The progestins used in hormonal replacement therapy (HRT) and contraception have varying pharmacologic properties according to the molecule from which they derive. Very small structural changes may induce considerable difference on their effects. Since the publication of the Women’s Health Initiative (WHI) study’s results, controversies arose about the risks of progestins without distinction between medroxyprogesterone acetate (MPA), the progestin used in the WHI study, and the other progestins. Given the differences in the pharmacology of the molecules it seems though inappropriate to consider the effects of the progestins as a class-effect.

The synthetic progestins used so far for contraception are derived either from testosterone (19-nortestosterone derivatives) or from progesterone (17-OH progesterone derivatives and 19-norprogesterone derivatives). Among the 19-nortestosterone derivatives, the estrane group includes norethisterone (NET) and its metabolites, and the gonane group includes levonorgestrel (LNG) and its derivatives. The later, including desogestrel (DSG) and its derivative etonogestrel, gestodene (GES) and norgestimate (norelgestromin), have been referred to as third-generation progestins. By convention the first generation refers to norethynodrel, the first progestin synthesized and the second generation includes NET and LNG. The later compounds exert a partial androgenic effect.

Several new progestins have been synthesized in the last decade and may be considered as a fourth-generation of progestins. Dienogest is referred to as a hybrid progestin being derived from the gonane group with a 17α-cyanomethyl group, and drospirenone derives from spirolactone. These 2 progestins have no androgenic effect but a partial antiandrogenic effect. The later exerts anti-mineralocorticoid effects. This property leads to a decreased salt and water retention and a lowering in blood pressure in users of pills containing this progestin. The 19-norprogesterone derivatives appear more specifically progestational and do not possess any androgenic, estrogenic or glucocorticoid activity. They are referred to as “pure” progestational molecules as they bind almost exclusively to the progesterone receptor (PR) and do not interfere with the other steroid receptors. This category includes trimegestone, Nestorone®, promegestone, and nomegestrol acetate. Nestorone® is not active orally but proved to be a potent anti-ovulatory agent when given in implants, vaginal rings or percutaneous gel. Trimegestone and Nestorone are the most potent compounds to date for their progestational effect measured on the endometrium, followed by the gonanes, ketodesogestrel and levonorgestrel. The new molecules, drospirenone and dienogest are less potent on the animal bioassays.

Non-androgenic progestins would appear neutral on metabolic factors and on the vessels and would have the advantage of avoiding acne. Progestins with antiandrogenic properties may also be used for the treatment of women with preexisting androgen related conditions. Further randomised-controlled HRT studies including other molecules than the steroids used in the WHI would be needed to confirm the neutrality of progesterone-related compounds on the cardiovascular and the breast cancer risks.