

Review Article

Practical aspects of the use of combined hormonal contraceptives in venous thromboembolism

Aspectos práticos do uso de contraceptivos hormonais combinados no tromboembolismo venoso

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ABSTRACT

Combined oral contraceptives (COCs) are widely used by Brazilian women, offering additional benefits beyond contraception. The objective of this study was to analyze the relationship between the use of COCs and venous thromboembolism (VTE), as well as to identify measures that can be adopted to minimize this risk, considering different COC formulations. Data were collected from the literature, including current guidelines addressing the proposed topic. COCs represent a low risk for VTE, with prevalence varying according to the hormonal formulation used and the individual profile of each patient. Moreover, it was observed that the risk of VTE decreases with continuous use of COCs over time, being highest during the first months of therapy. The careful selection of a COC formulation can help reduce the risk of VTE in women of reproductive age who choose this form of contraception. An individualized risk assessment is recommended before prescribing COCs, considering factors such as personal or family history of VTE, age, body mass index, and smoking. The continuation or discontinuation of COC use during periods of immobilization, surgery, and the postpartum period should be carefully evaluated to minimize potential thromboembolic complications.

RESUMO

Os contraceptivos orais combinados (COCs) são amplamente utilizados pelas mulheres brasileiras, oferecendo benefícios adicionais à contracepção. O objetivo deste estudo foi analisar a relação entre o uso de COCs e o tromboembolismo venoso (TEV), bem como identificar medidas que podem ser adotadas para minimizar esse risco, considerando as diferentes formulações de COCs. Foram coletados dados na literatura, incluindo as diretrizes atuais que abordam o tema proposto. Os COCs representam um risco baixo para o TEV, com prevalência variando conforme a formulação hormonal utilizada e o perfil de cada paciente. Além disso, observou-se que o risco de TEV diminui com o tempo de uso contínuo dos COCs, sendo mais elevados nos primeiros meses de terapia. A escolha criteriosa da formulação do COC pode ajudar a reduzir o risco de TEV em mulheres em idade fértil que optam por essa forma de contracepção. Recomenda-se uma avaliação individualizada do risco antes da prescrição, considerando fatores como histórico pessoal ou familiar de TEV, idade, índice de massa corporal e tabagismo. A continuidade ou descontinuidade do uso de COCs durante períodos de imobilização, cirurgias e puerpério deve ser cuidadosamente avaliada para minimizar potenciais complicações tromboembólicas.

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INTRODUCTION

In Brazil, one in five women uses combined oral contraceptives (COCs). In addition to their efficacy and safety in contraception, modern COCs offer benefits such as reduced menstrual bleeding, dysmenorrhea, relief of premenstrual syndrome, migraines, acne, and hirsutism. Furthermore, in the long term, they decrease the incidence of endometrial, ovarian, and colorectal cancer. Venous thromboembolism (VTE) is a rare but potentially serious complication of COC use. COCs increase the risk of VTE from a baseline rate of 4.7/10,000 women-years among non-users to 9.1/10,000 women-years among users. To maintain perspective, it is important to note that the risk of VTE during pregnancy is 29.1/10,000 women-years and ranges from 300 to 400/10,000 women-years in the postpartum period.

MATERIALS AND METHODS

This is a bibliographic review study, considering publications available on the virtual platforms PubMed, Scientific Electronic Library Online (SCIELO), and the Latin American and Caribbean Literature in Health Sciences (LILACS) database, spanning the period from 1961 to 2024. The descriptors used were "venous thromboembolism," "thrombosis," "contraceptives," and "women," excluding articles that only tangentially addressed the proposed topic. Based on the abstracts of the 121 articles identified, 51 articles in Portuguese, English, and Spanish were selected, while 60 articles were excluded. This manuscript was translated with the assistance of ChatGPT, an AI language model developed by OpenAI.

RESULTS AND DISCUSSION

Hemostatic Alterations Induced by COCs and Risk Profile

The risk of VTE in women using COCs is associated with alterations in baseline hemo-

stasis¹. Estrogens increase coagulation factors (prothrombin, FVII, FVIII, FX, and fibrinogen) and reduce serum concentrations of natural anticoagulants, such as proteins C and S and antithrombin². These changes can be particularly dangerous in women with hereditary thrombophilias (**Table 1**)³ or acquired thrombophilias, as well as in obese and smoking individuals⁴. However, it is important to note that systematic screening for thrombophilias is not recommended before the initial prescription of COCs, being indicated only for patients with a high-risk profile for VTE, particularly those with a personal or family history (**Table 2**)⁵⁻⁸.

Composition of COCs and Influence on VTE Risk

Ethinylestradiol (EE) is a bioactive estrogen derived from estrone, widely used orally in many COCs. Early generations of COCs, which contained higher levels of EE (>50 µg), had a greater risk of VTE compared to current COCs, which contain less than 50 µg⁹. However, the reduction in risk associated with the use of COCs containing 20 µg of EE, compared to those containing 30 µg, has not yet been clearly proven⁶.

Many COCs with less than 35 µg of EE are currently marketed, and while they cause fewer systemic side effects related to estrogen, there is no evidence indicating a reduced risk of VTE. Additionally, COCs with less than 20 µg of EE are more likely to cause breakthrough bleeding, which may be intolerable for some women¹⁰.

Replacing EE with estradiol, norgestrel acetate, or estradiol valerate (E2V) combined with dienogest (DNG) reduces the amount of estrogens recirculating in the liver, potentially resulting in less coagulation activation. However, clinical data supporting this concept remain limited¹¹.

The type of progestogen used also influences the risk of VTE. Second-generation progestins (levonorgestrel [LNG] and norethisterone) are considered safer than third- (desogestrel, norgestimate, or gestodene) and fourth-generation (drospirenone, cyproterone, or chlormadinone) progestins, which have fewer androgenic effects^{12,13}. The possible explanation for these findings is the direct impact of different progestogens on hemostasis¹⁴⁻¹⁶.

Baseline hemostasis does not show significant changes with progestin-only pills, as well as in implants containing LNG, LNG-releasing intrauterine devices, or depot medroxyprogesterone acetate injections¹⁷⁻¹⁹.

Given the popularity and widespread use of COCs, any increase in the relative risk of VTE associated with a specific formulation could result in a significant increase in absolute case numbers.

VE2/DNG as an Alternative for Contraception Across All Ages

Recent epidemiological evidence indicates that EE and androgenic progestogens are not the only options for minimizing the VTE risk associated with COC use. The combination of VE2/DNG has been shown to be as safe as EE/LNG²⁰. However, risk factors such as age, obesity, smoking, genetic predisposition, and family history of VTE can significantly contribute to the increased risk of the condition²¹.

In the INAS-SCORE study²², some of these biases were corrected, revealing a lower risk of VTE associated with the use of VE2/DNG compared to other COCs. These findings lead to two considerations: the VE2/DNG combination was already perceived by physicians and patients as safer than other COCs and was therefore prescribed and used by women at higher risk for VTE. After correcting for known risk factors for the disease, it was still associated with a lower risk of VTE.

It is crucial to remember that COCs containing VE2 retain a pro-coagulant effect, which should not be overlooked during prescription. For women with additional risk factors for VTE, VE2-based COCs do not constitute a safe alternative to progestin-only contraceptives²².

However, the reduced impact of VE2 compared to EE on hemostasis is reflected in fewer VTE events among VE2 users, particularly when associated with progestogens other than LNG. Consequently, COCs containing VE2 may reduce the total incidence of VTE and be used as an alternative to COCs containing EE/LNG²². Nonetheless, the results obtained with the VE2/DNG combination should not be extrapolated to other formulations.

Relationship Between VTE and Duration of COC Use

Notably, the risk of VTE decreases with the duration of COC use, with an odds ratio (OR) of 4.1 during the first three months, 2.1 during the first 12 months, and 1.9 during the first 48 months after initiating COC use²³.

Individual Risk Assessment for VTE

The main determinant of absolute VTE risk is individual predisposition, which includes personal and/or family history of thromboembolic events, age over 50 years, BMI ≥ 30 kg/m²,

Table 1. Relative Risk of Hereditary Thrombophilias Associated with the Use of COCs.

Hereditary Thrombophilia	Relative Risk
Factor V Leiden (heterozygous)	9,3
Factor V Leiden (homozygous)	34,4
Prothrombin gene mutation 20210 (heterozygous)	6,8
Prothrombin gene mutation 20210 (homozygous)	26,4
Protein C deficiency	4,8
Protein S deficiency	3,2
Antithrombin deficiency	4,7

Adapted from: Robertson, L. O. et al. Br J Haematol, 2006.³⁴

smoking, relevant or anticipated paresis, immobilization, major surgery, and thrombophilias (in patients or first-degree relatives). These factors should be carefully evaluated for each patient during the VTE risk assessment prior to prescribing a specific contraceptive method²⁴.

Investigation of Thrombophilias Before Prescribing COCs

The guidelines of the International Society on Thrombosis and Hemostasis (ISTH) do not recommend testing for hereditary or acquired thrombophilias in patients without a personal or family history of VTE. While such tests may offer potential benefits, it is important to recognize their high cost and reliance largely on functional assays, which may have limited sensitivity and specificity (**Table 1**).

Abnormalities in thrombophilia tests can be temporary, such as during anticoagulant use or viral infections, or common but associated with a minor increase in VTE risk, such as heterozygous factor V Leiden mutation—the most common alteration. Testing for thrombophilias without clinical indication can lead to unnecessary concerns, inappropriate interventions, and unwarranted screening of relatives. Thus, these tests should be limited to patients or relatives with a clear probability of achieving clinically relevant benefits.

Furthermore, it is important to emphasize that patients may be at high risk for VTE even in the absence of detectable abnormalities in laboratory tests, as not all prothrombotic states are identifiable (**Table 2**).

Therefore, the clinical risk factors mentioned above should form the rational basis for VTE risk assessment, and test results should be interpreted with due consideration and caution.

Use of COCs by Bedridden Women

Acute or chronic immobilization, limb paresis, and medium or major surgeries are common scenarios among women of reproductive age, often associated with an increased risk of VTE. Studies have shown that COC users with below-knee fractures or undergoing major surgeries have an elevated risk of VTE compared to non-users of these contraceptives^{25,26}.

However, discontinuation of COCs in such situations is not recommended, as the risk of an unplanned pregnancy—accompanied by a higher VTE risk during gestation—outweighs the risk associated with continuing hormonal contraception. In this context, since COC use increases the risk of VTE, the implementation of preventive measures becomes essential.

On the other hand, patients should avoid initiating COCs if acute immobilization or significant surgery is anticipated in the future, as the associated VTE risk is particularly high during the first 12 months of use²³.

Recurrent VTE Risk Associated with COC Use

Regarding the increased risk of recurrent VTE associated with COC use, the current guidance document from the ISTH Scientific and Standardization Committee classifies COCs as a

Table 2. Indications for Screening for Hereditary Thrombophilia Before Initiating COC Use,

Indications for Screening for Hereditary Thrombophilia
Unprovoked VTE in patients <50 years
VTE at an atypical site (not located in lower limbs)
Recurrent unprovoked VTE
VTE associated with a low-risk factor
VTE secondary to COCs and pregnancy

Adapted from: World Health Organization (WHO), 2015.²⁹

weak but important and transient risk factor. The risk of recurrence may be reduced by approximately 50% if COCs are discontinued in women who cease anticoagulant protection²⁷.

However, limited evidence is available regarding the use of COCs in women with a personal history of VTE. This is likely because, for many years, international guidelines and position statements considered COC use an unacceptable health risk for patients with a history of VTE²⁸.

A more balanced recommendation has been provided by the National Guideline Clearinghouse in the United States, which advises COC use only in women with VTE unrelated to pregnancy or estrogen exposure.

To assess the effects of progestin-only contraceptives, a prospective French cohort study included 419 women with a first VTE event. Of these, 163 used progestin-only contraception during an average follow-up of 4.4 years (30 µg LNG orally, LNG-releasing intrauterine systems, or 75 µg desogestrel orally). A total of 35 women experienced a recurrent VTE event, six of which occurred during hormone exposure, resulting in incidence rates of 6.9/1,000 patient-years for women without hormonal contraception and 10.6/1,000 patient-years for women using progestin-only contraception. This increased risk was not statistically significant (incidence rate ratio 1.6; 95% CI: 0.3–7.8).

As a result of these findings, current World Health Organization (WHO) guidelines²⁹ do not recommend COC use for women with a history of VTE without additional anticoagulant protection. However, since progestin-only contraceptives have not been associated with an increased risk of a first VTE event, their use appears reasonable in patients with a history of VTE.

Concerning the question of whether COCs increase the risk of recurrent VTE in anticoagulated patients, it is common practice to discontinue COCs immediately after the diagnosis of acute VTE. This is based on evidence showing that initial use (12 months) increases VTE risk and, with less certainty, the risk of recurrence.

This immediate discontinuation is often rooted in outdated guideline recommendations

and package inserts. Surprisingly, the package inserts for progestin-only contraceptives also list acute VTE as a contraindication. However, this approach does not reflect evidence indicating that the absolute risk of VTE associated with COCs is relatively low, nor does it account for the fact that patients with acute VTE are treated with anticoagulants that effectively counteract the weak prothrombotic effects of estrogens.

Contraception Switching or Discontinuation and Pregnancy Risk

Unplanned pregnancies represent a clinically challenging situation for patients at risk of acute or recurrent VTE, in addition to posing potential social, financial, and familial challenges³⁰.

Vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) are the usual medications of choice for the acute and long-term treatment of VTE. However, during pregnancy, VKAs carry up to a 10% risk of embryotoxicity, while DOACs pose a lower risk but still carry potential complications, including intrafetal bleeding, particularly in the central nervous system.

Consequently, women of reproductive age with acute VTE require an effective and safe contraceptive method. In such cases, discontinuation of the contraceptive method during an acute VTE event may be more harmful than its continuation during the anticoagulation period.

Risk of Vaginal Hemorrhagic Complications

Anticoagulation increases the risk of vaginal bleeding and heavy menstrual bleeding. Moreover, discontinuing COCs has been shown to cause irregular and heavier menstrual bleeding, at least temporarily. If oral anticoagulation and COC discontinuation occur simultaneously, menstrual and vaginal bleeding complications can be severe. Indeed, the continuation or even initiation of a new hormonal contraceptive is accepted as a preventive or therapeutic measure for women at risk of heavy menstrual bleeding, including those requiring anticoagulation for acute VTE³¹.

Continuation of COCs During Anticoagulation

The question of whether COCs increase the risk of recurrent VTE during anticoagulation remains unresolved. Unfortunately, there is limited evidence to address this issue. The most reliable data come from a post hoc analysis of the EINSTEIN-DVT and PE studies, which compared rivaroxaban versus warfarin in over 8,000 patients with acute DVT or pulmonary embolism (PE). In this analysis, 475 women were exposed to hormones during anticoagulation (306 with COCs, 217 with progestogen-only contraceptives, and 48 using sequential hormonal contraceptives). These patients had a similar risk of VTE recurrence compared to 1,413 women under 60 who were not using hormones during the study period.

The overall risk of VTE recurrence during anticoagulation was similar among women exposed to COCs or progestogen-only contraceptives. Overall, there is no evidence suggesting that hormonal contraception increases the risk of thromboembolic complications during oral anticoagulation. Conversely, evidence suggests that continuing hormonal contraception can prevent unplanned pregnancies and reduce the risk of pregnancy or severe metrorrhagia.

The ISTH issued a guidance statement in 2012, which includes the continued use of COCs as a contraceptive option for anticoagulated women and does not recommend the immediate discontinuation of COCs or other contraceptive methods at the time of VTE diagnosis³². It is worth noting that for patients with VTE, the use of low- to moderate-risk COCs containing low doses of estrogens in combination with norgestimate or LNG is recommended³³. Notably, this recommendation applies only during the anticoagulation treatment period.

As most young VTE patients are anticoagulated for three to six months, it is essential to discuss long-term contraception strategies after this initial period.

Elective Surgery and COCs

When necessary, women using COCs

with a planned elective surgery should discontinue the contraceptive four weeks before and reintroduce it 12 weeks after the surgical procedure. These timeframes are required for COCs to stop affecting hepatic production of coagulation factors and for the surgery-related VTE risk to return to baseline levels. However, this approach may result in an unplanned pregnancy.

The currently recommended procedure is to maintain COC use, provided it has been used for over a year, along with prescribing thromboprophylaxis based on risk scores and in accordance with ISTH guidelines. The use of COCs is an additional factor in the Caprini score, which stratifies and determines the thromboprophylaxis method in patients undergoing elective surgical procedures.

The relationship between COCs and VTE has been well established in the literature since the 1960s, yet their use in various clinical scenarios remains a practical challenge. Some practices already established in guidelines help guide clinical decisions in common situations. The fact remains that the VTE risk associated with COC use is low and decreases over time. However, obese women, smokers, or those with a personal or family history of VTE face an increased risk.

Attention should not only be given to the hormone dosage in each COC but also to the specific combinations. For example, COCs with EE/LNG and VE2/DNG present the lowest VTE risk, while those containing third-generation progestogens carry a 1.5 to 2.5 times higher VTE risk compared to second-generation progestogens.

Women with acute VTE on anticoagulation may continue using COCs to avoid unplanned pregnancies or heavy bleeding. Women with planned surgeries may also maintain COC use and undergo specific thromboprophylaxis after VTE risk evaluation, as the risk of an unplanned pregnancy poses a greater VTE risk than maintaining COCs with proper prophylaxis.

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