

The paradigm for cardiovascular effects of hormonal contraceptives

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Hormonal contraceptives revolutionized the world in the 1960s, allowing women to separate sexual intercourse from procreation. However, since then, doubts exist over the long-term negative side-effects of hormonal contraceptives. Arterial thromboembolic phenomena were soon associated with the estrogen dose of the first pills, as well as alterations in the hepatic lipid profile, the synthesis of sex hormone-binding globulin (SHBG) and the clotting factors⁽¹⁾.

In the following decades, new formulations were successfully released, reducing the dose of ethinylestradiol, associating it to more selective progestogens, what caused fewer arterial cardiovascular events.

Non-oral hormonal methods were also developed, yet with no decreased incidence of venous thromboembolic phenomena. Only with the advent of natural estrogens (estradiol valerate and 17 β -estradiol) associated with selective progestogens, such as dienogest and nomegestrol, the incidence of venous disease starts to diminish⁽²⁾.

Even though, both absolute and relative incidence rates of venous thromboembolic phenomena in users of combined hormonal contraceptive methods currently commercialized are little frequent; of arterial, very rare⁽³⁾. The occurrence of 10 cases of deep vein thrombosis is estimated per each 10,000 users/year, with the risk being higher in the first year of combined use. The risk of a healthy woman in menopause to present this condition is 1-6 per each 10,000 women.

Third- (desogestrel and gestodene) and fourth-generation (drospirenone) progestogens, besides cyproterone, when associated with ethinylestradiol, seem to be of slightly higher risk than the association ethinylestradiol-levonorgestrel (second-generation progestogen).

In practice, due to the low incidence of venous thromboembolic outcomes, and even rarer arterial events, the national and international guidelines do not recommend routine laboratory investigation of thrombophilia for future users of combined hormonal contraceptives. However, anamnesis is important to investigate family cases and history of spontaneous thrombosis or migraine with aura.

In this issue of *Jornal Brasileiro de Patologia e Medicina Laboratorial (JBPM)*, there is an article comparing the lipid and inflammatory profile with the D-dimer levels in users of oral contraceptives⁽⁴⁾. The authors observed that those users had unfavorable lipid profiles, although the high-density lipoprotein (HDL) level was higher than in non-users; these results are similar to those of the literature. When evaluating different hormonal contraceptives, they also noted that a larger estrogen dose was associated with an increased D-dimer value, characterizing higher atherogenic potential, a result also supported by the literature.

The paradigm remains for detection of inflammatory and thrombogenic factors in users of combined pills, depending on estrogen dose and progestogen type, yet with low incidence in thromboembolic clinical outcomes, proving this phenomenon is multifactorial.

REFERENCES

1. Roach RE, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev.* 2015; (8): CD011054.
2. Dinger J, Do Minh T, Heinemann K. Impact of estrogen type on cardiovascular safety of combined oral contraceptives. *Contraception.* 2016; 94(4): 328-39.
3. Bastos, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, Dekkers OM. Combined oral contraceptives: venous thrombosis. *Cochrane Database Syst Rev.* 2014; (3): CD010813.
4. Guedes JVM, Nunes NR, Ferreira LGR, Vilar TG, Pinheiro MB, Domingueti CP. Evaluation of lipid profile, high-sensitivity C-reactive protein and D-dimer in users of oral contraceptives of different types. *J Bras Patol Med Lab.* 2018; 54(1): 14-20.



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