Clinical Relevance of Contraceptive Progestin Pharmacology

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Contraceptive Progestins
This section presents an overview of the clinical relevance of contraceptive progestin chemistry and pharmacology. Key topics include the role of progestins in OCs, and the basis for their development—specifically, how different formulations or chemical structures relate to function.

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Pharmacologic Actions of Progestin and Estrogen
OCs have 2 components—a synthetic estrogen and a synthetic progestin. Acting synergistically, both components inhibit pituitary and ovarian activity, which prevents ovulation. This is their primary contraceptive effect. Progestin also thickens cervical mucus and causes transformation and atrophy of the endometrium. To some extent, these actions are offset by estrogen, which thins and increases cervical mucus and causes the endometrium to proliferate. Together, the estrogen and progestin components provide cycle control.

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Pharmacologic Effects of Progestins in OCs
A number of pharmacologic effects contribute to the contraceptive effects of progestins. These include inhibiting ovulation by suppressing the function of the hypothalamic-pituitary-ovarian (HPO) axis; modifying the subsequent pituitary surge of luteinizing hormone (LH) and follicle stimulating hormone (FSH); slowing transport of the ovum through the fallopian tubes, which limits the time available for fertilization; thickening cervical mucus, which impedes sperm transit; and inhibiting the activation of spermatogenic enzymes required for ovum penetration (capacitation).

Reference:
Ruggiero RJ. Contraception. In: Koda-Kimble MA,
Chemical Structures of Contraceptive Progestins

Synthetic progestins used in OCs can be classified as those that are structurally related to progesterone or testosterone. Progestins structurally related to progesterone include progesterone itself and medroxyprogesterone acetate compounds that have 21 carbons. Progestins structurally related to testosterone are structural derivatives of testosterone and are not synthesized from testosterone. Removal of the methyl group from the testosterone molecule produces norethindrone, a compound with high progestational activity, high oral activity, and almost no androgenicity. Adding an additional methyl group forms an ethyl group and produces the compound norgestrel, which has even greater progestational activity than norethindrone. Norgestrel is synthesized chemically into dextro-norgestrel, an inactive form, and levonorgestrel, the active form. Another classification of progestins uses the terms gonane or estrane and is based on the number of carbons: gonanes have 17 carbons and estranes, 18 carbons.

Family Tree of Contraceptive Progestins

Chemical derivatives of levonorgestrel (gonanes) and norethindrone (estranes) are the progestin components of OCs. Levonorgestrel derivatives include desogestrel, norgestimate, and gestodene. Norethindrone derivatives include norethindrone acetate, ethynodiol diacetate, and lynestrenol.

*Not available in US.
Key Areas in Assessing Progestins

When assessing a contraceptive progestin, several factors need to be considered. The first consideration is whether the progestin is in active form or needs to be converted. Some progestins are prodrugs that must be converted to biologically active forms. The next is the progestin’s affinity for human tissues, including inhibition of ovulation and binding affinity to human receptors. The third consideration is the pharmacokinetic profile, including half-life and bioavailability. The clinical relevance of animal data compared to human data should also be assessed.

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Biologically Active Forms of Estrane Progestins

Five estrane progestins are in commercial use. Three of these—norethindrone acetate, ethynodiol diacetate, and lynestrenol*—are prodrugs. Before these 3 can exert progestational activity, they must undergo biochemical conversion to norethindrone, their biologically active form.

* Not available in US.

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Biologically Active Forms of Gonane Progestins

Levonorgestrel and gestodene* are gonane progestins that are active in their current forms. Desogestrel and norgestimate are prodrugs that must undergo biochemical conversion in the liver. Desogestrel is transformed to 3-keto-desogestrel, which is its only active form, whereas norgestimate is converted to levonorgestrel and levonorgestrel-3-oxime, which are its active forms.

* Not available in US.

References:
Stanczyk FZ. Pharmacokinetics of the new progestins and influence of gestodene and desogestrel on ethinylestradiol metabolism. Contraception. 1997;55:273-282; Stanczyk
FZ, Roy S. Metabolism of levonorgestrel, norethindrone, and structurally related contraceptive steroids. 


**Contraceptive Progestins: Bioavailability After Oral Intake**

The extent to which a contraceptive progestin enters the circulation without undergoing hepatic metabolism determines its bioavailability. There is a great deal of interindividual variability in the bioavailability of contraceptive progestins. The range goes from gestodene* (>90%) and levonorgestrel (~90%) to the metabolites produced by norgestimate (<25%). Norethindrone and 3-keto-desogestrel (active form of desogestrel) are in the intermediate range at approximately 64% and 62%, respectively.

* Not available in US.

**References:**


**Clinical Relevance of Higher Bioavailability**

Higher bioavailability after oral intake of certain contraceptive progestins may have clinical relevance. A reduced drug dose may be possible while maintaining both cycle control and contraceptive efficacy, and there may be less patient-to-patient variation in drug transformation.
Contraceptive Progestins: Average Serum Half-Lives

Serum half-lives of contraceptive progestins are not absolute values, but change depending on whether women receive progestin only or OCs with an estrogenic component. All progestins shown in this graph were given in combination with ethinyl estradiol (30 µg to 35 µg). Levonorgestrel is shown to have the longest half-life of 15 hours. Both 3-keto-desogestrel (the active form of desogestrel) and gestodene* have half-lives of 12 hours, and the half-life of norethindrone is 7 hours.

*Not available in US.

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Levonorgestrel and Norethindrone: Plasma Levels After Single Oral Dose

Plasma levels of norethindrone (1000 µg) and levonorgestrel (150 µg) after a single oral dose indicate that a considerably higher level of norethindrone (about 14 ng/mL) occurs within the first hour as compared with levonorgestrel (about 2 ng/mL). However, levels of norethindrone fall precipitously to undetectable levels—below 1 ng/mL at 24 hours compared to levonorgestrel, which is still detectable at 48 hours.

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Conditions Influencing OC Progestin Serum Levels

- Individual absorption/metabolism
- Drugs affecting steroid absorption and metabolism (e.g., griseofulvin, rifampin)
- Inconsistent OC use (missed pills, doubling up)

In clinical practice, patient factors can influence serum levels of progestins. These factors include individual metabolism, use of other drugs that affect absorption or metabolism, and inconsistent OC use, such as missing pills or taking more than 1 pill daily.

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Drugs That Decrease the Effectiveness of OCs

Anticonvulsants that induce hepatic enzymes can decrease serum concentrations of the estrogen or progestin component of OCs, or both. This effect has been observed with phenobarbital, phenytoin, carbamazepine, felbamate, and topiramate. Although studies demonstrate reduced serum levels of OC steroids during anticonvulsant use, and many of them demonstrated breakthrough bleeding, investigators did not observe ovulation or accidental pregnancy during anticonvulsant use. Pharmacokinetic evidence of lower serum steroid levels also exist for rifampin and griseofulvin.

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Drugs That Do Not Decrease the Effectiveness of OCs

Although there are many anecdotal reports of OC failure in women taking concomitant oral antibiotics, pharmacokinetic evidence of lower serum steroid levels exists only for rifampin and griseofulvin. Women who take rifampin or griseofulvin should use non-hormonal methods of birth control. Many oral anti-infective agents prescribed for acne treatment or for other reasons do not decrease hormonal steroid levels in women taking OCs. These include tetracycline, doxycycline, ampicillin, metronidazole, and quinolone antibiotics. Because the product information sheets accompanying many OCs suggest some antibiotics may be associated with reduced efficacy, acne patients who are prescribed antibiotics (other than rifampin or griseofulvin) should be forewarned and reassured that no large-scale prospective epidemiologic study has shown an association between oral antibiotics prescribed for acne and reduced OC
effectiveness. Patient education should include information that regular use of an OC is one of the most effective methods of birth control, but—like all other birth control methods, excluding abstinence—is not effective 100% of the time; in particular, strict compliance is an issue.

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### Relative Binding Affinities for Human Uterine Progesterone Receptor

In vitro studies of uterine progesterone receptor binding of progestins give a range of relative binding affinities (RBAs), depending on the species studied, various study parameters, and compounds used for comparison. Caution must be used when applying animal data to humans to evaluate the progestational, androgenic, and other activities of progestin (PROG). Whenever possible, clinical decisions should be based on human data. Compounds such as levonorgestrel (LNG) have a very high affinity for the human uterine progesterone receptor, as does 3-keto-desogestrel (3-keto-DSG), levonorgestrel-17-acetate (LNG-17-acetate) and gestodene (GSD).* Two prodrugs, desogestrel (DSG) and norgestimate (NGM), do not bind to the human uterine progesterone receptor. Among the norgestimate metabolites, levonorgestrel-3-oxime (LNG-3-oxime) has a very low RBA for human uterine progestin receptors, even though serum levels may be high. Levonorgestrel-17-acetate, however, has substantial progestational activity, but is barely detectable in serum following administration of norgestimate.

* Not available in US.

**Reference:**

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Progestin Dose Required for Ovulation Inhibition

In studies looking at various progestins combined with 30 µg to 35 µg ethinyl estradiol, the progestin dose needed for ovulation inhibition varied widely from high doses for norethindrone (approximately 400 µg per day) and norgestimate (200 µg per day), to levonorgestrel and desogestrel (60 µg per day), to smaller doses for gestodene* (approximately 30 µg per day).

* Not available in US.

Reference:

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Is There Clinical Relevance?

It is difficult to determine the clinical relevance of the fact that different progestins bind differently to the human uterine receptor. Animal models show different results from human models, and OCs exert system-wide effects, including a combination of effects on the uterus and ovary. The clinical relevance of the fact that different doses are required to inhibit ovulation with various progestins is not yet determined, as these differences are compensated for by dose increases. However, these differences may be relevant to compliance with OC use.

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There Are No Differences in Androgenicity of Progestins

All OCs are anti-androgenic because they suppress the ovaries, which produce androgens, and contain estrogen, which is anti-androgenic. The myth that OCs are androgenic is based on a misinterpretation of studies involving male rats where some progestins were shown to be more androgenic than others—that is, more conducive to weight increases in the ventral prostate when given at high doses. These data are not considered relevant to the effect of low-dose OCs in female humans for 2 reasons. First, the relative binding affinities of progestins to androgen receptors in animals and humans are substantially different. Second, the progestin dose included in OCs is more than 100 times lower than the
progestin dose required to show an androgenic effect in male rats.

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**Gap Between Doses for Anti-Ovulatory vs. Androgenic Activity**

This slide shows data from a study comparing the dose of a progestin (levonorgestrel) needed to inhibit ovulation in female rats to the dose needed to increase the weight of the ventral prostate in male rats. The results show that the dose stimulating a weight increase in the ventral prostate was more than 100 times greater than the dose needed to inhibit ovulation. Very little progestin is required to inhibit ovulation, even when used alone rather than in combination with an estrogen.

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**Myth: OCs Are Androgenic**

Contrary to the myth, low-dose OCs are anti-androgenic. They decrease androgenic conditions such as acne and hirsutism, and do not induce androgenic conditions such as male pattern baldness, excessive hair growth, clitoral enlargement, deepening of the voice, or increased sebum production.

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Effect of OCs on SHBG/Testosterone

This slide shows the results of a study comparing 7 OCs with regard to their effect on sex hormone binding globulin (SHBG), total testosterone (total T), and free testosterone (free T). The OCs all contained ethinyl estradiol (30 µg to 40 µg) but different types and doses of progestin. In this study, the increases in SHBG were extremely variable, and total T varied to a lesser degree. (One OC, CPA 2000 µg /EE 35 µg, actually caused total T to increase.) Despite these variations, all the OCs reduced free T to a similar degree. A decrease in free T is considered the most important factor when evaluating the effect of OCs on acne and other androgenic conditions.

Drug abbreviations: EE, ethinyl estradiol; LNG, levonorgestrel; NET, norethindrone; CPA, cyproterone acetate; GSD, gestodene; DSG, desogestrel.

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OC Effects on Androgens

This study compared the effects of two 20 µg ethinyl estradiol (EE) OCs, levonorgestrel (LNG) 100 µg and norethindrone acetate (NETA) 1,000 µg, on androgen levels and acne lesion counts. In addition, the study assessed directional changes of androgens associated with reduction in acne lesions in a subpopulation of women with significant acne at baseline. Patients were evaluated at baseline and during cycle 3 (days 17 to 21) for androgen and sex hormone binding globulin levels, acne lesion count, and weight. Results demonstrated that, among the 41 evaluable women at the end of the study, there were statistically significant reductions in all measured androgen levels.

Reference:

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Acne and Markers of Androgenicity: A Comparison of Two 20 µg EE OCs
At the end of 3 cycles, both 20 µg ethinyl estradiol (EE) formulations decreased androgens and increased sex hormone binding globulin (SHBG) from baseline, although the OC with norethindrone acetate (NETA) increased the mean SHBG more than the OC with levonorgestrel (LNG). There were no significant differences between treatment groups in the mean decreases in total inflammatory lesions, total comedones, and total lesions. Both formulations were associated with a significant correlation between the reduction in total lesion count (decrease of ~6.3) and decreased bioavailable testosterone in patients who had more than 15 lesions at baseline.

Reference:

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OC Effects on Androgens and Acne
Compared with the formulation consisting of ethinyl estradiol (EE) and levonorgestrel (LNG), the formulation consisting of EE and norethindrone acetate (NETA) was associated with 2 times greater relative increase in sex hormone binding globulin (SHBG). At the same time, the formulations had equivalent decreases in bioavailable testosterone, and both improved acne and were well tolerated. There was no significant change in weight associated with either formulation.

Reference:

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OC Changes in Biochemical Markers of Androgenicity
Changes in biochemical markers of androgenicity were studied in 58 young women (≥14 years old) randomized to placebo (n=29) or a low-dose OC, ethinyl estradiol (EE) 20 µg/levonorgestrel (LNG) 100 µg (n=29). Mean percentage changes from baseline were determined at the end of cycles 4 and 6. Cycle 6 results are shown on this slide and the slide that follows (n=15, OC group; n=15, placebo group). Statistically significant (P<.05) reductions were noted in 3α-androstanediol glucuronide (3α-diol G), as well as marked reductions in the treatment group in androstenedione (A), androsterone glucuronide (AG), dihydrotestosterone (DHT), total testosterone (TT), and dehydroepiandrosterone sulfate (DHEAS), although the reductions were not statistically significant. Statistically significant reductions in the OC group were observed for A, AG, and 3α-diol G vs. increases with placebo. The OC significantly decreased androgen levels in ovarian (A, TT) and peripheral (3α-diol G) compartments as compared to placebo.

Reference:

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Considerations for Contraceptive Progestins
When evaluating contraceptive progestins, a number of important factors should be considered. Progestins with minimal hepatic transformation have limited interindividual variation in metabolic rates. High target tissue affinity allows for lower drug dose. Prolonged half-life produces more sustained effects. And finally, higher bioavailability permits the use of a lower dose.

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