

**Review article****MECHANISMS OF HYPERCOAGULABILITY  
PROMOTED BY ORAL COMBINED CONTRACEPTIVES**

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**Abstract**

**Background:** Hormonal contraceptive pills are the most used reversible method for familiar planning in Brazil. The combined pill, with synthetic analogs of estrogen and progestin, is employed by 25% of Brazilian female population. Its use provokes an increase of blood pressure levels, takes patient to a hipercoagulability state and predisposes her to thromboembolic events. **Purposes:** We aimed to describe mechanisms of hypercoagulability promoted by oral combined contraceptives, to analyze the relative risk of cardiovascular events within users and to list the most common circulatory pathologies in these patients.

**Methods:** Three virtual medical databases were surveyed (Pubmed/Medline, BVS/LILACS and Scielo). Twelve studies were selected: clinical trials, case reports and articles of indexed medical periodic originally published in Portuguese and English about synthetic hormones, oral contraception, coagulation disorders and cardiovascular morbimortality. **Results:** Synthetic estrogen promotes an increase of some clotting factors' levels (VII, VIII, IX, X, XII, XIII and fibrinogen), such as a reduction of their inhibitors (S protein and antithrombin). Because of this, etinilestradiol is the component most related to venous thrombosis and ischemic diseases of brain and heart. It also improves the releasing of hepatic angiotensinogen, taking to a increase of blood pressure levels. **Conclusions:** The prescription of oral combined contraceptives needs criteria, notably due to adverse effects of etinilestradiol. It is recommended to avoid the administration of these drugs for patients elder than 35 year-old or with risk factors. For these patients, the use of progestagen-only pills seems to be safer.

**Key Words:** *contraception, hormone, estradiol, thromboembolism*

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**BACKGROUND** Oral contraceptives or birth control pills are known medications employed on familiar planning. They are the most used reversible method to avoid pregnancy in Brazil and worldwide. About 25% of Brazilian female

population makes chronic use of this kind of medication. It is also the contraceptive method referred as the most know by women: 87.4% of them cited pills<sup>[1]</sup>.

The hormonal contraceptives include four basic types: combination oral

contraceptive pills (usually referred as COC or OCP), progestin-only pills, injectable and implants<sup>[2]</sup>. They are noted to work by three different mechanisms: the inhibition of ovulation by suppression of hypothalamus-pituitary-ovarian axis, through cancelling gonadotrophin releasing; the inhibition of sperm transport through the cervix by thickening the cervical mucus; the changes in endometrial lining, decreasing possibilities of implantation (“hostile endometrium theory”)<sup>[3]</sup>.

Young women should present low rates of stroke and thromboembolic events incidence. However, since the widespread use of oral contraceptives, around 1970, the incidence levels of these ischemic episodes became progressively greater. Several studies and clinical trials tried to demonstrate the relationship between the use of hormonal contraceptive methods and an increased risk for some cardiovascular pathologies<sup>[4]</sup>. They disclosed effects of synthetic estrogens of contraceptives on disturbing the homeostatic balance of clotting factors, what, in last analysis, carries to developing of ischemic pathologies.

Efforts to decrease the risk of arterial thrombosis led to development of low-dose combined contraceptives, containing 50 or less micrograms of etinilestradiol. Industry also made efforts to develop new generations of drugs, especially on progestogen-only pills. Other synthetic progestogens like levonorgestrel composes a lineage called second-generation oral contraceptives, which promote a smaller influence on cardiovascular risk<sup>[5]</sup>.

In addition to the influence of oral contraceptives on coagulation and clotting factors, the high effectiveness of synthetic hormone contained on these drugs changes the metabolism of mineralocorticoids and increase blood pressure levels<sup>[6]</sup>, predisposing some patients to hypertension and amplifying even more their risk for cardiovascular injuries.

### Methods

Three virtual medical databases were surveyed (Pubmed/Medline, BVS/LILACS and Scielo). The terms used were “combined oral contraceptive”, “etinilestradiol”, “progestagen”, “ischemic events”, “cerebrovascular accidents”, “deep-vein thrombosis” and “coagulation”, separated or associated. This search returned 54 papers in 5 languages.

It was made a selection in between these results. Twelve studies were chosen: clinical trials, case reports and articles of indexed medical periodic originally published in Portuguese and English with similar purposes and relevant information. We reviewed this data in addition to reference lists of books and guidelines regarding to familiar planning, cardiology and gynecology.

### Results and discussion

Three primary influences are related with the development of thrombus and are part of Virchow’s triad: endothelial lesion, stasis or turbulence of blood flow and hipercoagulability. Etinilestradiol and synthetic progestogens, substances contained on combined oral contraceptives, are related with changes

on third of these factors: hypercoagulability<sup>[2,3]</sup>.

Synthetic estrogen promotes a strong increase of fibrinogen, VII, VIII, IX, X, XII and XIII clotting factors. In addition to this increase, occurs a reduction of S protein and antithrombin, their natural inhibitors<sup>[2]</sup>. This balance between pro-coagulant and anti-coagulant factors, with a major expression of the first, results in a hypercoagulability state that turns patients more susceptible for developing clots and having thromboembolic events, possibly taking them to death.

Etinilestradiol, the synthetic analog of endogenous estradiol employed on most of the contraceptive pills, is the isolated component that most predisposes the users of oral contraceptives to deep-vein thrombosis and cerebrovascular and myocardial ischemic diseases<sup>[5]</sup>. This predisposition represents an effective risk increase, but is not influenced by the augment of synthetic estradiol dose<sup>[6]</sup>. The progestin-like components of combined pills seem do not influence arterial events, what represents a slighter risk exposition for those patients using progestogen-only contraceptives<sup>[7]</sup>.

Etinilestradiol, has an effect which is 1.000 times more powerful than the natural estradiol, considering similar quantities and concentrations<sup>[2]</sup>. Because of this, it has an important effect on stimulating liver to release hepatic angiotensinogen. Consequently, this angiotensinogen, independently on natural renin-angiotensin-aldosterone complex, takes to a systemic vasoconstriction and elevates the blood pressure levels<sup>[8]</sup>.

Some of progestogens have a not well-established effect opposing to mineralocorticoid substances, notably aldosterone<sup>[9]</sup>. But the releasing of hepatic angiotensinogen provoked by oral contraceptives' etinilestradiol seems to overpass this anti-mineralocorticoid effect, increasing, therefore, the levels of arterial pressure. In a paradoxal way, the prescription and use of etinilestradiol and similar drugs in women after menopause have the opposite effect, relaxing vascular musculature, widening the lumen of blood vessels and resulting in a decrease of pressure<sup>[6,9]</sup>.

Approximately 50-70% of stroke in women are embolic events<sup>[10]</sup>. The first report of stroke occurrence in women using oral contraceptives was published in 1962, followed by many others<sup>[7]</sup>. Several pathologies can be related with chronic-use of hormones with objective on avoid pregnancy. Most of them have its origins on thromboembolic episodes. These events occur when a clot causes an occlusion of the lumen of an artery or a vein. The clinical signals will depend on where this clot is impacting blood flow and for how long it have been there, obstructing perfusion. Some of these pathologies, like ischemic cerebrovascular accidents or acute myocardial infarction, can take patients to death in minutes. Other conditions, although do not kill patient as fast as these, can cause several problems and disabilities.

For example, the chronic use of oral contraceptive pills accounts on 9-18% of all mesenteric thrombosis episodes in young women<sup>[8]</sup>, on about 22% of pulmonary thromboembolism<sup>[12]</sup> and on over 60% of deep-vein thrombosis<sup>[13]</sup>.

These are conditions who, if do not kill patient fast, can provoke several injuries.

Medical literature records disclose that the use of any type of oral contraceptives increases the risk of ischemic stroke<sup>[14]</sup>. The 2002 RATIO Study confirms the existence of a 2-fold risk rate for patients in chronic use of generic contraceptive pills compared with those who do not use. Obviously, the increase of risk rates is even more elevated when in combination with the presence of other clinical or lifestyle conditions, like smoking, systemic hypertension, hypercholesterolemia or obesity. In this study, almost all of the sample patients were Caucasian. That's why its findings probably should be limited to this ethnic group.

RATIO Study also revealed that this increase risk tendency for stroke in patients using contraceptives is observed in using of any type of oral contraceptives, even progestagen-only pills, which seem to be safer, due to lack of etinilestradiol and consequent minor pro-coagulation effects. In patients aged 18 to 29 years, Odds-ratio index was lower, probably due to high prevalence of oral contraceptives use on this age-group. 81% of this age-group women used hormonal therapy to avoid pregnancy, versus 78% of general sample<sup>[9]</sup>.

The World Health Organization study, more recently, and many others, tried to find a relationship between estrogen and progestin dose and the increased cardiovascular risk for the users, but all of them failed on find a trend according to estrogen dose after adjustment of progestogen types<sup>[13,15]</sup>. In addition to this, some studies approaching the effect of hormonal contraceptives for ischemic

strokes do not show important influence of estrogen dose<sup>[16]</sup>. Almost all of them are focused on comparison between second-generation and third-generation combined contraceptive pills<sup>[17]</sup>.

## Conclusion

Information about risks inherent to combined oral contraceptives can make doctors more attentive to its prescription and patient more conscious about potential risks of these chronic-use drugs. The prescription of combined contraceptives needs criteria, notably due to adverse effects of etinilestradiol, present in almost all of formulations.

Medical literature considers it is strongly recommended to avoid the administration of these drugs for patients elder than 35 year-old or with associated risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, smoking or alcohol. For these patients, the use of progestagen-only pills seems to be safer, due to minor influence of progestagen components on promoting hypercoagulability. Second-generation contraceptives are already widely available and represent, nowadays, the safest option on oral contraception.

## Competing interests

The authors declare that they have no competing interests

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