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REVIEW ARTICLE

Progestins in Combined Contraceptives

José A. Guerra [1], Francisco López-Muñoz [1,2]*, Cecilio Álamo [1]

[1] Pharmacology Department, Faculty of Medicine, University of Alcalá, Madrid, Spain
[2] Faculty of Health Sciences, Camilo José Cela University, Madrid, Spain

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While the estrogen component of oral contraceptive pills is kept at 20–30 μg of ethinyl estradiol/day, attention in the development of new combined contraceptive drugs has been focused on the progestin component. Most of the antiovulatory effects of oral contraceptive pills derive from the action of the progestin component. The estrogen doses in these drugs are not sufficient to produce a consistent antiovulatory effect. The estrogenic component of combined contraceptives potentiates the action of the progestin and stabilizes the endometrium so that breakthrough bleeding is minimized. Besides the natural progestin, progesterone, there are different classes of progestins, such as retroprogesterone, progesterone derivatives, 17α-hydroxyprogesterone derivatives, 19-norprogesterone derivatives, 19-nortestosterone derivatives, and spironolactone derivatives. In addition to the progestrogenic effect, which is similar for all progestins, there is also a wide range of biological effects. The objective of this review article is to provide recent data on progestins currently available worldwide for contraception.

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 progesterone. 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 antigonadotropic 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 coactivators and 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 antiandrogenic 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

* Corresponding author. Francisco López-Muñoz, Faculty of Health Sciences, Camilo José Cela University, C/Gasómetro, 11, Portal 3, 2° A, 20005 Madrid, Spain.
E-mail: F. López-Muñoz <francisco.lopez.munoz@gmail.com>

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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 (E_2) or together with a synthetic E_2, the final effect of a progestin on the target organs depends upon the potency of the E_2. The potency differences among the E_2 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]

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]

4. Mechanism of action of progestins

The contraceptive action of progestins occurs in four ways[3]:

- *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 cilial 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.

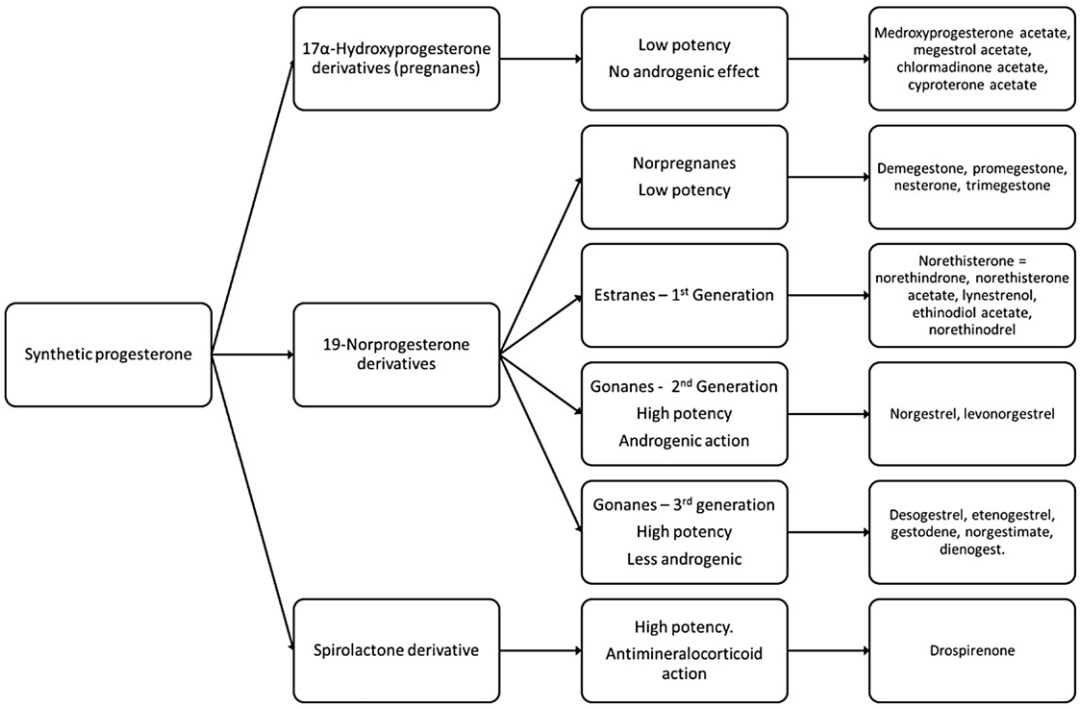

Figure 1 Classification of progestins.[3]