Progestins in Combined Contraceptives

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1. Introduction

The progestagens or progestogens include both progesterone, the hormone secreted by the ovaries and placenta, and the synthetic steroids or progestins that mimic the actions of endogenous progestogen. The new progestagens are, by definition, progestins, and this term will be used throughout the review. Several new progestins have been synthesized in the last decade for use in both contraceptives and hormone replacement therapies.¹

One of the main actions of progesterone or a progestin is the secretory transformation of an estrogen-primed endometrium. Both hormones prevent the over-proliferation of the endometrial tissue, but the degree to which this effect is achieved depends upon the antiestrogenic properties of the progestin and the dose and duration of treatment. As contraceptive agents, progestins with high anti-gonadotropic potency ensure suppression of ovulation and are combined with estrogen in most hormonal contraceptives, combined oral contraceptives (COCs), or nonoral delivery systems such as vaginal rings, transdermal patches, or gels. They are also used without estrogen as progestin-only contraceptive or progestin-only pills.

The effects of progestins are related to interactions not only with progesterone receptors, but also with other steroid hormone receptors: androgen receptors, estrogen receptors, glucocorticoid receptors, or mineralocorticoid receptors. These interactions may either induce transactivation of a steroid receptor or prevent activation. In the target organ, the balance between the receptor corepressors recruited by a progestin determines whether the overall effect of the molecule will be agonistic or antagonistic.² All progestins bind to the progesterone receptor and have the expected effect on the uterine endometrium, but each progestin has a distinctive profile of activity in other target tissues, a profile not necessarily shared by other members of the same class.

Secreted by the corpus luteum after ovulation, progesterone has several biological actions. It maintains pregnancy through its antiestrogenic action, preventing contractions of the uterus; it transforms the endometrium into a secretory tissue to permit implantation of a fertilized ovum, preventing further ovulation through its antigonadotropic action. In addition, progesterone has an anti-androgenic effect. Progesterone competitively inhibits the action of androgen, as it is a preferred substrate to the enzyme 5α-reductase, preventing the conversion of testosterone into its active metabolite dihydrotestosterone.² Progesterone also interacts with the mineralocorticoid receptor; competitive binding to this receptor by progesterone prevents its transactivation and inhibits the mineralocorticoid effect. This antagonistic effect prevents sodium retention and instead induces the excretion of sodium and water.

The older progestins, synthesized in the 1960s and 1970s, were designed for contraceptive use. For this reason, a major design target is the antigonadotropic action.² The new progestins synthesized in the last 2 decades have been designed with the objective of creating the “ideal” progestin. A progestin with potent

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progestational and antiestrogenic actions on the endometrium with a strong antigonadotropic effect but without any androgenic or glucocorticoid effects is thought of as producing the benefits of progesterone without undesirable effects, such as causing acne, a decrease in high-density lipoprotein cholesterol, bloating, and water retention. In addition, other beneficial actions of progesterone, such as its antiandrogenic and antimineralocorticoid effects, are incorporated into the design of some new progestins. Antiandrogenic progestins may have several potentially beneficial effects, such as reducing endogenous androgen action and decreasing the incidence of acne or hirsutism.

When given in the presence of naturally secreted estradiol (E2) or together with a synthetic E2, the final effect of a progestin on the target organs depends upon the potency of the E2. The potency differences among the E2 and their varying effects on the liver, which are determined by their molecular structure as well as by the mode of delivery, may change the way a specific progestin, given at a certain dose, affects not only the endometrium but also the lipid profile, the blood vessels, and, possibly, breast tissue.

2. Classification of progestins

In addition to natural progesterone, there is a broad spectrum of steroids with progesterone-like actions, derived from different parent compounds. Figure 1 summaries the classification of progestins.

3. Pharmacokinetics of progestins

Progestins can be given by various routes, which include oral, intramuscular, vaginal, percutaneous, intranasal, sublingual, and rectal administration. Although the oral route of progestin administration is the most common, there is increasing interest in obtaining an effective parenteral route for progestins, primarily to avoid the hepatic first-pass effect, requiring to be administered in relatively high doses due to its extensive biotransformation in most instances. In addition, oral progestin administration may have a substantial, albeit transient, dose-dependent effect on certain hepatic proteins.

There is little information about the pharmacokinetics of most orally administered progestins, and much less about that of parenterally administered progestins. Table 1 summarizes reported bioavailabilities and half-lives of different progestins.

4. Mechanism of action of progestins

The contraceptive action of progestins occurs in four ways:

- Affecting the ovulation in a dose-dependent manner: This activity occurs by suppressing the midcycle peaks of LH and FSH. It should be remembered that it is the progestin component that provides the contraceptive effect; estrogen is added only to guarantee better bleeding regularity.

- Producing thick cervical mucus plug: This action prevents the penetration of sperm into the endometrial cavity.

- Making the endometrium unsuitable for nidation: Inhibiting the synthesis of progesterone receptors can increase the stromal tissue and decrease the number of glands and stromal edema, making endometrium unsuitable for nidation of a fertilized ovum.

- Reducing tubal motility and ciliary action: Various progestins in various nonequivalent doses and with various administration types may render their contraceptive action quantitatively in various ways, but to some extent all the above-mentioned effects are qualitatively available with all progestins.

5. Descriptions of individual progestins

In the section, we will describe three major categories of progestins. The chemical structure for a prototype of each category will be given.
Venous thromboembolism (VTE) was very low, with only two cases. The contraceptive efficacy and cycle control of COCs is an area of concern for young women. In the vast majority of adolescents and adult women, COCs/EE reduced the incidence of dysmenorrhea more than halved in adolescent and adult women following COCs/EE treatment, an effect that was observed in both conventional and extended cycles.

Androgynic symptoms are a common complaint in COC users, although the introduction of COCs with antiandrogenic properties, such as COCs/EE, has helped minimize this complication. As expected, conventional and extended cycles of COCs/EE reduced symptoms of seborrhea and acne by as much as 50% in adolescent and adult women. Weight gain is another area of concern for COC users. In the vast majority of adolescents and adult women, COCs/EE produced no or negligible changes in weight and body mass index (BMI). These findings are in accordance with reports that COCs/EE has no impact on appetite. In a recent study, the incidence of venous thromboembolism (VTE) was very low, with only two cases reported in adolescent women and four cases in adults during COCs/EE intake. This equated to a VTE incidence of 3.4/100,000 women/year for adolescents and 2.1/100,000 women/year for adults, which is comparable with other studies using low-dose COCs where the range has been 1.5–4/100,000 women/year.

The information available demonstrates that the administration of the 17α-acetoxyprogesterone derivative CMA, available since 1965, has no statistically significant effect on weight or systolic blood pressure. Blood sugar, fasting insulin cholesterol, triglycerides, and high-density lipoprotein cholesterol are not affected. CMA has a strong antiandrogenotropic effect and seems to have no negative effect on antithrombin III. Postmarketing studies monitoring the effects of CMA in combination with EE have found it to be a well-tolerated and effective contraceptive with advantages for those with preexisting hyperandrogenic skin and hair conditions and dysmenorrhea—without increasing the risk of VTE.

Furthermore, contrary to the concerns of many women, evidence suggests CMA/EE formulations neither reduce libido, worsen depression/mood, nor cause relevant weight gain.

### 5.1. 17α-Hydroxyprogesterone derivatives: chlormadinone acetate

#### 5.1.1. Contraceptive efficacy and cycle control

Chlormadinone acetate (CMA) is a derivative of naturally secreted progesterone that shows high affinity and activity at the progesterone receptor. It has an antiestrogenic effect and, in contrast to natural progesterone, shows moderate antiandrogenic properties. CMA acts by blocking androgen receptors in target organs and by reducing the activity of skin 5α-reductase. It suppresses gonadotropin secretion and thereby reduces ovarian and adrenal androgen production.

The contraceptive efficacy of the combination ethinyl estradiol (EE)/CMA has been demonstrated in two Phase III clinical trials. In the first, a combination of EE/CMA (0.03/2 mg/day) was evaluated in 1655 women during 22,337 cycles. At the end of the study, a real Pearl index (IP) of 0.698 [95% confidence interval (CI) 0.389–1.183] and a theoretical IP of 0.291 (95% CI 0.115–0.650) was obtained. In the second trial, the information from 29,262 cycles was analyzed in 2620 women, giving a practical IP of 0.4 and an exact index IP of 0.04. In a recent study, Schramm et al. pooled data were evaluated from six noninterventional trials with CMA/EE intake over four to 12 cycles. The data pool included 62,218 women (345,964 cycles), of whom 60,508 were analyzed in 2620 women, giving like result like turned out a not.

### 5.2. 19-Nortestosterone derivatives (gonanes)

#### 5.2.1. Efficacy and cycle control

The main representative of the second generation progestins is levonorgestrel (LNG). Traditional monthly COC regimens, involving 21 days of hormone treatment followed by 7 days of placebo, during which withdrawal bleeding occurs, use a combination of low-dose EE/LNG 20 μg/100 μg and an oral, continuous, daily hormonal treatment regimen with no hormone-free interval has recently been designed with the aim of reducing or eliminating cyclical menstruation-like periods and decreasing cycle-related adverse effects, using EE/LNG, 20 μg/90 μg. The efficacy of LNG COCs (Table 2) taken in a traditional monthly oral contraceptive regimen and in continuous use combination is similar.

Taken as a class of compounds, third generation progestins (desogestrel/etonogestrel, gestodene, norgestimate) have common characteristics: higher affinity for progesterone receptors than their predecessors, lower affinity for androgen receptors, higher selectivity of action, higher central inhibitory activity, higher potency at the level of the endometrium, and overall metabolic neutrality, in terms of effects on lipid and carbohydrate metabolism. They have a similar efficacy and cycle control.

#### 5.2.2. Safety and side effects

Two types of clinically relevant adverse effects must be discussed for women taking progestational compounds: changes in lipid metabolism and bleeding irregularities. In any case, the safety profile of gonanes is comparable to the newest progestins, including a low impact on lipid profile and bleeding irregularities.

Given these characteristics, it was to be expected that third-generation progestins, already the most widely used compounds today in Europe, would become more and more the progestational components of choice for COCs of the 21st century. Unfortunately, as was almost inevitable in the more than 50 years of the history of COCs, a cloud has been hanging over these steroids since 1995, when a World Health Organization (WHO)-sponsored study found an increased risk of VTE in women taking COCs containing third-generation progestins, compared to those using second-generation ones.

More than 17 years later, the controversy is far from being over and, whereas a majority of studies undertaken to verify the validity of the WHO findings have substantiated their results (the mean relative risk being 1.7), others have argued that the increase can be due to a selection bias. This possible increased risk of venous pathology must be quantified and weighed against the possibility that third-generation COCs may have a beneficial effect on arterial diseases, a much less frequent pathology in young women but potentially a
the WHO Scientific Board estimated the relative risk of 0.5, utilizing the mortality rate of 30% reported by Drospirenone (DRSP; 6β,7β,15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone) is an analogue of the antimineralocorticoid spironolactone that is synthesized from androstenolone. As a COC, it is available in formulations containing EE/DRSP 20 μg/3 mg and EE/DRSP 30 μg/3 mg.

5.3. Spirolactone derivative: drospirenone

Drospirenone (DRSP; 6β,7β,15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone) is an analogue of the antimineralocorticoid spironolactone that is synthesized from androstenolone. As a COC, it is available in formulations containing EE/DRSP 20 μg/3 mg and EE/DRSP 30 μg/3 mg.

5.3.1. Contraceptive efficacy and cycle control

The contraceptive efficacy of the combination EE/DRSP, in a 21/7 regimen, has been evaluated in two Phase III trials. The exact IP obtained from the collated information from the studies of efficacy give a value of 0.09. The calculated global IP of 0.57 derives from the 13 pregnancies registered during the treatment; nevertheless, only two of them could be imputed to failure of the method, with an IP of 0.09.

In two 1-year (13 contraceptive treatment cycles), non-comparative, international and EU trials enrolling 1,027 and 1,101 healthy women aged 17–36 years, respectively, oral drospirenone/ethinylestradiol 3 mg/20 μg (24/4) provided 99% contraceptive protection. The uncorrected IP was 1.29 vs. 0.49 and the cumulative pregnancy rates were 1.26% and 0.5% in the international and EU trials, respectively.57,58

5.3.2. Safety and side effects

The combination EE/DRSP was generally well tolerated, with adverse events generally typical of those experienced with other COCs and which were most likely to occur in the first few cycles. Irregular bleeding (actively solicited), headache, nausea and breast pain were the most common adverse events; all tended to decrease over time in the 1-year, international trial. There were no clinically significant changes in potassium levels or other laboratory investigations and no abnormalities in adequate-sample endometrial biopsies after 12 cycles.58 By contrast, DRSP does not induce adverse changes in lipid parameters and hepatic function.39,40

Studies evaluated in a review by Sehic and Smith59 showed that women utilizing a DRSP-containing COC did not have a higher risk of VTE when compared to women utilizing other progestins. The crude incidence rate ratio for VTE in women taking a COC containing DRSP compared to a COC containing other progestins ranged from 0.9 to 1.7 (95% CI 0.5–2.4). Several studies have evaluated the risk of VTE in users of COC containing drospirenone compared with other progestins, and none were able to show a significantly increased risk of VTE with DRSP. The recent media attention regarding VTE risk and drospirenone-containing COCs does not seem to be well supported by the research currently available.

### Table 2 Norgestimate (NGM) and norelgestromin (NGNM) efficacy studies15–28

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Design</th>
<th>Combined contraceptive</th>
<th>Users (n)</th>
<th>Cycles</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Traditional monthly oral contraceptive regimen</td>
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</tr>
<tr>
<td>15</td>
<td>OL, MC</td>
<td>LNG/EE (100 μg/20 μg)</td>
<td>1,708</td>
<td>26,554</td>
<td>IP = 0.88; cumulative pregnancy rate = 1.9%</td>
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<td>16</td>
<td>OL, MC</td>
<td>EE/LNG (20 μg/100 μg)</td>
<td>463</td>
<td>N/A</td>
<td>Comparable efficacy for all preparations</td>
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<tr>
<td></td>
<td>EE/DSG (ed)(20 μg/10–130 μg)</td>
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<td></td>
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<tr>
<td></td>
<td>EE/NGM (ed)(35 μg/180–215–250 μg)</td>
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<tr>
<td></td>
<td>Continuous use of LNG/EE combination</td>
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<tr>
<td>17</td>
<td>R, MO, CL</td>
<td>EE/LNG (30 μg/100 μg)</td>
<td>91 d ER</td>
<td>456</td>
<td>IP = 0.60 vs. 1.78 Pregnancy rate = 0.9% vs. 1.3%</td>
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<tr>
<td></td>
<td>EE/LNG (30 μg/150 μg)</td>
<td>28 SC</td>
<td>226</td>
<td></td>
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<tr>
<td>18</td>
<td>MC, R</td>
<td>EE/LNG (0.5 mg/0.25 mg)</td>
<td>900</td>
<td>3,364</td>
<td>Pregnancy rate = 0% vs. 1.04%</td>
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<td>EE/LNG (0.5 mg/0.25 mg) continuous use</td>
<td></td>
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<td>3,726</td>
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<td></td>
<td>NGM/NGNM</td>
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<td>Oral</td>
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<td>19</td>
<td>OL, MC, C</td>
<td>NGM/EE (250 μg/35 μg)</td>
<td>1,473</td>
<td>19,718</td>
<td>Comparable efficacy (IP = 0.39 vs. 0.24)</td>
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<tr>
<td>20</td>
<td>OL, MC</td>
<td>NGM/EE (250 μg/35 μg)</td>
<td>59,701</td>
<td>342,348</td>
<td>IP = 0.25</td>
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<tr>
<td>21</td>
<td>OL, MC</td>
<td>NGM/EE (180–215–250 μg/35 μg)</td>
<td>661</td>
<td>6,511</td>
<td>High efficacy (IP = 0.55)</td>
</tr>
<tr>
<td>22</td>
<td>OL, MC</td>
<td>NGM/EE (180–215–250 μg/35 μg)</td>
<td>4,234</td>
<td>22,312</td>
<td>Comparable efficacy (IP = 0.13 vs. 0.34)</td>
</tr>
<tr>
<td></td>
<td>LNG/EE (50–75–125 μg/30–40–30 μg)</td>
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<td></td>
<td>TP</td>
<td></td>
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</tr>
<tr>
<td>23</td>
<td>R, OL, C, PG</td>
<td>TP: NGM/EE (150 μg/20 μg)</td>
<td>1,417</td>
<td>9,275</td>
<td>Comparable efficacy with better compliance in patch group (IP = 0.99 vs. 1.25)</td>
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<tr>
<td></td>
<td>NGM/NGNM</td>
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</tr>
<tr>
<td>25</td>
<td>R, OL, C, PG</td>
<td>TP: LNG/EE (150 μg/20 μg)</td>
<td>1,489</td>
<td></td>
<td>Comparable efficacy (IP = 0.28 vs. 0.66), with better compliance in patch group</td>
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<tr>
<td>26</td>
<td>MC, OL</td>
<td>LNG/EE (2 mg/30 μg)</td>
<td>2,291</td>
<td>24,719</td>
<td>IP = 0.5</td>
</tr>
<tr>
<td>27</td>
<td>OL</td>
<td>LNG/EE (2 mg/30 μg)</td>
<td>16,807</td>
<td>92,146</td>
<td>IP = 0.14</td>
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<tr>
<td>28</td>
<td>MC, OL</td>
<td>LNG/EE/ZV</td>
<td>1,377</td>
<td>Unadjusted IP = 0.73; adjusted IP = 0.34</td>
<td></td>
</tr>
</tbody>
</table>

**C** – controlled; **DNG** – desogestrel; **DSG** – desogestrel; **E2V** – estradiol valerate; **ed** – escalating dose; **EE** – ethinylestradiol; **ER** – extended regimen; **IP** – Pearl index; **LNG** – levonorgestrel; **MC** – multicenter; **OL** – open label; **PG** – parallel groups; **R** – randomized; **SR** – standard regimen; **TP** – transdermal patch.
In conclusion, progestins have been in use for contraception for more than 30 years. The main goal has been to develop a contraceptive method devoid of the metabolic or clinical side effects associated with the use of estrogens. Modern COCs offer excellent contraceptive efficacy, and adherence is good. The occurrence of serious adverse events such as VTE, including pulmonary embolism, are rare with contemporary low dose combinations of EE and different progestins, but individualized risk assessment should always be undertaken to identify women who would be better advised to use other forms of contraceptives.

References