

## CLINICAL VIGNETTE

### Four Generations of Progestins in Oral Contraceptives

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Combined oral contraceptives contain two synthetic steroid hormones, an estrogen and a progestin. The first synthetic progestin compounds capable of being used for an oral contraceptives were Norethisterone (Norethindrone), synthesized by Carl Djerassi and his student Luis Miramontes in Mexico in 1951 and Norethynodrel, developed by Frank Colton at Searle & Co in Chicago in 1952. The first oral contraceptive pill Enovid was approved by the FDA in June 1960. It was a combination of 10 mcg of Norethynodrel and 150 mcg of Mestranol. In hormonal contraceptives, progestins are the most important agent that suppresses ovulation through their anti-gonadotropic properties<sup>1</sup>. Progesterone has other effects that potentiate the anti-gonadotropic effect on contraception, which include changes in the quality of the mucus, endometrial changes and alteration in the motility of the Fallopian tube<sup>2</sup>. These secondary effects are important as ovulation is not always inhibited by progestins. Previous data showed that Desogestrel administered at a dose of 60–75 µg/day inhibits ovulation completely but Levonorgestrel 30 µg/day prevents ovulation in only 40% of cycles<sup>3</sup>.

All progestins bind to the Progesterone receptor (PR), but also with other steroid receptors: estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR) and mineralocorticoid receptor (MR)<sup>4</sup>. All progestins have a similar effect on the endometrium but different effects in other tissues related to an agonist or antagonist effect on various receptors.

The older progestins were developed mainly for their anti-gonadotropic effect. Over the more recent decades, newer progestins were developed, with the goal of finding a potent progestational and antiestrogenic effect in the endometrium, coupled with a strong anti-gonadotropic effect and with minimal androgenic and increased mineralocorticoid

effects. Such progestins have less androgenic side effects like acne and lowering of the HDL and mineralocorticoid effects which decrease bloating or water retention. Additionally, antiandrogenic progestins reduce the effect of the endogenous androgen and this decrease the incidence of acne and hirsutism. The ratio of desired agonistic progestational binding to undesired secondary agonistic androgenic binding is referred to as the Selectivity Index. A selective progestin has progestational effects at low concentrations and androgenic effects at high concentrations<sup>5</sup>. Concentrations of progestins have decreased from 500 µg in the 1960s to less than 100 µg today.

Figure 1: Four generations of progestins in oral contraceptives

- **First generation:**
  - 1) **Estranes derived from testosterone**  
norethindrone, norethynodrel,  
norethindrone acetate, ethynodiol diacetate
  - 2) **Pregnanes derived from 17-OH progesterone**  
medroxyprogesterone acetate,  
chlormadinone acetate
- **Second generation: Gonanes derived from testosterone**  
levonorgestrel, norgestrel
- **Third generation: Gonane (Levonorgestrel) derivatives**  
desogestrel, gestodene,  
norgestimate/norelgestromine,  
etonorgestrel
- **Fourth generation**
  - 1) **Non ethylated estranes:** dienogest,  
drospirenone
  - 2) **Pregnanes (19-norprogesterones)**  
nestorone, nomegestrol acetate,  
trimegestone

Progestins of the first generation were derived from testosterone. The initial progestins differed from testosterone by lacking a methyl group at the 19 position and having an added ethinyl group at the 17 position (Norethindrone).

The second generation progestins were estrane derivatives of testosterone. They had acetate groups added at the 3 and/or 17 positions. Later second-generation 19-norprogesterone derivatives had a methyl group added to the C-18 methyl group to create an ethyl group at C-13 (Norgestrel). They have a high binding affinity to the androgen receptor, making it difficult to eliminate some of the undesirable androgenic effects.

Third-generation progestins were modified by adding a methylene group at the 11 position (Desogestrel) or an acetate group at the 17 position (Gestodene).

The fourth generation compounds were developed to bind specifically to the progesterone receptor but not to the other steroid receptors. Drospirenone is the only progestin currently used in combined hormonal contraceptives in the US that is not derived from 19-nortestosterone. Drospirenone is derived from 17 $\alpha$ -spiro lactone<sup>6</sup>. Spironolactone and drospirenone have antiandrogenic and antimineralocorticoid activity, but only drospirenone has progestogenic activity<sup>7</sup>.

Progesterone is also available as natural and micronized natural progesterone, derived from Mexican yams, soybeans or animal sources. The value of micronization of natural progesterone is that increases its absorption and bioavailability.

The micronized progesterone has fewer metabolic and vascular side effects than the synthetic progestins<sup>8-9</sup>. It has not been used yet in hormonal contraceptives in the US, but it probably will be introduced soon.

A recent Cochrane database review focused on the available evidence in regards to various progestins in combined oral contraceptives with respect to effectiveness, discontinuation rates and reasons for discontinuation, cycle control and side-effects<sup>10</sup>. The authors concluded that the quality of evidence is poor and without blinding as to treatment group, comparisons cannot be made between various "generations" of progestins used in oral contraceptives.

## Thrombotic risk of different progestins

In a meta-analysis of eight observational studies, the use of progestin-only contraception was not associated with an increased risk of venous thromboembolism compared with non-users of hormonal contraception<sup>11</sup>. When administered with ethinyl estradiol, the newer generation progestins have an increased risk of venous thromboembolism compared to their older counterparts.

Table 1:

Increase in venous thrombotic risk	FDA 2011 (14)	Relative risk Vs. Levonorgestrel + Ethinyl estradiol (LNG + E) (12)
LNG + E		1
Drospirenone +E	1.74	2.1
Gestodene +E		2.1
Desogestrel + E		2.2
LNG only (13)		0.59
LNG IUD (13)		0.9
Desogestrel only (13)		1.82
Norelgestromin +E patch	1.55	
Etonorgestrel + E vaginal ring	1.56	

In regards to the arterial thrombotic risk, a recent study showed that the progestin type did not significantly influence the risk of arterial thrombotic events (15).

## Conclusion

The quest for a perfect progestin has been going on for many decades and while the selectivity index has increased for the newer progestins, allowing for less androgenic side effects, the venous thrombotic risk has increased. Micronized progesterone may be the next form of progestin to be introduced in combined oral contraceptives, because of superior absorption and bioavailability and less side effects. For now, clinicians should consider prescribing older progestins to their older reproductive age patients in order to minimize the associated risk of venous thromboembolism.

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