceptives because they are inexpensive and easy to produce. Because many are derivatives of testosterone, some progestins can bind androgen receptors and are associated with side effects [29,37]. The ratio of desired agonistic binding to undesired secondary agonistic binding is referred to as the Selectivity Index. For progestins, this is the ratio of the desired progestational response to

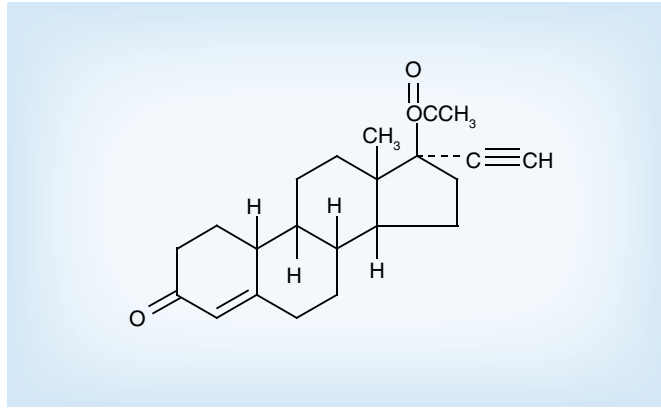

Figure 2. Norethindrone.
Reproduced from [101].

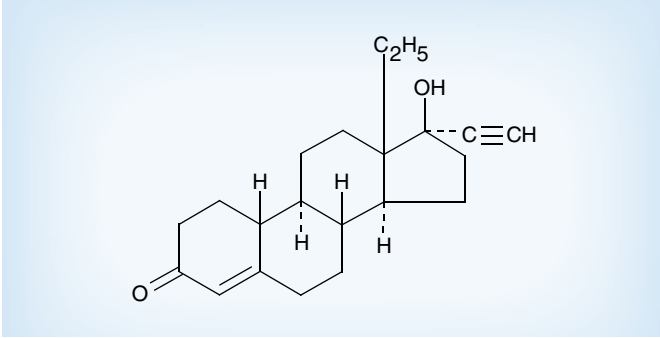

Figure 3. Norgestrel.
Reproduced from [101].

the undesired androgen response. A selective progestin has progestational effects at relatively low concentrations and androgenic effects are seen only at high concentrations [38]. There has been a reduction in the concentration of progestins since the earliest formulations. Concentrations have decreased from 500 µg in the 1960s to less than 100 µg today [39].

Estrogens

Estradiol & ethinyl estradiol

The natural estrogenic hormone 17β-estradiol is commonly referred to as E2. Initial compounds were not active when take orally. To make E2 orally active, an ethinyl group was added to its 17α position (Figure 5).

The methylation of ethinyl estradiol (EE) at position three converts it into mestranol (Figure 6). Mestranol is still found in a generic 1/50 oral contraceptive. Mestranol is eventually demethylated and converted back it into EE. The reconversion rate is 60–80%, which means that 50 µg mestranol yields 30–40 µg (average 35 µg) EE. This dose of mestranol thus represents no increase over the estrogenic dose in several current formulations [40].

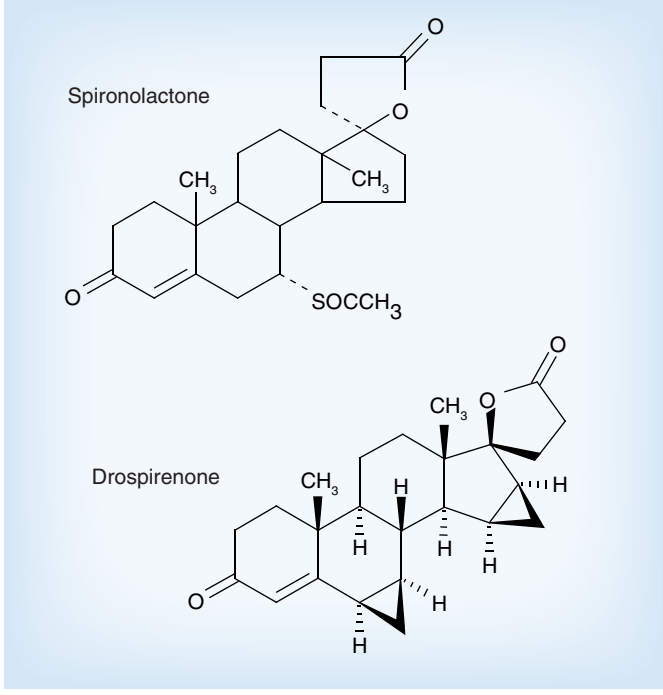

Figure 4. Spironolactone and drospirenone.
Reproduced from [101].

Ethinyl estradiol was the most commonly used estrogen component in early formulations. Its dose has been gradually reduced to 20 µg in order to decrease side effects and, in turn, increase acceptability. Formulations containing more than 50 µg of estrogen have not been available in the USA since 1988 [41].

Estradiol valerate (E2V) is an esterified form of natural 17β-estradiol, the same estrogen that is naturally produced. E2V is well absorbed from the gastrointestinal tract and is rapidly hydrolyzed to E2 in the intestinal mucosa. The pharmacokinetics and pharmacodynamics of E2V are comparable to micronized E2 (1 mg E2V corresponds to 0.76 mg micronized EE). At this time, there is one combined oral preparation that contains E2V.

Estradiol cypionate is also an esterified form of natural 17β-estradiol. It is used in monthly injectable forms of combined contraception including Cyclofem®. It is also used for hormone replacement. There are currently no combined oral methods that contain estradiol cypionate.

The 'natural' estrogens are sometimes thought of as being superior because they are metabolized faster than synthetic EE, have a lower bioavailability and have less of an impact on hepatic function [42,43]. Although data suggest that the impact of natural estrogens may be less, physiologic markers are still altered; therefore, the contraindications do not change [44].

History of COCs

The first oral contraceptives marketed were monophasic, the type and dosage of ingredients contained in each active pill was the same. A biphasic formulation that varied hormonal content during the latter half of the active-pill treatment cycle was introduced. The initial biphasic pill did not demonstrate an advantage over the monophasic, so it never had much use.

Triphasic pills were subsequently introduced. These contain three different doses of estrogen and/or progestin throughout the cycle. This formulation has achieved wide popularity. However, a 2006 Cochrane review of 18 studies did not identify differences in effectiveness between monophasic and triphasic preparations. Although several of these randomized, controlled trials suggested less spotting, breakthrough bleeding or amenorrhea with triphasic formulations, discontinuation rates were not significantly different between preparations [45].

Newer COC regimens

Initial pills on the market contained 21 days of active pills followed by 7 days of no pill. This allowed users to have a withdrawal bleed. This regimen was developed to mimic naturally occurring menstrual cycles. The traditional 28-day cycle produced by birth control pills was not designed out of medical necessity, rather it was due to cultural and social practices of the 1950s [45]. In fact, the hormone-free week is often associated with an increase in adverse symptoms in some users (Table 1) [46].

Including a hormone-free week each cycle may also increase the failure rate of an oral contraceptive. Pituitary sensitivity to follicle stimulating hormone rapidly returns after cessation of oral contraceptives, as in cyclically dosed oral contraceptives [47,48]. A small pilot pharmacokinetic and pharmacodynamic study of normal weight (BMI <25 kg/m^2) versus obese (BMI >30 kg/m^2) women given levonorgestrel 100 µg/EE 20 µg for two cycles found that both groups demonstrated hypothalamic–pituitary activation at the end of the 7-day hormone-free interval [49].

Table 1. Hormone-withdrawal symptoms in oral contraceptive users.

Symptom	21 days active (%)	7 days hormone-free (%)	p-value
Pelvic pain	21	70	<0.001
Headache	53	70	<0.001
Breast tenderness	19	58	<0.001
Bloating/swelling	16	38	<0.001
Use of pain medication	43	69	<0.001

Data taken from [47].

Extended cycle

Extended cycle regimens have demonstrated increased contraceptive efficacy over 21-day regimens. In an extended cycle, active pills are taken for 24 days, followed by 4 days of placebo. This regimen has a lower Pearl Index compared with 21-day formulations of similar hormones. This regimen also has the advantages of improvement of dysmenorrhea, premenstrual syndrome, premenstrual dysphoric disorder, anemia from menorrhagia and so on. Other benefits of an extended cycle include: decreased bleeding; maintenance of the 28-day cycle that provides marker for lack of pregnancy; and safety and tolerability similar to 21-day regimens [50].

Continuous cycle

Continuous cycle regimens are another relatively new regimen in which a monophasic pill is taken for 84 days followed by a 7 day hormone-free interval. An oral contraceptive that allows users to avoid having a menstrual period has the benefits of improved compliance, the maintenance of routine activities and less time from work, and decreased expense for feminine hygiene products [45,51].

The progestin effect achieved by the continuous exposure results in a thin, atrophic endometrium. Several menstrual-related symptoms improve with continuous cycle pills, including menorrhagia, endometriosis, dysmenorrheal and premenstrual dysphoric disorder [46].

Continuous

The continuous use of a COC with no hormone-free interval is another option. There is one brand available on the US market with US FDA approval for this indication. However, any low-dose monophasic pill can be used [52].

Starting COCs

The package inserts of oral contraceptives describe various methods to start a new pill. Options include starting on menstrual cycle day 1, day 4, day 7, start on the first Sunday after day 1 and quick start or same-day start. There is some evidence that delaying pill start until cycles day 4 and 7 may increase the risk of development of a dominant follicle; however, it has not been linked to actual ovulation [53]. Sunday starts are another option. Some propose that this may help women better remember when to start the pill. Some women also prefer this method as a means to avoid menses on a weekend.

Quick start or same-day start is another method that is thought to increase compliance with pill use [54]. Patients who are requested to delay initiation of their pill until the subsequent menses may forget instructions on how to properly use the medication [55]. A significant number of patients, up to 25%, who are instructed to delay pill start never start taking them [56]. A urine pregnancy test should be done; however, there are still concerns that an early pregnancy may not be ruled-out. There is no known risk of teratogenicity from exposure to COCs [55,57–59].

COC use in presence of medical comorbidities

Despite their immense popularity, the risks of COCs include nausea, breast tenderness and a relative increase in a hypercoagulable state, leading to a rare risk of vascular accidents including myocardial infarction, cerebral vascular accident and deep venous thrombosis (DVT) [60]. COC use is not recommended for women who have a contraindication to estrogen and progestogens (e.g., women with breast or endometrial cancer) or women who may have a higher than baseline risk of a complication from a hypercoagulable state (such as women over age 35 years who smoke or have diabetes) [61]. Another popular contraceptive is the birth control patch (Ortho Evra™). The media

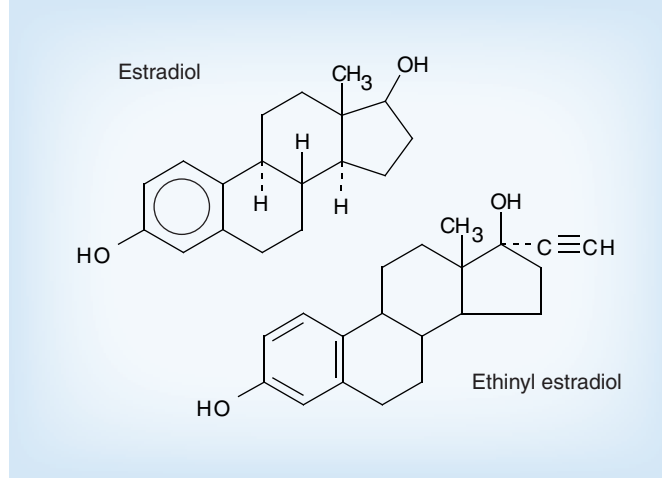

Figure 5. Estradiol and ethinyl estradiol.
Reproduced from [101].

Table 2. Risk of deep venous thrombosis when using contraception or in pregnancy.

Population	Risk of deep venous thrombosis (per 10,000)
Nonpregnant women using no hormones	1
Oral contraceptive (containing ethinyl estradiol 20–35 µg) users	3–4
Contraceptive patch users	3–6
Women with Factor V Leiden mutation using no hormones	6.5
Pregnant women	7

has recently highlighted rare instances of fatal DVT associated with the birth control patch, prompting a package labeling to inform users about the increased risk of DVT. Subsequent large, post-marketing surveillance studies of patch users have found mixed results, ranging from no increased risk of DVTs compared with COCs users to twice the risk of DVTs in birth control patch users [62–65]. Table 2 outlines the risk of DVT among nonsmoking women for various conditions, highlighting that commonly used contraceptives have a relatively lower side effect profile than pregnancy [65].

The WHO has published and regularly updates medical eligibility criteria for contraceptive use. These criteria provide evidence-based guidelines to clinicians for use in individualizing a patient's risks and benefits when considering whether to initiate or continue a contraceptive method. These risks and benefits must be considered in light of the side effects of alternative contraceptive methods, and ultimately, the risks of an unintended or mistimed pregnancy where no contraceptive method is used. As part of these guidelines, the WHO developed a standardized category system by which use of contraceptive methods is graded based on a woman's underlying medical conditions as detailed in Table 3.

The US CDC also released revised recommendations, largely based on the 2008 WHO medical eligibility criteria [66]. Owing to the relative hypercoagulable state that is induced with estrogen, there is concern for increased risk of clotting in patients with medical comorbidities. In addition, owing to the metabolism of estrogen in the liver with oral regimens, concern exists for patients with altered liver function. Of note, administration of estrogens by other non-oral routes is not associated with a more favorable profile on lipid metabolism and does not exhibit decreased effects on liver proteins [45,67]. For estrogen-containing COCs, Table 4 details the medical conditions in which COC use is usually inadvisable (category 4 or 3), as determined by the WHO and the CDC.

Table 3. WHO medical eligibility criteria for contraceptive use (4th edition, 2008 update).

Category	Description of medical condition
1	A condition for which there is no restriction for the use of the contraceptive method
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method
4	A condition which represents an unacceptable health risk if the contraceptive method is used

Data taken from [66].

Use of COC postpartum

The CDC recently updated its 2010 safety classifications to address the use of COC postpartum. The risk of venous thromboembolism increases postpartum due to an increase in coagulation factors and fibrinogen, along with a decrease in endogenous anticoagulants [68]. The risks of venous thromboembolism in postpartum women are 22-times greater than other similar reproductive age women [69]. This risk returns to baseline at 42 days postpartum. The reviewers also considered other concomitant risk factors, such as obesity and having had a cesarean delivery. Based on their findings, women who are less than 21 days postpartum should not use COCs (category 4). Women 21–42 days postpartum with no other risk factors can use COCs (category 2). In women 21–42 days postpartum with other risk factors, the risks often outweigh the benefits; therefore, COCs should not be used in general (category 3). There are no restrictions on COC use after 42 days postpartum (category 1). Breastfeeding remains category 3 at less than 1 month postpartum because of concerns of effects on breastfeeding.

Effects of COC use on bone density

Combined oral contraceptives tend to be very popular among adolescents and young women. Some of these women may not have met their peak bone mass. Data on the effects of exogenous estrogen from oral contraceptives on bone mass have been inconclusive. With newer formulations containing concentration of EE less than 30 µg, and some of the newer very low-dose EE products, there is renewed concern over effects on bone mineral density. Recent studies do suggest that there may be a decrease in bone mass in young women who take low-dose COCs [70,71]. This potential risk may not increase the risk of a fracture, and should be considered in the context of risks associated with an unintended pregnancy.

COC effectiveness in obese versus lean women

There are opposing concerns for obese women taking COC. Obesity is associated with anovulation, subfertility and polycystic ovarian syndrome, on the one hand. Conversely, steroid metabolism may be different in obese women, resulting in lower drug concentrations and a higher likelihood of breakthrough ovulation. The most robust, recent data on this issue comes from the International Active Surveillance of Women Taking Oral

Table 4. 2008 WHO/CDC safety classification for combined oral contraceptives.

Medical condition	WHO/CDC category: COC use
Warning primarily based on concern regarding hypercoagulable state	
History of DVT/PE	4
Acute DVT/PE	4
DVT/PE on established anticoagulant therapy	4
Major surgery with prolonged immobilization	4
SLE with positive or unknown antiphospholipid antibodies	4
Smoker ≥15 cigarettes per day and age ≥35 years	4
Hypertension systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg	4
Vascular disease	4
Current and history of ischemic heart disease	4
Stroke or history of stroke	4
Complicated valvular heart disease (including pulmonary hypertension, risk of atrial fibrillation and history of subacute bacterial endocarditis)	4
Peripartum cardiomyopathy <6 months	4
Moderately or severely impaired cardiac function (New York Heart Association class III or IV)	4
Migraine with aura at any age	4
Migraine without aura age ≥35 years old	4
Diabetes with nephropathy, retinopathy or neuropathy	4
Diabetes of >20 years duration or with vascular disease	4
Complicated solid organ transplantation (graft failure, rejection, cardiac allograft vasculopathy)	4
Multiple risk factors for arterial cardiovascular disease (older age, smoking, diabetes, hypertension)	3/4
Breastfeeding less than 1 month postpartum	3
Postpartum less than 21 days	4
Postpartum 21–42 days	3
Smoker (<15 cigarettes per day) and ≥35 years old	3
Adequately controlled hypertension	3
Hypertension systolic blood pressure 140–159 mmHg or diastolic blood pressure 90–99 mmHg	3
Peripartum cardiomyopathy ≥6 months	3
Warning based on concern for metabolism of oral estrogen via liver or gut	
Acute or flare viral hepatitis	4
Severe decompensated liver cirrhosis	4
Hepatocellular adenoma or adenocarcinoma	4
Rifampin or rifabutin therapy	3
Lamotrigine therapy	3
Anticonvulsant therapy	3
Ritonavir-boosted protease inhibitors	3
Bariatric surgery with malabsorptive procedures	3
Warning based on concern for estrogen potentiating estrogen-sensitive tumors	
Current breast cancer	4
History of breast cancer with no evidence of disease for 5 years	3

COC: Combined oral contraceptive; DVT: Deep venous thrombosis; PE: Pulmonary embolism; SLE: Systemic lupus erythematosus.
Data taken from [66].

Table 5. Currently available combined oral contraceptive pills.

Regimen	Estrogen	Dose (μg)	Progestin	Dose (mg)	US market
21-day regimen					
Monophasic	Ethinyl estradiol	20	Levonorgestrel	0.1	Aviane-28, Lessina, Lutera, Sronyx
	Ethinyl estradiol	20	Norethindrone	1	Junel 1/20, Junel 1/20 Fe, Loestrin-21 1/20, Loestin Fe 1/20, Microgestin 1/20, Microgestin Fe 1/20
	Ethinyl estradiol	30	Levonorgestrel	0.15	Levora, Nordette-28, Portia-28
	Ethinyl estradiol	30	Norgestrel	0.3	Cryselle-28, Low-Ogestrel-21, Low-Ogestrel-28, Lo/Ovral-28
	Ethinyl estradiol	30	Norethindrone acetate	1.5	Junel 1.5/30, Junel Fe 1.5/30, Loestrin 1.5/30–21, Loestrin Fe 1.5/30, Microgestin 1.5/30, Microgestin Fe 1.5/30
	Ethinyl estradiol	30	Desogestrel	0.15	Apri, Desogen, Ortho-Cept, Reclipsen, Solia
	Ethinyl estradiol	30	Drospirenone	3	Ocella, Yasmin
	Ethinyl estradiol	35	Ethynodiol diacetate	1	Kelnor, Zovia
	Ethinyl estradiol	35	Norgestimate	0.25	Ortho-Cyclen-28, MonoNessa, Previfem, Sprintec
	Ethinyl estradiol	35	Norethindrone	0.4	Ovcon-35, Balziva, Femcon Fe chewable, Zenchent
	Ethinyl estradiol	35	Norethindrone	0.5	Brevicon-28, Modicon-28, Necon 0.5/35, Nortrel 0.5/35
	Ethinyl estradiol	35	Norethindrone	1	Necon 1/35–28, Norinyl 1+35–28, Nortrel 1/35–28, Ortho-Novum 1/35–28
	Mestranol	50	Norethindrone	1	Necon 1/50, Norinyl 1+50
	Ethinyl estradiol	50	Norethindrone	1	Ovcon-50
	Ethinyl estradiol	50	Norgestrel	0.5	Ogestrel 0.5/50–28
	Ethinyl estradiol	50	Ethynodiol diacetate	1	Zovia 1/50–28
	17 β-estradiol	1.5 mg	Nomogestrol acetate	2.5	Recently approved in Europe with US FDA approval expected in early 2012
Biphasic	Ethinyl estradiol	20 × 21 days, placebo × 2, 10 × 5 days	Desogestrel	0.15	Azurette, Kariva, Mircette
	Ethinyl estradiol	35	Norethindrone	0.5 × 10 days, 1 × 11 days	Necon 10/11
Triphasic	Ethinyl estradiol	20 × 5 days, 30 × 7 days, 35 × 9 days	Norethindrone	1	Estrostep Fe, Tilia, Tilia Fe, Tri-Legest Fe
	Ethinyl estradiol	25	Norgestimate	0.18 × 7 days, 0.215 × 7 days, 0.25 × 7 days	Ortho Tri-Cyclen Lo, Tri Lo Sprintec

Adapted from [81].

Table 5. Currently available combined oral contraceptive pills (cont.).

Regimen	Estrogen	Dose (µg)	Progestin	Dose (mg)	US market
21-day regimen (cont.).					
Triphasic (cont.)	Ethinyl estradiol	25	Desogestrel	0.1 × 7 days, 0.125 × 7 days, 0.15 × 7 days	Caziant, Cesia, Cyclessa, Velivet
	Ethinyl estradiol	30	Levonorgestrel	0.05 × 6 days, 0.075 × 5 days, 0.125 × 10 days	Enpresse, Trivora
	Ethinyl estradiol	35	Norgestimate	0.18 × 7 days, 0.215 × 7 days, 0.25 × 7 days	Ortho Tri-Cyclen, TriNessa, Tri-Previfem, Tri-Sprintec
	Ethinyl estradiol	35	Norethindrone	0.5 × 7 days, 1 × 9 days, 0.5 × 5 days	Aranelle, Leena, Tri-Norinyl
	Ethinyl estradiol	35	Norethindrone	0.5 × 7 days, 0.75 × 7 days, 1 × 7 days	Ortho-Novum 7/7/7, Nortrel 7/7/7, Necon 7/7/7
Quadrephasic	Estradiol valerate	3 mg × 2 days, 2 mg × 22 days, 1 mg × 2 days	Dienogest	None × 2 day, 2 × 5 days, 3 × 17 days, none × 4 days	Natazia
Extended-cycle regimen	Ethinyl estradiol	10 × 26 days	Norethindrone	1 × 24 days	Lo-Loestrin Fe
	Ethinyl estradiol	20 × 24 days	Norethindrone	1 × 24 days	Loestrin-24 Fe
	Ethinyl estradiol	20 × 24 days	Drospirenone	3 × 24 days	Beyaz, Gianvi, Yaz
Continuous-cycle regimen	Ethinyl estradiol	20 × 84 days, 10 × 7 days	Levonorgestrel	0.1 × 84 days	LoSeasonique
	Ethinyl estradiol	30 × 84 days	Levonorgestrel	0.15 × 84 days	Introvale, Jolessa, Seasonale, Quasense
	Ethinyl estradiol	30 × 84 days, 10 × 7 days	Levonorgestrel	0.15 × 84 days	Seasonique
Continuous	Ethinyl estradiol	20	Levonorgestrel	90 µg	Lybrel

Adapted from [81].

Contraceptives (INAS-OC) and the European Active Surveillance Study on Oral Contraceptives (EURAS-OC), which followed over 100,000 women every 6 months for up to 5 years taking oral contraceptives from 2000–2008 [72,73].

The EURAS-OC study found no effect of BMI and weight on overall contraceptive efficacy [73]. There was also little variation in contraceptive failure, stratified by BMI and progesterone type for desogestrel, dienogest, drospirenone and levonorgestrel [73]. The only exception to this was a significant association of contraceptive failure in chlormadinone acetate-containing COC, which is highly lipophilic, among women with a high BMI (≥30 kg/m^2; p = 0.028) [73]. The average BMI of women enrolled in the EURAS-OC study was 22.1 ± 4.1 kg/m^2 compared with 26.3 ± 7.3 kg/m^2 in the US arm of the INAS-OC study [72,73]. Importantly, the US cohort of the INAS-OC study included a higher percentage of women in the WHO obesity classifications II and III (BMI: 35 kg/m^2 or more) [72].

In the INAS-OC study a cohort of US oral contraceptive users (73,629 woman-years) were followed every 6 months for a 5-year follow-up period to estimate typical use effectiveness of oral contraceptive pills, with respect to BMI and dosing regimen (21 vs 24 days) and progestogen (drospirenone vs other progestogens) [72]. The overall contraceptive failure rate for the US cohort in the INAS-OC study was a Pearl Index of 2.2 (95% CI: 2.1–2.3) [72], with 86% of oral contraceptive failures associated with skipping pills [73]. The 24-day regimen containing a progestogen with a longer half-life (drospirenone) showed lower failure rates, after adjusting for age, BMI, education level, parity and tobacco use [72]. The authors reasoned that the 3 day placebo window and the longer half-life of drospirenone (30 h) was more forgiving of missed pills than the 7-day placebo window [73]. Morbidly obese women (BMI 35 or higher) had a significant increase in failure rates, regardless of product, with a hazard ratio: 1.5 (95% CI: 1.3–1.8; adjusted for age, parity and education level) [72]. The authors hypothesized that in obese women, lower drug concentrations, due to a higher volume of distribution, may make even a 24-day regimen less forgiving to imperfect use [73].

The INAS-OC and EURAS-OC cohorts were not powered to examine the specific opposing end points of obesity-associated anovulation versus drug metabolism in obese versus lean women,

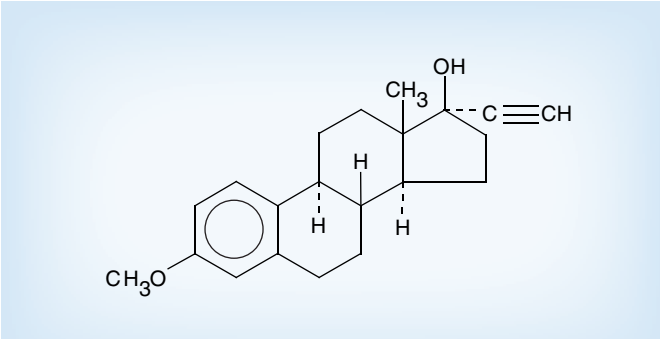

Figure 6. Mestranol.
Reproduced from [101].

but the sum of these opposing factors was increased contraceptive failures among women with a BMI of 35 or more in the INAS-OC cohort [73]. These data are the most recent and robust that exist on obesity and contraceptive failure in current COC on the US market.

Expert commentary

Combined oral contraceptive pills have been available as a means to prevent unwanted pregnancy since 1960. Their popularity has increased immensely over the past several decades. Today, COCs are the most common method of contraception in the USA. Their popularity has also increased due to additional benefits including menstrual cycle control and the reduction of other menstrually-related symptoms. With the increased popularity, there have also been observations of increased risks including cardiovascular and thromboembolic events. The concentrations of both the estrogen and progestin components have undergone significant reductions in order to increase acceptability and safety.

Efforts have been taken to increase the accessibility of oral contraception to consumers. Changes have been made by the pharmaceutical industry, insurance industry, clinicians, researchers and medical societies. There has been extensive research to decrease the dose and to develop new estrogens and progestins. Generic versions of many formulations are available that are much more affordable for patients. Medical societies, such as the American College of Obstetrics and Gynecology, have published guidelines and recommendations to help and educate clinicians in decision making regarding the best contraceptive options for their patients. With these guidelines clinicians are less likely to introduce barriers to birth control, such as requiring a pelvic exam and screening for cervical dysplasia [74]. See Table 5 for a comprehensive list of COCs that are currently available in the USA.

Five-year view

Research has focused on lowering the dose of estrogen and progestogens in COCs, extending the dosing regimens to make COC regimens more forgiving of missed pills and adding placebo components of iron, calcium and folic acid supplements. Guidelines have focused on reducing the barriers to starting and continuing women on COC, including not requiring cervical cancer screening and simplifying start regimens with 'Quick Start'. All of these advances aim to enhance the contraceptive and non-contraceptive benefits of these widely acceptable medications. There will be continued emphasis on moving oral contraceptives to an over-the-counter status. Groups have shown that women are able to self-screen for contraindications to COC use, such as uncontrolled hypertension [75,76]. In addition, experts have demonstrated that the benefits of avoiding an unintended or mistimed pregnancy likely outweigh the potential medical risks of COC use [77,78]. Current COCs do not protect against sexually transmitted infections or HIV. There is growing interest in developing methods of contraception that have a dual purpose, including the prevention of pregnancy and the prevention of sexually transmitted infections [79,80]. Most of the current research on multitechnology methods focus on the vaginal delivery of combined products. Future pill products may also take advantage of this concept and add antivirals to prevent herpes or antiretrovirals to decrease the risk of HIV infection.

Key issues

- Combined oral contraceptives (COCs) are the most widely used method of contraceptive worldwide.
- With compliant use, the contraceptive efficacy of COCs is high.
- Product development with COCs has focused on reducing the dose of hormones and extending regimens, which makes typical use potentially more forgiving to missed pills.
- Although the contraceptive efficacy of COCs in obese women is still high and acceptable, data exist that contraceptive efficacy may be relatively reduced among morbidly obese women, particularly among morbidly obese women who use COC with shorter progestational half lives and longer placebo intervals.
- Although COC use poses less medical risks than the medical and psychosocial problems of unintended or mistimed pregnancy, healthcare providers must be cognizant of the relative and absolute contraindications to COC use among women with medical comorbidities.

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. You are seeing a 35-year-old woman who wants to initiate oral contraceptives after the birth of her third child. What should you consider regarding the actions of combined oral contraceptives (COC)?
   - ☐ **A** Drospirenone has both antiandrogenic and antimineralocorticoid activity
   - ☐ **B** Triphasic COCs are more effective than monophasic COCs
   - ☐ **C** Women are less likely to discontinue triphasic COCs vs monophasic COCs
   - ☐ **D** Adverse symptoms are generally lower in the 7-day placebo period of 21-day regimens
2. What should you consider when initiating a COC for this patient?
   - ☐ **A** Continuous cycle regimens are associated with improved compliance
   - ☐ **B** Continuous COC treatment can include only one brand of COC
   - ☐ **C** The higher risk for venous thromboembolism (VTE) associated with postpartum use of COC returns to normal within 2 weeks after delivery
   - ☐ **D** A urine pregnancy test is unnecessary prior to quick-start COC
3. Which of the following is the most significant contraindication to the use of COCs in this patient?
   - ☐ **A** She is only 50 days postpartum
   - ☐ **B** A history of adequately controlled hypertension
   - ☐ **C** A history of migraine with aura
   - ☐ **D** A history of diabetes mellitus without complications for the last 3 years
4. The patient is concerned regarding the long-term safety and efficacy of COCs. What can you tell her?
   - ☐ **A** COCs are associated with twice the risk for DVT compared with pregnancy
   - ☐ **B** Contraceptive patches have favorable effects on the lipid profile compared with oral COCs
   - ☐ **C** Low-dose COCs increase bone mass among young women
   - ☐ **D** Body mass index of 35 kg/m^2 may reduce the efficacy of COCs