AUCTORES
Globalize your Research

Journal of Obstetrics Gynecology and Reproductive Sciences
Kravtsov Pavel *

Open Access

Short Communication

# Undesirable Vascular Reactions in the use of Combined Oral Contraceptives: Myth or Reality?

**Markin S.M [1], Kravtsov P.F [2]*, Artemova A.S [3]. Kudinova E.A [1]**

[1]Federal State Budgetary Health Care Institution "St. Petersburg Clinical Hospital", Russian Academy of Sciences, 194017, St. Petersburg, Russian Federation.

[2]Federal State Budgetary Educational Institution of Higher Education "Samara State Medical University", Ministry of Health of the Russian Federation, 443099, Samara, Russian Federation.

[3]LLC Multidisciplinary Medical and Diagnostic Center "Dynasty", 197758, St. Petersburg, Russian Federation.

***Corresponding Author:** Kravtsov Pavel, Federal State Budgetary Educational Institution of Higher Education "Samara State Medical University", Ministry of Health of the Russian Federation, 443099, Samara, Russian Federation.

**Received date:** December 23, 2024; **Accepted date:** January 02, 2025; **Published date:** January 17, 2025.

**Citation:** Markin S.M., Kravtsov P.F, Artemova A.S, Kudinova E.A, (2025), Undesirable Vascular Reactions in the use of Combined oral Contraceptives: Myth or Reality? *J. Obstetrics Gynecology and Reproductive Sciences*, 9(1) **DOI:**10.31579/2578-8965/249



**Abstract:**

Combined oral contraceptives (COCs) are among the most common drugs in gynecologic practice. There is conflicting scientific evidence regarding adverse reactions that develop during the administration of COCs. This primarily concerns the risks of the appearance of unaesthetic lower limb veins and the development of venous thromboembolism (VTE). In the literature, no reliable data on the association between the occurrence of non-aesthetic veins and COC intake have been found. The authors describe the reversible effect of COCs on venous wall tone and the formation of hormone-induced phlebopathy, which is safely eliminated by original phlebotonics. The risks of VTE development depend on the terms of COCs intake and their composition. At the same time, it is established that COCs administration has no significant effect on the hemostasis system.

**Conclusion:** COCs intake affects the venous wall, but the development of chronic vein diseases, as a rule, is not directly related to it. There are risks of VTE, but they are significantly lower than certain natural physiologic states of a woman.

**Keywords:** combined oral contraceptives; hemostasis; adverse events; venous thromboembolism; phlebopathy

## Introduction

Combined oral contraceptives (COCs) have been actively used in gynecological practice for just over half a century. In such a short time, this group of drugs has taken the leading position in the contraceptive market, as it has undeniable advantages: COCs are effective, easy to use and their effect is reversible. On the other hand, the long and extensive use of COCs has led to a number of adverse reactions in some patients. It is quite obvious that such adverse effects have become the object of attention of a number of scientific studies. Unfortunately, heterogeneity and inconsistency of the obtained data often do not allow us to assess the risks of development of each adverse event for a specific clinical situation. Within the framework of this article we tried to summarize the data on the development of adverse vascular events when taking COCs.

The data of the survey of American women taking COCs showed that among all adverse vascular reactions they put the appearance of telangiectasis and reticular veins in the first place [1]. The leading role of risks of deterioration of aesthetic appearance of lower limbs, appearance of dilated veins is explained by the fact that taking COCs, as a rule, is carried out by young women who are not burdened with chronic diseases. Reticular varicosis, which is characterized by dilation of intradermal veins - reticular and telangiectasis - up to 3 mm in diameter, is a separate nosological group [2]. The described vascular elements represent a purely aesthetic problem and can occur in healthy individuals [3]. Despite this, many patients and physicians consider reticular varicosis to be varicose veins. The high prevalence of this nosology, which according to some data reaches 35,6-37,4% [4,5], contributes to this.

The true causes of the development of reticular varicosis remain incompletely established. We evaluated the Pubmed database for the entire period and found that this issue became most relevant in the 70-80s of the 20th century. The intake of COCs in some cases leads to an intensification of the venous pattern due to the formation of dilated telangiectasis. At the same time, in a number of studies devoted to the study of risk factors for the development of chronic venous disease (CVD), the intake of COCs is not

even mentioned [3,6]. Thus, it is not obvious that taking this group of drugs is a significant risk factor for the development of non-aesthetic vascular reactions. On the other hand, there are studies describing the frequency and nature of the development of undesirable skin effects against the background of taking COCs. It was found that the frequency of adverse skin reactions averaged 2.7-5% [7]. It is characteristic that most of the described aesthetic disorders were represented by melasma and chloasma, and only one third were related to undesirable vascular events. The low incidence of such reactions is also directly stated in the instructions for COCs. In particular, for Belara (chlormadinone and ethinylestradiol) the manufacturer does not indicate the risk of telangiectasis, and the risk of varicose veins is estimated as a rare reaction with the frequency of occurrence ≥1/10000 and <1/1000 [8]. Thus, when using COCs, the risks of such clinically insignificant and prognostically safe nosologic form as reticular varicosis cannot be considered as a factor limiting the prescription of this category of drugs. This approach is consistent with the concept of contraceptive safety [9,10].

Nevertheless, at present we cannot completely exclude potential risks of negative vascular reactions caused by taking COCs and manifested by a decrease in venous wall tone and subsequent development of signs of chronic venous insufficiency (CVI) [11]. Moreover, a number of authors distinguish subjective manifestations of CVI, developing as a consequence of taking COCs, into a separate nosological form - hormone-induced phlebopathy [12,13]. This pathological condition is characterized by changes in the capacitive function of the venous system of the lower extremities, which leads to a decrease in tolerance to physical loads. The condition leads to the development of clinical picture characteristic of CVD: the appearance of a feeling of heaviness in the legs, paresthesias, edema. An important difference from "true" CVD is the reversibility of such a condition. Ultrasonography revealed a significant decrease in orthostatic gradient of vascular diameter during COC administration. These disorders were noted not only in patients with varicose and reticular varicose veins, but also in the absence of non-aesthetic veins. The studies noted that subjective symptoms of CVD and ultrasound changes regressed with the use of original diosmin at a dosage of 600 mg per day for 2 months. The same changes were recorded during planned withdrawal of COCs [12,13]. A search for scientific evidence to evaluate the efficacy of topical therapies to eliminate the clinical manifestations of hormone-induced phlebopathy and unaesthetic vessels did not reveal relevant studies.

We were also unable to find information on the ability of medical compression devices to reduce the likelihood of developing symptoms of CVD while taking COCs. To a large extent, the use of medical compression devices is motivated by the desire to reduce the risks of another vascular complication, thrombosis [14].

Superficial and deep vein thrombosis are among the most significant venous thromboembolism (VTE), potentially developing as a result of taking COCs. The risks of such complications are estimated to be 2-3 times higher in patients taking oral contraceptives than in patients without such therapy. Is this risk high? Such physiologic conditions of a woman as pregnancy and postpartum period increase such risks by 4-5 and 8-15 times, respectively [15,16]. At the same time, the risks of VTE development are maximal at the initial stages of COC therapy. In the study by S. Suissa et al. [17] found that after several months of growth they significantly decrease by the end of the first year of treatment.

The dose of the drug received also affects the incidence of VTE. The meta-analysis published in 2013 by Stegeman B.H. et al. [18], including a review of 26 studies, found not only an increased risk of recurrent VTE on the background of taking OCs (OR 3,5; 95% CI: 2,9-4,3), but also revealed its increase with increasing the dose of the drug. Risks of VTE development increase with the content of ethinylestadiol in the composition of COCs above 30-35 mg. Separately noted potentiation of procoagulant effect in combination of ethinylestadiol with cyproterone acetate, desogestrel, gestodene or drospirenone.

The meta-analysis published in 2017 by the American Society for Reproductive Medicine found no significant difference in the risk of VTE when taking oral contraceptives with 2nd and 3rd generation progestins [19]. This publication points out the inadmissibility of prescribing COCs to women with an inherently high risk of VTE. This once again indicates the need for careful collection of personal and family history before prescribing COCs, since a positive personal history of VTE is itself a contraindication to the prescription of oral contraceptives [9].

This leads to a legitimate question: "Should not laboratory screening for thrombophilia and assessment of hemostasis be performed in all patients before prescribing COCs? The World Health Organization considers routine screening in patients with uncomplicated initial forms of CVD to be inappropriate because of the high probability of false-positive results and the high cost of diagnosis. On the other hand, some authors point to the fact that in the presence of factor V Leiden, prothrombin II mutation, deficiency of proteins S and C, antithrombin, the prescription of COCs is an absolute contraindication [9].

## Conclusions

COCs have a certain influence on the state of the venous system of the lower limbs, but their role in the appearance and progression of CVD is questionable. The risks of VTE are undoubtedly present on the background of COCs use, but they are significantly lower than the risks on the background of pregnancy or postpartum period, and in some cases are comparable with those in women without COCs therapy. Specific clinical manifestations of COCs use include the development of hormone-induced phlebopathy, characterized by a decrease in venous wall tone. However, this phenomenon is reversible and is effectively controlled by taking diosmin and using medical compression garments.

## References


1. Wilson NM, Browse NE. (1993). Venous disease. In: Clement DL, Shepherd JT, editors. Vascular diseases in the lower limbs. St Louis: Mosby Yearbook;
2. Raetz J, Wilson M, Collins K. (2019). Varicose Veins: Diagnosis and Treatment. Am Fam Physician. 1;99(11):682-688. PMID: 31150188.
3. Gloviczki P, Lawrence PF, Wasan SM et al. (2023). The 2022 Society for Vascular Surgery, American Venous Forum, and American Vein and Lymphatic Society clinical practice guidelines for the management of varicose veins of the lower extremities. Part I. Duplex Scanning and Treatment of Superficial Truncal Reflux: Endorsed by the Society for Vascular Medicine and the International Union of Phlebology. J Vasc Surg Venous Lymphat Disord. 11(2):231-261.e6. doi: 10.1016/j.jvsv.2022.09.004.
4. Zolotukhin I.A. и др. (2017). Prevalence and Risk Factors for Chronic Venous Disease in the General Russian Population // Eur. J. Vasc. Endovasc. Surg. T. 54. № 6. C. 752–758.
5. Prochaska JH, Arnold N, Falcke A et al. (2021). Chronic venous insufficiency, cardiovascular disease, and mortality: a population

study. *Eur Heart J.* 42(40):4157-4165. doi: 10.1093/eurheartj/ehab495. PMID: 34387673.

6. De Maeseneer MG, Kakkos SK, Aherne T et al. (2022). Editor's Choice - European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. *Eur J Vasc Endovasc Surg.* 2022 Feb;63(2):184-267. doi: 10.1016/j.ejvs.2021.12.024. Epub 2022 Jan 11. Erratum in: *Eur J Vasc Endovasc Surg.* 2022 Aug-Sep;64(2-3):284-285. doi: 10.1016/j.ejvs.2022.05.044. PMID: 35027279.
7. Deharo C, Berbis P, Privat Y. (1988). Complications dermatologiques des contraceptifs oraux [Dermatological complications caused by oral contraceptives]. Fertil Contracept Sex. 16(4):299-304. French. PMID: 12342376.
8. Instructions for medical use of the drug Belara. Film-coated tablets, reg. No.: LP-N (000127)-(RG-RU) from 29.01.21 – Indefinitely (2015).Medical eligibility criteria for contraceptive use.
9. (2017). Practice Committee of the American Society for Reproductive Medicine. "Combined hormonal contraception and the risk of venous thromboembolism: a guideline." Fertility and sterility 107.1 43-51.
10. Tsukanov IuT, Tsukanov AIu, Bazhenov VN. (2008). [The effect of oral contraceptives on the orthostatic diameter of lower limb major veins and its correction]. Angiol Sosud Khir. 14(1):75-7. Russian. PMID: 19156033.
11. Tsukanov IuT, Tsukanov AIu. (2007). [Results of administering Phlebodia 600 in fertile women with orthostasis-dependent phlebopathy]. Angiol Sosud Khir. 13(3):107-12. Russian. PMID: 18382403.
12. Tsukanov IuT, Tsukanov AIu, Bazhenov VN, Kornienko IF, Vasilevich VV. (2009). [Drug-mediated correction of negative phlebotropic effects of hormone replacement therapy in women]. *Angiol Sosud Khir.* 15(3):87-91. Russian. PMID: 20092188.
13. Rabe E. et al. (2018). Indications for medical compression stockings in venous and lymphatic disorders: An evidence-based consensus statement, Phlebology. 33(3):163-184. doi: 10.1177/0268355516689631
14. Mazzolai L, Ageno W, Alatri A et al. (2022). Second consensus document on diagnosis and management of acute deep vein thrombosis: updated document elaborated by the ESC Working Group on aorta and peripheral vascular diseases and the ESC Working Group on pulmonary circulation and right ventricular function. *Eur J Prev Cardiol.* 29(8):1248-1263. doi: 10.1093/eurjpc/zwab088. PMID: 34254133.
15. Kearon C, Ageno W, Cannegieter SC et al. (2016). Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *J Thromb Haemost.* 14(7):1480-3. doi: 10.1111/jth.13336. Epub 2016 Jun 7. PMID: 27428935.
16. Suissa S, Blais L, Spitzer WO et al. (1997). First-time use of newer oral contraceptives and the risk of venous thromboembolism. Contraception. 56(3):141-6. doi: 10.1016/s0010-7824(97)00119-4. PMID: 9347203.
17. Stegeman B.H., De Bastos M., Rosendaal F.R. et al. (2013). Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis // BMJ. Vol. 12(347). P. 5298.
18. Practice Committee of the American Society for Reproductive Medicine. "Combined hormonal contraception and the risk of venous thromboembolism: a guideline." *Fertility and sterility* 107.1 (2017): 43-51.



**DOI:10.31579/2578-8965/249**