CLINICAL PHARMACOLOGY

PRESCRIBING COMBINED ORAL CONTRACEPTIVES FOR WOMEN WITH PRE-EXISTING MEDICAL CONDITIONS

Hormonal contraceptives are among the most widely used medicines. They contain either synthetic oestrogen and progestin in combination or progestin alone. This article reviews the use of combined oral contraceptives (COCs) in women with co-morbidity.

The physiology of menstruation

The hypothalamus releases gonadotrophin-releasing hormone which stimulates the gonadotrophs in the anterior pituitary to produce follicular-stimulating hormone (FSH) and luteinising hormone (LH). The gonadotrophins stimulate the ovaries to produce oestrogen and progesterone which regulate the menstrual cycle. Fig. 1 illustrates the average 28-day ovulatory cycle with the changes that occur during the follicular phase, ovulation and the luteal phase.

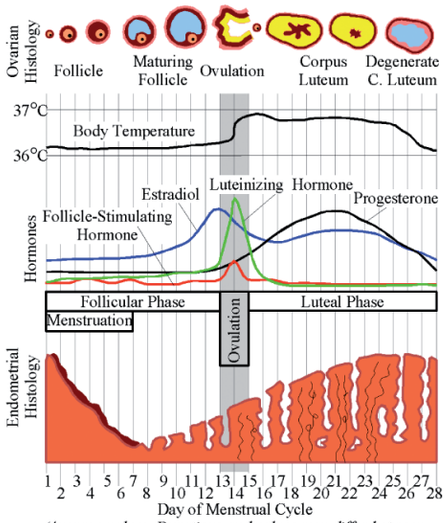

Fig. 1. This Wikipedia and Wikimedia Commons image is from the user Chris 73 and is freely available at ***http://commons.wikimedia.org/wiki/Image:MenstrualCycle.png*** *under the creative commons cc-by-sa 2.5 licence.]*

Combined oral contraceptives

The COCs are available in a wide range of preparations. The oestrogen most commonly used is the synthetic ethinyloestradiol in doses between 15 µg and 50 µg. The progesterone is usually norethisterone or levonorgestrel. The regimens may be fixed or phased. The fixed regimen contains equal doses of oestrogen and progesterone. Phased regimens have an incremental increase in progesterone dose in 2 or 3 phases. The day reminder blister packs usually contain 21 active pills with or without 7 inactive pills. Table I illustrates examples of different oral contraceptives available.

Pharmacology

Oral contraceptives inhibit ovulation by negative feedback of oestrogen on the hypothalamus, with subsequent suppression of the gonadotrophin release. Progesterone inhibits ovulation by suppressing the preovulatory LH surge. In addition, the progesterone causes thick tenacious cervical mucus that is resistant to sperm migration, reduces sperm survival, causes endometrial atrophy and alters fallopian tube secretions which affect the sperm and ovum motility. With correct use, the active pills are taken continuously for 21 - 24 days, followed by a pill-free interval. During the pill-free interval, hormonal withdrawal bleeding occurs.

Oral contraceptives are absorbed in the gut and undergo first-pass metabolism in the liver and then undergo enterohepatic circulation. In the liver, they are metabolised by the cytochrome P450 enzyme system and undergo conjugation. Certain medicines that induce liver enzymes decrease the plasma levels of the steroids and hence decrease their efficacy; similarly, enzyme inhibitors increase the levels of the steroids. A further important drug-drug interaction is the interference of broad-spectrum antibiotics with the normal gut flora, which deconjugate oestradiol allowing enterohepatic circulation. When the normal flora is altered, the conjugated oestradiol is excreted in the stool without undergoing enterohepatic circulation. Some common drug interactions are highlighted in Table II. Alternative or additional contraception is recommended if women are long-term users of the inducing drugs mentioned in Table II, because the benefit of increasing the hormone dose is unclear. Women on long-term enzyme inhibitors should avoid high-dose COCs.

Risks and benefits

COCs are patient dependent, and the failure rate is less than 1% with correct and consistent use. Side-effects are

Table I. **Examples of combined oral contraceptives**

Classification	Ethinyloestradiol content (µg)	Active pills (*N*)	Inactive pills (*N*)
Ultra low-dose pills	15	24	4
Low-dose pills	20 - 35	21	7
High-dose pills	50	21	7

Table II. **Commonly used drugs which induce or inhibit the cytochrome P450 isoenzymes responsible for metabolising steroids, resulting in altered steroid levels**

Inducers

Antimicrobials: rifampicin, griseofulvin
Anticonvulsants: phenytoin, carbamazepine, barbiturates, topiramate
Antiretrovirals: nevirapine, ritonavir (including ritonavir-boosted protease inhibitors)
Other: St John's wort, tobacco smoking

Inhibitors

Antimicrobials: azole antifungals
Antiretrovirals: efavirenz

usually minor and may improve during the first six weeks of use. These include mood changes, breast tenderness, breakthrough bleeding, weight gain or fluid retention, nausea and loss of libido. If side-effects persist, changing the dose of oestrogen or type of progesterone may alleviate the symptoms.

Severe adverse effects are rare and usually involve the cardiovascular system. The risk of venous thromboembolism, pulmonary embolism, ischaemic heart disease or stroke increases if a patient has other cardiovascular risk factors. Because COCs are metabolised by the liver, there is concern of worsening liver function in women with existing liver disease. Table III lists the absolute contraindications for COC use.

Importantly, COCs do not protect against HIV and sexually transmitted infections, although they may reduce the incidence of pelvic inflammatory disease.

The different oestrogens have equivalent efficacy; however, different progesterones differ in their potency and pharmacological actions. For example, cyproterone acetate and drospirenone have anti-androgenic properties and are prescribed for severe acne and hirsutism. Other non-contraceptive indications for COCs are dysmenorrhoea, menorrhagia and endometriosis. Studies have shown evidence of protection from endometrial cancer, ovarian cancer, ovarian cysts and benign breast disease. COC use is also associated with a low incidence of osteoporosis.

Criteria for prescription

The choice of COC should be decided on by the clinician and the patient based on safety, efficacy and acceptability. A full medical and sexual history must be obtained and an appropriate clinical examination performed to identify any potential risks to the individual's health, which may be increased by a COC.

It is important to discuss the advantages and disadvantages of available choices. The most successful COC is likely to be the one the woman chooses; therefore the clinician must ensure that the woman makes an informed choice. Table III highlights the conditions which present an unacceptable health risk if a COC is used.

Table III. **WHO absolute contraindications for COC use**

Breastfeeding < 6 weeks postpartum
Smoking ≥15 cigarettes /day at age ≥ 35 years
Multiple risk factors for cardiovascular disease
Hypertension (systolic ≥160 mmHg or diastolic ≥100 mmHg)
Hypertension with vascular disease
Current and history of venous thromboembolism
Major surgery with prolonged immobilisation
Known thrombogenic mutations
Current and history of ischaemic heart disease
Stroke
Complicated valvular heart disease (pulmonary hypertension, risk of AF, history of bacterial endocarditis)
Migraine without aura at age ≥ 35 years and with aura at any age
Current breast cancer
Diabetes ≥ 20 years or of any duration with severe nephropathy, retinopathy or neuropathy or with other vascular diseases
Active viral hepatitis
Severe (decompensated) cirrhosis
Benign or malignant liver tumours

The risk of myocardial infarction, stroke and venous thromboembolism increases with age. Smoking is an important contributing factor, therefore smokers > 35 years old are advised against COC use. Smokers < 35 years old may use COCs, but should be encouraged to stop smoking.

Obese women who use COCs also are at increased risk of venous thromboembolism. The benefit of using COCs has been shown to outweigh the risk of pregnancy and venous thromboembolism, but alternative contraceptive methods should be considered.

Venous thromboembolism is a major cause of perioperative morbidity and mortality, and COCs should be discontinued 4 weeks before major elective surgery. COCs may be recommenced at the first menses at least 2 weeks after full mobilisation. If discontinuation is not possible, thromboprophylaxis is recommended.

Systemic lupus erythematosus (SLE) is more common in women and sex hormones have previously been demonstrated to be involved in the pathogenesis. However, in a recent study of women with SLE, the use of COCs did not increase the disease activity, incidence of flares, time to first flare, and incidence of adverse effects compared with other contraceptives (IUD and progesterone-only pill).

Table IV. **WHO selected practice recommendations – missed pill rules**

Missed pill scenario	Action
One or two 30 - 35 µg EE or One 20 µg EE at any time	• Take pill as soon as remembered and the next one at the usual time • No additional contraceptive protection necessary
Three 30 – 35 µg EE or Two 20 µg EE (**two for twenty** or **three for thirty** rule)	• Take pill as soon as remembered • Continue taking remainder at usual time • Condom use or abstinence until 7 active pills have been taken (7 days in a row) In addition • If pills missed in week 1, consider emergency contraception if unprotected sex occurred during the PFI or in week 1 • If pills missed in week 3, omit the inactive pills or PFI

EE = ethinyloestradiol; PFI = pill-free internal.

Condoms and COCs

Women need to be counselled on the need for dual protection – the combined use of hormonal contraceptives and condoms if there is a risk of sexually transmitted infections, including HIV. Dual protection is also advisable if broad-spectrum antibiotics or enzyme-inducing drugs are co-administered.

Missed pills: recommendations

Loss of contraceptive efficacy may occur if active pills are missed at the beginning or the end of the cycle. If the pill-free interval is extended (> 7 days), ovulation may occur. Table IV outlines the WHO recommendations for missed pills. However, if a woman has missed more than seven consecutive active pills, she must be viewed as having stopped the pill and the 'missed pill rules' do not apply.

Further reading

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PHUMLA SINXADI
MB ChB, DA (SA)

MARC BLOCKMAN
MB ChB, BPharm, MMed (Clin Pharmacology), Dip International Research Ethics

Division of Clinical Pharmacology
University of Cape Town

IN A NUTSHELL

COCs are safe and effective when used correctly and consistently.

COCs have non-contraceptive benefits, e.g. anti-androgen.

If the woman has significant cardiovascular risk factors, alternative methods should be considered.

The risk of venous thromboembolism is lower with COC use than with pregnancy.

Dual protection is recommended if there is risk of transmission of sexually transmitted infections including HIV.

If a woman is taking medication which lowers the efficacy of the low-dose COC (< 35 µg EE) an alternative or additional method is recommended.

For missed pills, apply the two for twenty and three for thirty rule.