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Desogestrel

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Desogestrel (13-ethyl-11-methylene-18, 19-dinor-17-alpha-pregn-4-en-20-yn-17-ol) belongs to a new generation of progestogens that, although introduced to the United States only in recent years, have been used in other countries for more than a decade. The rationale to develop a new progestogen for the 1990s lies in the need to decrease side effects and undesirable metabolic changes to make oral contraceptives acceptable to more women. Desogestrel was developed in response to perceived drawbacks of the classic oral progestogens, especially their inherent androgenic effect and specifically, the concern of the negative effect on plasma lipids, and the possible clinical consequences of the described changes.

It also was believed that the advantages of lowering the doses of the old progestogens contained in the traditional oral contraceptives and even the use of different dose combinations, mainly triphasic formulations, had already delivered their potential advantages, and that a new generation of progestogens with different properties was overdue. It also was necessary for the new progestogens to maintain the high levels of contraceptive effectiveness achieved with the old oral contraceptives, and have a low incidence of side effects to minimize patient noncompliance.

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Chemical Composition and Metabolism

Desogestrel, together with norgestimate and gestodene, is one of a generation of progestogens developed in the laboratory in the past decades that have proven safe, efficacious, and clinically useful in contraception.

Desogestrel is a compound that although developed "de novo" in the laboratory, is a gonane and as such, is similar in chemical structure to levonorgestrel (Figure 1). As such, it shares common characteristics, mainly, the absence of a methyl group between rings A and B, and an ethinyl group in a 17-alpha position. Desogestrel has an ethyl group in position 13. Its principal metabolite is 3 ketodesogestrel, although a small percentage is metabolized to levonorgestrel.[1]

Selectivity is a pharmacologic concept that compares the ratio between the desirable or expected effect of a drug or compound and the undesirable or toxic effects that may render it inappropriate for the use in clinical settings. Selectivity ratios can be narrow, so that a drug may require strict supervision and follow-up, or very wide, allowing its safe use even as an over-the-counter medication.

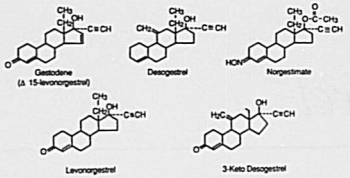

FIG. 1. Structures of the third-generation progestins, including norgestimate, which is characterized by an oxime group at position 3. (Reprinted with permission from Intl J Fertil. 1993;3:104)

In the case of the synthetic progestogen found in oral contraceptives that are 19-nor-androgen (testosterone) derivates, the desirable effect is their progesterone-like action, such as ovulation inhibition and endometrial effects. The undesirable effects are mainly the residual androgenic potency that may affect plasma lipids and have other clinical androgenic effects encountered by oral contraceptive users. It has been shown that the new progestogens have a much higher selectivity ratio than the old ones. The molecular changes have resulted in enhancing the separation between the good effect, that of a potent progestogen, from its negative effect—androgenic potency. Because the androgenic properties of progestogen are not required for contraceptive effect and may contribute to undesirable side effects, a high selective ratio, such as the one offered by the new progestogens, appears desirable.

Metabolic Effects

Oral contraceptives produce metabolic effects in addition to their antiovulatory action. Because of the combination of an estrogen with several different progestogens, it is difficult to determine the precise metabolic impact of oral contraceptives and the relative contribution of each steroid and to make valid comparisons between them. Numerous studies have investigated the effect of desogestrel in several areas, and some conclusions can be drawn, despite the reservations presented.

CARBOHYDRATE METABOLISM

Initially, the estrogen component of oral contraceptives and the progestogen have been implicated in the changes observed in glucose metabolism. It is believed that although progestogens have the most important effect, estrogens also have a role in this complex interaction,[2] perhaps by decreasing the number of insulin receptors.[3]

Oral contraceptives cause an increase in glucose and insulin serum levels and a decrease in glucose tolerance. The effect of desogestrel in carbohydrate metabolism has been shown to be less than that of levonorgestrel.[4] Petersen et al. found no changes,[5] and Van der Vange et al. also showed no change in the area under the curve for insulin and glucose, and that several other variables of glucose homeostasis did not increase during treatment.[6] Jandrairs et al. showed that desogestrel induced minimal changes in plasma insulin and plasma c-peptide, and a slight rise in plasma glucose levels was seen at 12 months, with glucose tolerance remaining within normal limits.[7] However, Liukko et al.[8] found a significant increase in fasting blood sugar at 2 months and Prasad et al.[9] showed a deterioration of the glucose tolerance test.

It is safe to assume that oral contraceptives, even those containing one of the new progestogens at very low doses, still have some mild effects on glucose metabolism, and patients should be monitored accordingly, especially if they have a previous history of carbohydrate metabolism alterations.

LIPID METABOLISM

The effect of oral contraceptives on lipid metabolism is controversial. The negative effect on lipids profile, total cholesterol, HDL-cholesterol, and LDL-cholesterol, is due to the androgenic properties of the

progestogen. Whether the demonstrable changes in plasma lipids have clinical relevance or significance is debatable. In any event, desogestrel, as a progestogen with very low androgenic potency, has been shown to exert minimal changes.

Most studies on desogestrel show no effect on total cholesterol and an increase in HDL-cholesterol levels. The effect on LDL-cholesterol is less clear, but the HDC/LDC ratio is increased. Bergink et al.[10] found significant increases in HDL, and Gevers[11] reported a decrease in LDL, although triglycerides rose in the first 3 months. The consensus of most studies is that desogestrel either induces no significant lipid changes or that they are positive, although long-term studies are rare.[12]

COAGULATION FACTORS

Because of reports in the early 1970s, based on the effects caused by the use of high estrogen doses,[13] a major concern of oral contraceptive users and their doctors is the possible effect on coagulation and its relationship to clinical manifestations, such as clotting disorders, thrombosis, and stroke. The new progestogen have a reduced effect on the coagulation mechanism.

The complexity of the clotting mechanism makes any conclusion tentative at best. Although some authors have found mild increases in some clotting factors, others have found no changes or decreases. The consensus is that oral contraceptives have different effects on the different components of the clotting cascade. The changes are mild in magnitude, and most of the observed changes are due in part to estrogen, with the progestogen playing a modifying role. The effects are probably dose-related.

Daly and Bronnar[14] described a series of changes, including an elevation in factors VII and X, and a decrease in antithrombin III, plasminogen, fibrinogen, and fibrinolytic activity, while others found the changes irregular and not systematic. Stubblefield,[15] in a review of desogestrel effects, reported no increase in the risk of thromboembolic events in European users. He concluded that desogestrel should be as safe as the lowest dose preparations containing the old progestogen, and the risk of thrombotic episodes should be low.[16]

The preliminary results of the large ongoing "Nurses Health Study" [17] show that for women without risk factors (age, obesity, smoking, diabetes, and others) low estrogen oral contraceptive use does not appear to be a risk factor for cardiovascular events, such as myocardial infarction. Neither duration of exposure, nor time after discontinuation of oral contraceptive use appears to affect the incidence of cardiovascular risks.

EFFECT ON BLOOD PRESSURE

Oral contraceptive use has been associated with mild elevations of the blood pressure[13,18,19] in the order of 1–2 mm diastolic and 3–5 mm systolic. The development of true hypertension, as defined by a blood pressure over 140–90 is rare and occurs in about 5–8% of users. It is reversible in the majority of cases.

Reckers[20] reported no changes in the average blood pressure in patients using desogestrel for up to 24 months, although five patients developed hypertension during the trial. Liukko et al.[21] found no changes in blood pressure in a group of women followed-up for 2 years. Dieber and Van Beek reported that 2.92 women per thousand women-years drop out of the treatment because of hypertension, although the mean changes in blood pressure for the 3,421 women studied were small.[22] Low-dose oral contraceptives can be given to young women with mild to moderate hypertension and to those with a history of pregnancy-induced hypertension. They require follow-up and adequate control,[19] and women with risk factors, such as diabetes, obesity, smoking, should be screened out.

Biologic Activity

Desogestrel is a strong progestogen that binds strongly to the progesterone receptor

and inhibits ovulation at very low doses. The study of its biologic activity is difficult because of the use of different formulations and the added effect of the estrogen. Nevertheless, it has been shown to be potent in its effect on estrogen-primed endometrium and in the capacity to delay menses, two bioassays commonly used to estimate biologic potency. In the four classic biologic tests used to evaluate progestational potency: inhibition of ovulation, delay of menses, transformation of endometrium, and binding to progesterone receptors. Desogestrel is far more potent than norethindrone. Some of the increased progestational effects of desogestrel, even at very low doses, may be attributed to a relatively long half-life of about 38 hours, versus about 10 hours for norethindrone.

Desogestrel has been found to achieve a steady-state serum concentration in about 8–10 days.[16] Only about 4–5% of desogestrel circulates in the free from, about 65% is bound to albumin, and 30% is bound to to sex hormone-binding globulin (SHBG).

Desogestrel, together with the estrogen contained in oral contraceptives, exerts its primary contraceptive mechanism by inhibiting ovulation. Animal studies have shown that desogestrel is a potent ovulation inhibitor, as compared to levonorgestrel and norethindrone, even at the lower doses used.[23]

Cullberg et al.[24] showed that ovulation was suppressed with a dose as low as 60 μg of desogestrel when given alone daily. Van der Vange et al.[25] showed a similar effect when combined with 30 μg of ethinyl estradiol. Ovulation seems adequately suppressed, although follicular growth up to 10 mm in diameter can be seen in up to 40–50% of treated women. Nevertheless, Lanes et al.[26] showed a decrease in the incidence of functional ovarian cysts in women using oral contraceptives as compared with nonusers, even those using less than 35 μg of estrogen. Therefore, desogestrel is an effective antiovulatory agent at doses much lower than those needed to suppress ovulation using the traditional progestogen.

Desogestrel has about 50% of the affinity for the androgen receptors than levonorgestrel. As such, it is a very weak androgen, as estimated by bioassays, such as the increase on the prostate or seminal vesicles weight of experimental animals.[1] However, desogestrel has basically no estrogenic effect, failing to bind to estrogen receptors to any significant degree.[27]

EFFECT ON SHBG

An important effect of desogestrel is the increase in plasma levels of SHBG and a decrease in free testosterone, reported by several authors. In this effect, desogestrel shares with the other new progestogens a potentially useful clinical feature, in cases in which patients that require contraception have one of several hyperandrogenic conditions.

One hundred fifty μg of desogestrel, in combination with 30 μg of ethinyl estradiol, produces an increase of more than 200% of the plasma concentrations of SHBG.[28] SHBG levels appear to increase from treatment day 1–21, reaching levels that are threefold higher than before treatment and that remain elevated during the pill-free interval period.[29] The clinical implications of this lowering of the free testosterone plasma levels will be discussed later.

Availability

Desogestrel is available in different combinations and being marketed by two companies (Table 1).

TABLE 1. Desogestrel in the United States

	Desogestrel	Ethinyl/ Estradiol	
Monophasic	150 mg	30 μg	
Triphasic	50 mg	35 μg	Days 1–7
	100 mg	30 μg	Days 8–14
	150 mg	30 μg	Days 15–21

Clinical Studies

A large number of studies, many of them in Europe, have been done using desogestrel-containing oral contraceptives. A good body of evidence has been collected—enough to establish this new progestogen as an effective agent with adequate cycle control and few side effects.

CYCLE CONTROL

Adequate cycle control is required to minimize patient's complaints and inconvenience. Spotting, amenorrhea, and breakthrough bleeding are side effects that negate one of the perceived advantages of oral contraceptives—regular, predictable, normal menses. Patients do not accept irregular bleeding, even mild spotting. They associate it with some pathology of the normal menstrual cycle, and this is one of the reasons for noncompliance. Billota and Favilli[30] reviewed 13,290 women completing 74,967 cycles and described good cycle control with a low incidence of spotting and breakthrough bleeding. The incidence decreased with long-term use.

Vaginal bleeding appears unrelated to plasma levels of ethinyl estradiol or progestogen of the type of desogestrel and gestodene. Wide intra and inter-individual variations have been reported, without any correlation with patients spotting or intermenstrual bleeding,[31] including those who spotted on the first cycle and those whose bleeding persisted for up to 12 cycles.

For all oral contraceptives, the incidence of breakthrough bleeding and spotting is usually around 15–20% in the initial cycles, decreasing to about 5–10% after six cycles.[32] Despite the low concentration of desogestrel in the available oral contraceptives, several studies have shown a similar pattern. Borglin et al.[33] described a higher initial incidence of irregular bleeding because of a high incidence of missed tablets. However, spotting and breakthrough bleeding decreased during the first six cycles studied.

In a randomized comparison, Shoupe[34] concluded that cycle control of the triphasic desogestrel preparation was superior to that of triphasic norethindrone, although the dose of ethinyl estradiol was slightly higher in the norethindrone preparation. The incidence of amenorrhea was around 3% and was not affected by time. About 10% of users complain of heavy menstrual flow, decreasing to about 3% by six cycles. The incidence of amenorrhea is between 0.5% and 1.3%. Breakthrough bleeding occurs in about 8.5% of cycles. The incidence of menstrual irregularities is similar to that encountered by users of the older formulations.

CONTRACEPTIVE EFFECTIVENESS

Clinical efficacy of oral contraceptives depends mainly on their ability to adequately suppress ovulation, because their other biologic effects on cervical mucus or the endometrium play a secondary role.

Several studies have been conducted on the efficacy of the new progestogen, mainly in Europe. In general, for desogestrel, the Pearl Index data show pregnancy failures around 1% per year. Bilotta and Favilli[30] in 1988 reported only 3 pregnancies in 13,290 women followed-up for almost 75,000 cycles, for the monophasic preparation. Others reported no pregnancies for the triphasic preparation in a multicenter study, involving 639 women followed-up for more than 3,000 cycles. Cullberg et al.[35] reported 3 pregnancies in 193 women who were followed-up for 6 months.

Data from Phase III trials indicate that desogestrel-containing oral contraceptives are as effective in preventing pregnancy as those containing any of the traditional progestogens. Most studies show a method failure of one or less per 100 women-years of use. These clinical data correlate well with the reported excellent ovulation inhibition capacity exhibited by this potent progestogen.

It is safe to assume that the contraceptive efficacy of desogestrel is comparable to that of other oral contraceptives. The failure rate per method is always lower than the user's

failure rate, which is generally in the 1% per year range. Patient failure will depend on other factors, such as motivation, level of education, type of support available, and varies with the different population studied.

SIDE EFFECTS

Patients taking desogestrel-containing oral contraceptives complain of the usual side effects, mainly headaches, nausea, vomiting, breast tenderness, and depression. Billota and Famillí[30] showed that nausea stabilized at about 1.2% by cycle six, and that the incidence of headaches was 2.8% by cycle six, a drop from an incidence of 10% before starting the trials. Gutmann and Corson[27] reported that breast tenderness had an incidence of about 8%, and headaches were observed in about 6% of patients by cycle six.

Androgen-related side effects, such as acne and hirsutism, also had a lower incidence by cycles three and six. Weight gain between 0.3 and 1.2 kg during 12 cycles were observed; the highest gain was observed for women younger than 20 years of age. Weight gain is important because more than 10% of women who discontinue the use of oral contraceptives give weight gain as their primary reason. Nausea, vomiting, and menstrual irregularities usually rank lower.

The discontinuation rate for minor side effects was 4.2% after 24 cycles in a study involving 1,613 women, published by Reckers in 1988.[20]

ANTI-ANDROGENIC EFFECTS

Desogestrel has a profound effect on the plasma levels of SHBG, and as a consequence of its elevation, there is a significant drop of the circulating levels of free, active testosterone. Plasma concentrations of SHBG that are double and triple the pretreatment levels have been reported consistently. The increase is seen during the first treatment cycle and persists until cycle 24.[32] As a consequence, total testosterone and free testosterone plasma levels decrease, reducing androgenic-related adverse metabolic and clinical effects. This property, in addition to its low inherent androgenic potency, results in laboratory and clinical evidence of useful anti-androgenic effects that could be used therapeutically in patients that suffer from increased androgenic status, such as polycystic ovarian syndrome.

Several clinical studies performed in Europe have shown dramatic changes in several signs of hyperandrogenism. Hirsutism showed a significant diminution in hair growth speed and hair shaft diameter by cycles six to eight.[12,30,36] Acne scores also decrease significantly by cycle six in several reports.[30,37,38] In one study, in androgenized women, treatment levels were less than half the pre-treatment levels, becoming similar to normal controls.[12]

These characteristics may make oral contraceptives containing desogestrel or other new progestogens the contraceptive of choice for women with hyperandrogenic status, such as polycystic ovarian disease, idiopathic hirsutism, adult onset of adrenal androgenism, and/or moderate to severe acne. It is important to stress that the Food and Drug Administration has not approved nor issued labeling for the use of desogestrel as an anti-androgen medication.

USE IN PERI-MENOPAUSE

Although in the United States desogestrel is approved by the Food and Drug Administration for contraception only, in Europe, interest in its use in peri-menopausal women has increased. This will be used for not only regulating menstrual cycles, but also preventing the increased bone turnover and the decrease in bone density described in women in this age group who experience an impaired ovarian function and a decrease in estradiol production.

In peri-menopausal women, it has been shown that a combination of 150 μg of desogestrel with 20 μg of ethinyl estradiol increases vertebral bone density, and at the same time decreases the excretion of urinary hydroxyproline.[39] Because of the neg-

ligible effect on plasma lipids, desogestrel could become an alternative to the use of 17-alpha-dydroxy-progesterone (Cycrin; Wyeth-Ayerst Laboratories, Philadelphia, PA or Provera; The Upjohn Company, Kalamazoo, MI) in menopausal women with uterus.

Summary

Desogestrel is a new, potent progestogen with very low androgenic properties. When used as a contraceptive, it is a strong antiovulatory compound, even at low doses. The clinical efficacy is as good as that of the old progestogens. It has a low incidence of side effects and complications, similar to other progestogens. It may have a role as an antiandrogen in women with hyperandrogenic symptoms in need of adequate oral contraception.

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