

REVIEW ARTICLE

Oral Contraceptives in Dermatology

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Abstract. Patients with hyperandrogenic syndromes and diseases exacerbated by pregnancy and those taking common dermatologic drugs associated with risk to the fetus require prescription of contraceptives by the dermatologist. In healthy, nonsmoking women, oral contraception does not increase the risk of cerebral or cardiac vascular disease and is associated with major benefits besides avoiding pregnancy. These include prevention of ovarian and endometrial carcinoma, ectopic pregnancy, pelvic inflammatory disease, ovulation pain, and menstrual cycle disorders. This article will review the mechanism of action, side effects, health risks, contraindications, initiation of the oral contraceptive regimen, and patient follow-up, as well as interactions between contraceptives and other drugs.

Key words: androgenization, congenital abnormalities, oral contraceptives, adverse effects, indications, non-contraceptive benefits.

CONTRACCIÓN HORMONAL ORAL EN DERMATOLOGÍA

Resumen. Tanto los síndromes de androgenización y las enfermedades que empeoran con el embarazo, como la medicación de riesgo para el feto de uso habitual en Dermatología precisan la prescripción de contraceptivos por parte del dermatólogo. En mujeres sanas, no fumadoras, la anticoncepción oral no aumenta el riesgo de enfermedad cardiovascular (cerebral o cardíaca), y está asociada a grandes beneficios no anticonceptivos, incluidos la importante prevención del carcinoma de ovario y de endometrio, de la gestación ectópica, la enfermedad inflamatoria pélvica, el dolor ovulatorio y los trastornos del ciclo menstrual. Se revisan el mecanismo de acción, los efectos secundarios, los riesgos para la salud, las contraindicaciones, el inicio y el seguimiento del uso de los anticonceptivos orales, así como las interacciones de los anticonceptivos con otros fármacos.

Palabras clave: androgenización, teratogenia, anticoncepción oral, efectos adversos, indicaciones, beneficios no anticonceptivos.

Introduction

Hyperandrogenism is an important subject in the management of skin disease in women because both sebaceous gland function and hair growth depend on androgens. Skin is a target tissue for the hormonal action of both circulating and locally produced androgens. In the skin, low-potency circulating androgens, such as ovarian and testicular testosterone and the adrenal androgen hydrocortisone sulfate are transformed into more

potent androgens, such as dihydrotestosterone. Between 10% and 20% of women present some clinical sign of hyperandrogenism, such as seborrhea, acne, hirsutism, or hair loss. A subgroup of this cohort have menstrual abnormalities and are very often obese. Some of these patients also exhibit a varying degree of insulin resistance, and the group is characterized by an increased incidence of type 2 diabetes mellitus and an unfavorable serum lipid profile. Thus, hyperandrogenism is not always a minor problem. Moreover, since the signs and symptoms of this condition have a marked psychological impact, diagnostic tests must be sensitive and specific and the therapy applied should be effective. Oral contraceptive treatment plays an important role in these situations.

Certain diseases are exacerbated by pregnancy and in others genetic counseling may lead patients to decide to avoid reproduction. In both cases, oral contraceptives (OCs) may be necessary.

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Another area of interest in this context is the common use in dermatology of drugs that require concomitant contraceptive treatment, either as an adjunct to the therapy or to prevent high-risk pregnancies. According to the Food and Drug Administration (FDA), this category includes retinoids (isotretinoin, adapalene, tretinoin, and acitretin), some antibiotics (such as the tetracyclines), antiandrogens (cyproterone acetate, finasteride, spironolactone, and flutamide), antineoplastics (such as 5-fluorouracil), and immunosuppressants (methotrexate, cyclosporine, and thalidomide).

In the present article, we review the most important aspects of oral contraception and its use in dermatology.

Oral Hormonal Contraception

The world population has increased exponentially since 1965 and is expected to double within 50 years of that date (whereas prior to 1965 it took 200 years to double). Although contraception is seen as a modern phenomenon and a recent advance in human history, the struggle to limit reproduction is an ancient one and the only modern twist is the use of sex steroids as contraceptives.

Haberlandt¹ proposed using hormones as a method of birth control in 1931, but his premature death in 1932 brought his work to an end. In the 1950s, Pincus and Rock made the first attempts to develop a contraceptive pill for oral administration using 9.65 mg of norethynodrel and 150 µg/d of mestranol. It was not until 1960, however, that the FDA approved Enovid 10 (a combination of 10 mg of norethynodrel and 0.015 mg of mestranol) for contraceptive use. The first contraceptive pill marketed in Europe was Anovlar, a preparation approved in 1961 that contained norethisterone 4 mg and ethinyl estradiol 0.05 mg.

In 2003, when 2140 Spanish women were surveyed on the subject of oral contraception,² it was found that the number of women using some method of contraception had increased and that the condom was the method most often used followed by hormonal OCs (the method of choice for 10.6% of Spanish women aged between 15 and 49 years).

Hormonal contraceptives can be prescribed either as a daily regimen (the contraceptive pill) or using other routes of administration and regimens (contraceptive injections or patches, vaginal rings, and intrauterine devices that release hormones).

In the present article, we will only deal with oral hormonal contraceptive pills taken daily. These pills provide highly effective contraceptive cover, they ensure total privacy, they do not require vaginal insertion, and they afford excellent control of the menstrual cycle. Moreover, they provide certain additional health benefits that are

discussed below. These include control of the clinical manifestations of hyperandrogenism caused by increased production of androgens, in particular testosterone. Oral hormonal contraception also has potential drawbacks including the fact that the pill is only effective when taken every day and that side effects can lead users to abandon treatment, particularly in the early months. Furthermore, the use of OCs can give rise to serious health risks, such as thrombosis or stroke, although statistically such events are very rare. Fortunately, by way of a good personal and family medical history, the serious complications associated with the use of OCs can largely be avoided by ensuring that this type of contraception is never prescribed to patients with risk factors. It is of interest, therefore, to provide a short description of the pharmacology, mechanism of action, most common and, above all, the most serious adverse effects of OCs in order to clarify both the indications and the relative and absolute contraindications for this contraceptive method.

Pharmacology of Steroid Contraceptives

Steroid contraceptives are generally composed of either a combination of estrogen and progesterone or progesterone alone.

Depending on their composition, they are classified as:

1. Monophasic: continuous administration of estrogen and progesterone for 21 days
2. Biphasic: an initial phase during which the dose of progesterone is lower followed by a second phase during which the dose of progesterone is higher.
3. Triphasic: a regimen that attempts to imitate the body's natural cycle by using 3 different doses of progesterone, each one higher than one before
4. Sequential: an initial phase with only estrogens followed by a second phase with a combination of estrogens and progesterone
5. Minipill: continual administration of progesterone alone without estrogens.

Furthermore, depending on the dose of estrogen and gestagen they contain, OCs are categorized as either high-dose or low-dose formulations.

Estrogen Component of Combination Hormonal OCs

Estradiol is the most powerful natural estrogen and the most important estrogen secreted by the ovaries. The chief obstacle to the use of sex steroids in contraception was that they lost activity when administered orally. In 1938, however, it was discovered that the addition of an

ethinyl group at the 17 position conferred oral activity on estradiol.¹ Ethinyl estradiol is a very potent oral estrogen and one of the estrogens found in all OCs. The other estrogen used is the 3-methyl ether of ethinyl estradiol, or mestranol.

As ethinyl estradiol and mestranol differ from natural estradiol they are deemed to be pharmacologic drugs. The reason mestranol is less potent than ethinyl estradiol is because it has to be converted to ethinyl estradiol in the body. Moreover, mestranol does not bind to the cellular estrogen receptor. In the case of both mestranol and ethinyl estradiol, the estrogen active in blood is ethinyl estradiol. All low-dose OCs contain ethinyl estradiol.

The metabolism of ethinyl estradiol varies between individuals (and individual variability has even been observed). This means that the same dose may produce adverse effects in one woman and not in another.

The estrogen content (dose) of the pill is important. Thrombosis, which is one of the most serious adverse effects of OCs, is a key factor in the increased risk of death associated in the past with high-dose preparations owing to a variety of circulatory disturbances. This adverse effect is caused by estrogens and is dose-related. Accordingly, the estrogen dose is of prime importance when choosing an OC.³

Progestogen Component of Hormonal OCs

The discovery (at the end of the 1930s) of the ethinyl radical and oral potency led to the development of ethisterone, an orally active derivative of testosterone. Removal of the 19 carbon from ethisterone to form norethindrone does not affect oral activity but modifies the chief hormonal effect, which is changed from being androgenic to being progestogenic. Thus, the progestogen derivatives of testosterone were called 19-nortestosterones. However, the androgenic properties of these compounds were not completely eliminated, and minimal anabolic and androgenic activity persists in their structure. Furthermore, norethindrone can be converted to ethinyl estradiol, but the conversion rate is very low and its effect would be due to a weak bond to the estrogen receptor. The estrogenic and androgenic activity of the progestational component are clinically insignificant because of the low doses present in the preparations currently available on the market.

Similar to what happens with the estrogen component, high doses of progestogens—and not only progesterone—have been associated with serious side effects (in older preparations), and low-dose formulations should therefore be used.

The norethindrone family includes the following 19-nortestosterone progestogens: norethindrone, norethynodrel, norethindrone acetate, ethynodiol

diacetate, lynestrenol, norgestrel, norgestimate, desogestrel, and gestodene.

Probably the factor that had the greatest influence on the work that gave rise to the new progestogens was the belief in the 1980s that androgenic metabolic effects were important, in particular in terms of cardiovascular disease. Accordingly, the pharmaceutical companies looked for ways to minimize the androgenic effects of gestagens. It is now known, however, that the cardiovascular side effects are due to stimulation of thrombosis by estrogens.

The new progestogens are norgestimate, desogestrel, and gestodene. The new formulations are similar to the earlier low-dose preparations with respect to control of the menstrual cycle (breakthrough bleeding and amenorrhea). All the 19-nortestosterone-derived progestogens can decrease glucose tolerance and increase insulin resistance. The effect of the earlier low-dose formulations on carbohydrate metabolism was minimal, and the effect of the new progestogens is negligible (of no clinical significance). The lower androgenicity of the new progestogens is reflected in a more marked increase in sex hormone-binding globulin and decrease in free testosterone levels than observed with older formulations.¹ This difference may be of clinical importance in the treatment of acne and hirsutism, although clinical studies have found similar effects with all OCs. Low-dose OCs are effective in the treatment of acne and hirsutism. The suppression of free testosterone levels achieved is similar to that obtained with higher doses. This beneficial clinical effect is comparable to that obtained with the low-dose formulations containing levonorgestrel, previously recognized as a cause of acne at high dose levels. Formulations with desogestrel, gestodene, and norgestimate are associated with greater increases in sex hormone-binding globulin and significantly decreased free testosterone levels. Comparative studies with OCs containing these progestogens have detected no differences between the older products in their effect on measures of androgenic activity. While, in theory, these products would be expected to be more effective in the treatment of acne and hirsutism, this hypothesis has not been confirmed by the clinical studies undertaken. Owing to the combined effects of the increase in sex hormone-binding globulin levels and the decrease in testosterone production, all the low-dose formulations probably produce a similar overall clinical response, particularly after 6 months or more of continued use. It is possible that the new gestagens, such as chlormadinone acetate, do not adversely affect cholesterol-lipoprotein profiles because of their lower androgenicity. The estrogen-progestogen balance of combined OCs may even produce favorable lipid changes (meaning that the new formulations may afford greater protection against cardiovascular disease). However, the data must be interpreted with caution as it is difficult to

accumulate enough evidence because of the low frequency of adverse events.

Drospirenone is a progestogen that is a spironolactone analog. Its biochemical profile is very similar to that of progesterone, including a high affinity for the mineralocorticoid receptor, producing an antiminerlocorticoid effect. The contraceptive efficacy of a combination pill containing 3 mg of drospirenone and 30 µg of ethinyl estradiol (Yasmin) is similar to that of other OCs. Because drospirenone is analog to spironolactone and has antiandrogenic and antiminerlocorticoid activity, caution is advised with respect to plasma potassium levels; this compound should not be prescribed to women with impaired renal, suprarenal, or liver function. OCs with drospirenone have been reported to be an effective treatment for premenstrual syndrome/premenstrual dysphoric disorder.

Definitions Used in Epidemiologic Studies⁴

1. Low-dose OCs: products containing less than 50 µg of ethinyl estradiol
2. First-generation OCs: products containing 50 µg or more of ethinyl estradiol
3. Second-generation OCs: products containing levonorgestrel, norgestimate, and other members of the norethindrone family and 20, 30, or 35 µg of ethinyl estradiol
4. Third-generation OCs: products containing desogestrel or gestodene with 20, 25, or 30 µg of ethinyl estradiol

Despite having weaker metabolic effects, these formulations are associated with a slightly increased risk of thromboembolism and should not, therefore, be prescribed to obese patients or patients with other thromboembolic risk factors.

Mechanism of Action of OCs

The combination pill, with both estrogen and progestogen components, prevents ovulation by inhibiting gonadotropin secretion through its effect on the hypothalamic and pituitary centers.⁵ The progestogen prevents ovulation by inhibiting luteinizing hormone secretion while the estrogens prevent the development of the dominant follicle by inhibiting the secretion of follicle-stimulating hormone. The estrogens in the compound also fulfill 2 other functions: they stabilize the endometrium, thereby minimizing irregular menstruation and breakthrough bleeding, and their presence is required to potentiate the action of the progestogens. This potentiating action, probably due to estrogen's effect in

increasing the concentration of intracellular progesterone receptors, has made it possible to reduce the dose of progestogen. Accordingly, only a minimal pharmacologic level of estrogen is necessary to maintain the efficacy of the combination pill.⁶

Given that the effect of the progestogen will take precedence over that of the estrogens, unless the dose of estrogen is increased enormously, the endometrium, cervical mucus, and perhaps tubal function reflect progestational stimulation. The progestogen gives rise to an endometrium with atrophied glands that is not receptive to ovum implantation, and the cervical mucus becomes thick and impervious to the passage of sperm.

Adverse Effects of OCs

A great deal has been written about the possible adverse effects of OCs. The publication in 1995 by the World Health Organization (WHO) of preliminary data that suggested that third-generation progestogens could increase the risk of thromboembolism led to a reduction in the use of these compounds during the following months.

OCs produce a series of metabolic changes:

1. Coagulation systems: a dose-dependent hypercoagulable state, increased platelet aggregation, and a reduction in antithrombin III levels. In addition, fibrinogen, plasminogen, and fibrinolytic activity are increased. None of these effects have repercussions in normal women, but they may increase the risk of thromboembolism in individuals who have a congenital coagulation disorder (such as antithrombin III deficiency or resistance to activated protein C).
2. Carbohydrate metabolism: OCs produce a dose-dependent increase in basal and stimulated insulin and glucose levels. In addition, they produce estrogen-induced insulin resistance. Blood sugar levels are also influenced by the increases in cortisol, prolactin, and growth hormone levels. Growth hormone is known to have considerable anti-insulin activity. However, follow-up studies of present and past users of OCs have failed to detect any increase in the incidence of diabetes mellitus or impaired glucose tolerance in this cohort. When low-dose OCs are prescribed to patients with type 1 diabetes, the patient's insulin requirement does not usually rise, and no increase in the incidence of retinopathy or neuropathy has been observed.
3. Lipid metabolism: estrogens increase triglycerides and high density lipoprotein-cholesterol (HDL-c), and decrease low density lipoprotein-cholesterol (LDL-c). Gestagens, on the other hand, have the totally opposite effect on the lipid profile, increasing

LDL-c and decreasing HDL-c (this effect depends on dose and androgenicity, particularly in third-generation gestagens). OCs containing third-generation gestagens (which have a low androgenicity profile) only slightly modify the action of the estrogens on the lipid profile, giving rise to a beneficial balance: no significant change in total cholesterol, an increase in HDL-c, and a decrease in LDL-c. The OCs currently used do not produce any risk of atheromatosis, and when such a condition develops it should be attributed to other risk factors, such as smoking or arterial hypertension.

4. Blood pressure: estrogens favor vasodilatation and reduce the accumulation of atheromatous plaques. However, gestagens with androgenic properties increase the accumulation of atheromatous plaques. Third-generation gestagens have no impact on blood pressure. Gestodene, because of its anti-mineralocorticoid action, may help to reduce mild hypertension. When hypertension does develop, it generally appears within the first 6 months of contraceptive use (in 5% of users) and is the result of modifications in the renin-angiotensin system.
5. Hepatic metabolism: the only absolute contraindication related to the liver is acute or chronic cholestasis. In patients with a history of hepatitis, OCs can be used once the acute phase of the disease has passed.

Minor Adverse Effects

1. Nausea and vomiting: these side effects usually only occur during the first 3 months of use. If they persist, improvement can be achieved by taking the pill in the evening after dinner.
2. Weight gain: this symptom, which is caused by water retention, occurs particularly during the first 3 months of use and is usually compensated later. If it persists, the patient can be switched to a preparation with a lower dose of estrogen.
3. Mastalgia: premenstrual breast pain or tenderness is usually caused by estrogen and if the side effect persists the patient can be switched to a preparation with a lower dose of estrogen.
4. Spotting: this side effect is more common with preparations containing a low dose of estrogen. It improves with triphasic or 30 µg preparations.
5. Headache: this symptom may improve with the use of preparations containing a lower dose of estrogen.
6. Hirsutism or acne: these conditions are caused by the androgenic action of the progestogens, and they are rare in patients taking low-dose formulations. In patients with acne or hirsutism, OCs with cyproterone acetate or chlormadinone acetate are usually used (although any low-dose contraceptive would be suitable).

7. Changes in libido: this effect is usually improved by increasing the estrogen dose or by using preparations with progestogen derived from nortestosterone.
8. Chloasma: if this occurs, the pill should be taken at night and the dose of progestogen reduced.

Major Adverse Effects

1. Superficial or deep vein thrombosis: OCs increase the risk of these conditions.
2. Coronary artery disease and acute stroke: the use of OCs increases the risk of these diseases. This risk is directly dependent on the dose of estrogen and progestogen and the androgenic potency of the gestagen (the more potent the androgenic effect, the more damaging the changes in lipid profile). The higher the dose of estrogen the greater the impact it will have on both the coagulation system (favoring hypercoagulability) and carbohydrate metabolism (increasing peripheral resistance to insulin). The higher the dose of gestagen and the more androgenic the profile, the more clinically significant will be the changes in carbohydrate metabolism and blood pressure. The following factors all serve to increase cardiovascular risk even further: obesity, smoking, familial hyperlipidemia, hypertension, and family history of coronary artery disease. Low-dose formulations are not associated with any increased risk of acute myocardial infarction or stroke, although the incidence of deep vein thrombosis remains high (15/100 000) and is even higher for third-generation gestagens, especially during the first 3 months of use. The risk is, however, lower than that of venous thromboembolism during pregnancy: 60/100 000).
3. Hepatocellular adenomas: these are extremely rare tumors (with an incidence of 3/100 000 users) which, in women, have been observed only in individuals who have been taking oral contraceptives containing high doses of estrogens—and in particular mestranol—for more than 5 years. Typically, they disappear when the patient stops taking OCs. In some cases, however, they have been associated with hepatocellular carcinoma, but because of their low incidence in women (1/100 000) and their higher frequency in men, it is not generally believed that any cause and effect relationship exists.

Controversial Major Adverse Effects

Breast Cancer

Irrespective of the preparation used, the results of cohort studies and meta-analyses have not demonstrated any relationship between the use of OCs and breast cancer; studies comparing women who have taken some kind

of oral contraceptive with women who have never taken such medication have not observed any significant increase in risk among the former. However, the risk of breast cancer is slightly higher among current users of oral contraception and women who have used such medication within the preceding 5 years (relative risk: 1.2). It should be noted, however, that women with breast cancer and users of OCs share certain risk factors, such as postponement of first pregnancy and in some cases nulliparity. The sensitivity of breast tissue to estrogens and gestagens is higher before full differentiation takes place; the risk-benefit profile should therefore be carefully assessed when these preparations are used in women under 25 years of age with a family history of breast cancer. Third-generation gestagens may be the best solution for women with risk factors, since they are the OCs with the weakest proliferative effect on the breast.

Cervical Cancer

The presence of multiple confounding factors (smoking, promiscuity, etc) has led to a lack of consensus about whether infection with the human papillomavirus gives rise to cervical cancer more frequently in users or ex-users of oral contraception than in women who have never used such medication. However, women using OCs do undergo regular gynecological examinations, a situation that favors early detection of premalignant cervical lesions (cytologic screening) at a stage at which effective treatment is possible (dysplasias).

Beneficial Noncontraceptive Side Effects

1. Decreased risk of endometrial cancer
2. Decreased risk of ovarian cancer
3. Protection against ectopic pregnancy.
4. More regular menstrual cycles: less blood loss, less dysmenorrhea, less anemia
5. Less salpingitis and greater protection against pelvic inflammatory disease due to the presence of a more viscid cervical mucus, which impedes the passage of bacteria
6. Decreased risk of functional ovarian cysts.
7. Possible decreased risk of fibroadenoma and fibrocystic disease of the breast.
8. Possibly affords protection against uterine myomas
9. Possibly affords protection against arteriosclerosis

There is scientific evidence that the use of OCs exercises a protective effect against ovarian and endometrial cancers even years after withdrawal. However, at this time it is not known whether low-dose estrogen preparations afford the same protective effect.

Unsubstantiated Beneficial Side Effects

1. Prevention of osteoporosis: it is possible that OCs may delay the onset and slow down the progress of osteoporosis.
2. Rheumatoid arthritis: oral contraception may modify the course of this disease and prevent mild cases from progressing to serious disease.

Disorders in Which Oral Hormonal Contraception is Commonly Used for Therapeutic Purposes

1. Hormonal treatment of hypothalamic amenorrhea
2. Premature ovarian failure
3. Functional ovarian cysts
4. Chronic anovulation
5. Dysfunctional uterine bleeding and Dysmenorrhea
6. Intermenstrual pelvic pain
7. The use of OCs can prevent the progression of mild endometriosis in current or recent users since, while it does not prevent the appearance of implants, it does inhibit their development.
8. Acne and hirsutism (OCs containing derivatives of 17-hydroxy progesterone)
9. Prevention of menstrual porphyria
10. Control of bleeding secondary to hematologic disease or anovulation
11. Improvement of premenstrual syndrome

Contraindications to the Use of Oral Hormonal Contraception

Contraindications to oral contraception can be absolute (when the indication of another method of contraception is obligatory) or relative (when prescription of an alternative method is advisable).

Absolute Contraindications

1. Smoking (15 or more cigarettes daily) in women over 35 year of age
2. Diabetes mellitus and angiopathic complications
3. Diagnosis of an estrogen-dependent tumor (breast cancer)
4. Metorrhagia of unknown etiology.
5. Chronic or acute liver disease or history of liver cancer
6. Pancreatic disease
7. Severe systemic hypertension
8. Porphyria
9. Less than 2 years of regular menstrual cycles (adolescents)

10. History of peripheral thromboembolism or thrombophlebitis
11. Congenital or acquired coagulation disorders (protein C or S)
12. History of angina pectoris or acute myocardial infarction

Relative Contraindications

1. Mild arterial hypertension
2. Diabetes mellitus
3. Epilepsy (because of possible drug interactions)
4. Hyperlipidemia
5. Cholelithiasis
6. Prolonged immobilization
7. Scheduled major surgery
8. Sickle cell anemia
9. Migraine
10. Ulcerative colitis
11. Idiopathic jaundice
12. Presence of chronic kidney disease
13. Breastfeeding
14. Any mental state that could affect compliance

Use of Oral Hormonal Contraception in Common Diseases and Situations

Systemic Hypertension

Although elevated blood pressure has been cited as a contraindication for oral contraception, it should be noted that low-dose OCs can be prescribed to nonsmoking women under 35 years of age whose blood pressure is well controlled by medication and who are otherwise healthy. In the case of pregnancy-induced hypertension, the patient can use OCs if blood pressure returns to normal after delivery.

Diabetes

In cases of gestational diabetes, low-dose contraceptive formulations do not produce a diabetic glucose tolerance response, and there is no evidence that OCs increase the incidence of overt diabetes. In women with a history of gestational diabetes, OCs can be used with annual monitoring of fasting blood sugar.

Nonsmoking diabetic women under 35 years of age with no diabetic vascular complications can use oral contraception as various studies have found no evidence that OCs increase the incidence of retinopathy nephropathy, or affect the lipoprotein or hemostatic biochemical markers of cardiovascular risk. Nor has any effect on cardiovascular mortality been detected.

Women with diabetes who have cardiovascular disease or major cardiovascular risk factors should avoid using oral contraception.

Scheduled Surgery

The recommendation that oral contraception should be suspended 4 weeks before scheduled major surgery to avoid the risk of postoperative thrombosis is based on data obtained with high-dose contraceptive pills. Nonetheless, when a period of prolonged immobility is foreseen after major surgery, this recommendation should be followed if possible.

Gallbladder Disease

Since OCs can trigger symptomatic attacks in women who have cholelithiasis or a history of gallbladder disease, they should not be used in these patients.

Hyperlipidemia

Since the effect of low-dose OCs on the lipoprotein profile is not clinically significant, hyperlipidemia is not an absolute contraindication except in patients with a very high triglyceride level (which could get worse with estrogens). In women with triglyceride levels higher than 250 mg/dL, estrogens should be prescribed with caution; they should be avoided altogether in the presence of any additional risk factor (especially smoking). OCs are absolutely contraindicated when hypertriglyceridemia is associated with vascular disease. The clinician should be aware that the response of triglyceride levels to estrogens is rapid and, when the patient's only problem is hypertriglyceridemia, the triglyceride test may be repeated within 2 to 4 weeks of starting treatment. A triglyceride level of 750 mg/dL or higher is an absolute contraindication to treatment with estrogens because of the risk of pancreatitis.

Smoking

OCs are absolutely contraindicated in smokers aged over 35 years as treatment with estrogens would represent an additional risk factor in these patients. Their only option is the gestagen-only minipill. Smoking 15 or more cigarettes per day is a relative contraindication in women under 35 years of age. The risk of cardiovascular events increases in women of all ages who smoke and take OCs, but actual incidence is very low among young women and increases with age. A former smoker who has not smoked for over 1 year is deemed to be a nonsmoker for the purposes of the prescription of oral contraception. Women with plasma nicotine levels secondary to nicotine patches or chewing gum are deemed to be smokers for this purpose.

A formulation with 20 µg of estrogens may be the best option for smokers irrespective of age (since this dose of estrogen has no effect on coagulation factors or platelet activation).

Obesity

An obese but otherwise healthy woman can take oral contraception, but obesity is an independent risk factor for venous thromboembolism, and studies show that this risk is added to those associated with oral contraception. Moreover, there are moderate indications that the failure rate of hormonal contraception increases with excess weight (over 70 kg). Since most clinical trials have excluded very overweight women, the effects of overweight on contraception has not been well studied. The choice of a product with 50 µg of estrogens for overweight women may prevent a higher failure rate, but such a dose will add the risks associated with the highest doses of estrogens to those already associated with the patient's obesity.

Behavioral Eating Disorders

In patients with anorexia nervosa, bone mineral density is linked to body weight. Response to hormonal therapy is altered in patients with abnormal weight. Failure to respond to estrogen treatment with an increase in bone mineral density may be due to the adverse effects on the bone of hypercortisolism associated with stress disorders. Since the increase in bone density in puberty is so large, adolescents in whom this increase does not occur may continue to have a deficit in bone mass despite hormone treatment. A reduction in menstrual function for any reason in early life (even after adolescence) may leave a residual deficit in bone density that cannot be remedied at a later stage with renewed menstruation or hormone treatment.

Use During Puberty

There is no evidence that the use of OCs during puberty affects growth or the development of the reproductive system. For most adolescents, the recommended contraceptive regimen is a continuous daily pill with 28-day packets, because it facilitates compliance.

Postpartum Use

Oral contraception is not the recommended option postpartum because the hypercoagulable state associated with pregnancy persists during this period. Nonetheless, when abortion of a fetus occurs within the first 12 weeks of pregnancy, oral contraception can be started immediately.

The usual OCs should be avoided in breastfeeding women because they may reduce milk production. There are, however, OCs that contain only gestagens, and the main indication for this formulation is in breastfeeding mothers.

Perimenopausal Use

During perimenopause, women may have anovulatory cycles that give rise to irregular and abundant bleeding, and it is impossible to rule out the possibility of spontaneous ovulation and the associated risk of undesired pregnancy. OCs can be prescribed if there are no risk factors that contraindicate their use. Very often, better control of bleeding is achieved with OCs than with the isolated use of gestagens, and their use has the added advantage of affording contraception. The dilemma arises because oral contraception prevents the vasomotor symptoms and amenorrhea characteristic of menopause so that there may be doubt about the best time to switch from oral contraception to the hormone replacement therapy indicated in postmenopausal women. It is important to make this switch because the estrogen dose in even the lowest dose OCs is 4 times that of the standard hormone preparations used during menopause and the dose-related risks associated with estrogen therapy become clinically significant with age. In this context, the level of follicle-stimulating hormone should be measured at yearly intervals after age 50 in order to determine whether menopause has begun. The blood sample should be extracted on the sixth or seventh day of the pill-free interval (when steroid concentrations have declined sufficiently to allow an increase in follicle-stimulating hormone if endogenous estrogens are low due to the onset of menopause). When follicle-stimulating hormone levels are above 20 UI/L under these conditions, it is time to switch to postmenopausal hormone replacement therapy.

Tests Required before Prescribing Hormonal OCs

While in certain special situations (very young women) all that is required before prescribing OCs is a detailed medical history including the pertinent information, the following is recommended in the general population:

1. A clinical history directed at ruling out contraindications: the clinician should obtain information concerning the patient's personal and family history of diabetes mellitus, acute myocardial infarction, pulmonary embolism, stroke, breast cancer, dyslipidemias, systemic hypertension, epilepsy, otosclerosis, smoking, etc). Advantage should be taken of both this visit prior to using oral contraception and subsequent follow-up

visits to offer health education, teaching the woman how to perform regular self-examination of the breast. Health information promoting self-care should also always be given.

2. A general physical examination should be performed, especially of the right hypochondria to rule out hepatomegaly.
3. A breast and gynecological examination is necessary if the woman has not visited her gynecologist in the preceding 2 years.
4. Additional tests: cervical-vaginal cytology (only when the woman has not been tested in the preceding 2 years), blood pressure, and body mass index. Laboratory tests should include complete blood count, coagulation studies, blood sugar, liver function tests, and lipid profile. Optionally, a gynecological ultrasound can be performed if it was not possible to establish the normality of the uterus and ovaries by way of a bimanual pelvic examination during the patient's most recent gynecological consultation (in the case of obese patients, for example).
5. Information: the patient should always be provided information in clear language about OCs and the possible most common adverse effects of their use.

Starting Treatment With Hormonal OCs

OCs can be prescribed to many women without examination of the breasts or pelvis. Problems that require a more detailed assessment can be identified by way of a meticulous medical history and measurement of blood pressure. In view of the greater safety afforded by the new low-dose formulations in healthy women without risk factors, these patients should be assessed annually as we will see below (after an initial visit 3 to 6 months after starting treatment with OCs). Before starting to use OCs, the patient should undergo the basic laboratory workup mentioned above (particularly in the case of women over 35 years of age and overweight younger women, and individuals with a history of gestational diabetes or a family history of heart disease, diabetes mellitus, or hypertension).

At the outset, the OCs prescribed should be preparations with low doses of estrogens and the patient should be informed about possible adverse effects. Above all, the patient should be told how to follow the contraceptive regimen correctly: starting the first day of menstruation (if possible in the evening), continuing for 21 days (always taking the pill at the same time of day), and taking no pill for the 7 days after finishing the 21-day package (withdrawal bleeding will occur during the pill-free interval). The following cycle should be started on day 8, using a new packet. Some preparations are dispensed in packages of 28 pills, the last seven of which contain

a placebo. This regimen is continuous and facilitates adherence in certain women.

Although no studies have investigated this aspect, it is recommended that contraceptive pills be taken at the same time every day, thereby creating a habit associated with a specific timetable to improve treatment adherence.

Use of Hormonal OCs

When a Pill is Missed

When a woman forgets to take a pill and realizes within 12 hours, the missed pill should be taken immediately and she should continue her usual pill taking schedule. In such cases there is no risk of failure of contraceptive cover.

When more than 12 hours have elapsed since the time the missed pill should have been taken, the woman should take the missed pill as soon as she remembers and the next pill at the normal time. However, because of the risk of gestation, barrier contraceptive methods should be used when this happens (although some authors assert that there is no decline in contraceptive cover until a period of more than 24 hours has elapsed after missing a pill if the missed dose is taken together with the normal dose).

When more than 2 consecutive doses are missed during the first 2 weeks of a cycle, that cycle should be suspended and the first pill of the new packet should be taken when 8 days have elapsed since the last pill was taken. In such cases, barrier methods should be used during the 14 days following the missed dose.

If a dose is missed during the last week of active treatment, the cycle should be abandoned and the patient should restart with a new package when 8 days have elapsed since the last pill was taken.

Vaginal Bleeding

The patient should be advised that when low-dose OCs are used there is a possibility of minor vaginal bleeds during the initial months, and that it is only when such bleeding persists beyond the first 3-month period that it is necessary to investigate the possible presence of disease, missed pills, or drug interactions. When all of these possible etiologies have been ruled out, the patient should be switched to a triphasic preparation or to a formulation with a higher estrogen content.

Amenorrhea

When a woman experiences amenorrhea while taking OCs, the physician should confirm that the pill has been taken correctly and pregnancy should be ruled out. If everything is normal, the patient should take another cycle. If amenorrhea persists after that, she should be

switched to a triphasic preparation or to one with a higher estrogen content.

Digestive Tract Disorders

When a patient vomits or has diarrhea (irrespective of the cause) within 4 hours of taking a pill, the dose should be repeated with the same pill from another packet (for this reason it is advisable always to have 2 packets available). If more than 4 hours have elapsed since the pill was taken, no action is required. If the digestive problem persists, the cycle should be cancelled due to the possibility of impaired absorption; a new cycle can be started on the first day of menstruation after the problem has resolved. Alternatively, a double dose can be administered vaginally while the digestive disorder persists.

Monitoring of Women Taking Oral Hormonal Contraception

The need for monitoring will depend on whether the user is under or over 35 years of age.

In Women Under 35 Years of Age Taking OCs

1. The first follow-up visit should take place between 3 and 6 months after prescription to verify adherence to the treatment regimen. The patient should be asked about possible adverse effects, and all risk factors should be reassessed using the medical history. At this visit, blood pressure should be monitored and information about the patient's sexual activity recorded.
2. Annually, personal and family medical history and risk factors should be updated, blood pressure and weight checked, and information concerning sexual behavior recorded.
3. Every 3 years, a pelvic examination and cytology should be performed. If sexual risk factors are present or the patient has not had at least 2 negative annual cytology test results, this should be performed annually.
4. Every 3 to 5 years, the follow-up should include an abdominal examination and a laboratory workup, including total cholesterol, HDL-c, triglycerides, and blood sugar.

Women Over 35 Years of Age Taking OCs

1. The first follow-up visit should take place within 3 to 6 months of starting, as required for younger women.
2. Annually, blood pressure, weight, and laboratory parameters (including total cholesterol, HDL-c, triglycerides, and blood sugar) should be monitored. Information should be obtained concerning habits such as smoking; OCs should be withdrawn if the patient is smoking.

3. Every 3 years, the follow-up should include abdominal and pelvic examinations and cytology (when the results of prior cytological examinations have been negative).
4. It is recommended that the first mammogram be obtained when the patient is 40 years of age, particularly if she has a first-degree family history of breast cancer or was under 20 years of age when she started taking OCs and took them for more than 5 years before that age.

Rest Periods and Factors Limiting the Use of OCs

There is no medical indication for rest periods, since they do not reduce the frequency of adverse effects.

In the preparations currently available, no limits of use are specified as long as the patient has no medical contraindication and no undesirable side effects occur.

After withdrawal of OCs, return to spontaneous ovulation may be delayed, although in 50% of cases it is reestablished within the first 3 months.

Drug Interactions Affecting OCs

1. Altered absorption: a) destruction of intestinal flora by antibiotics may result in impaired absorption of OCs; b) alteration of the enterohepatic circulation by drugs such as tetracyclines and griseofulvin may reduce absorption of OCs; and c) sulfation, drugs such as paracetamol and vitamin C may compete with ethinyl estradiol, increasing absorption capacity.
2. Enzyme induction: rifampicin, barbiturates, and anticonvulsants induce hepatic activation of cytochrome P450, favoring the clearance of ethinyl estradiol. As this effect appears after 2 weeks of continuous use, short courses of these drugs have no effect on the efficacy of OCs.
3. Enzyme inhibition: gestagens, cotrimoxazol, cimetidine, isoniazid, and disulfiram inhibit the metabolic systems and can potentiate adverse effects.
4. Binding to transport proteins: anticonvulsants increase the affinity of the sex hormone-binding globulin for gestagens, reducing their bioavailability due to sequestration in the transport system.

Interaction of OCs with Other Drugs

1. OCs reduce the clearance of benzodiazepines.
2. OCs potentiate the action of antifibrinolytics such as aminocaproic acid.
3. OCs reduce the action of anticoagulants (anti-vitamin K effect) and increase that of coagulation factors.

4. OCs reduce the effects of oral antidiabetic agents.
5. Higher doses of most analgesics are required in patients taking OCs.
6. OCs reduce the effect of antihypertensive medication.
7. OCs increase corticosteroid levels, and consequently increase all of the side effects associated with these drugs.
8. OCs decrease the effects of folates, and of vitamins B and C.

Conclusions

OCs are currently a very widely used method of contraception. Given the frequency of use of this method, many studies have been carried out. However, since the methodology used has not always been adequate, the results of this research must be evaluated critically. What is clear is that the widespread use of this method in the population has provided a great deal of information about both minor and potentially serious side effects. In any case, the low-dose OCs currently on the market are extremely safe when they are prescribed only to patients whose personal and family history reveals no contraindications.

It is very important to ensure that patients who are prescribed oral contraception are properly informed and educated, since the chief cause for abandoning contraception is fear of side effects. The prescribing physician must invest the time necessary to inform the patient in an appropriate manner about the risks of using OCs, while also emphasizing the beneficial effects.

With respect to the choice of preparation, the first choice should be a low-dose formulation containing less

than 50 µg of estrogen combined with a low dose of either a new or an old progestogen since the evidence available indicates that these are the safest formulations.

OCs can be used effectively in patients with hyperandrogenic syndromes, skin diseases requiring genetic counseling, and in patients receiving dermatologic medications that are contraindicated in pregnancy, so long as the pharmacological characteristics and clinical effects of such use are assessed.

Conflict of Interest

The authors declare no conflicts of interest.

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