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THE USE OF COMBINED ORAL CONTRACEPTIVES AND VENOUS THROM- BOEMBOLIC RISK: A BI- BLIOGRAPHIC STUDY

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Abstract: Oral contraceptives (OCs) are a very common form of contraception and can cause alterations in blood hemostasis, coagulopathy and venous thrombosis. We describe the association between the use of oral contraceptives and the risk of deep vein thrombosis. This is a bibliographic review using data from the Virtual Health Library (VHL), Latin American Health Sciences Literature (LILACS), U.S. National Library of Medicine (Pubmed) and Scielo. Full articles in Portuguese, Spanish and English, randomized controlled clinical trials, case studies and systematic reviews with meta-analysis were included. A total of 93 articles were found and 14 articles were used in total. It was found that thromboembolic events are multifactorial with a high incidence in women using COCs. **Keywords:** oral contraceptives, Thrombosis, Contraceptive Agents.

INTRODUCTION

Combined oral contraceptive pills (COCs) are a very common form of contraception worldwide, and include estrogen and progestogen as the main hormonal components (REISET et al., 2018). Although they are effective in preventing pregnancy, they can have serious side effects such as venous thrombosis (BRAGA; VIEIRA, 2013). One of the factors that can cause a change in blood hemostasis is the use of oral hormonal contraceptives (MORAIS; SANTOS; CARVALHO, 2019). According to Sousa and Álvares (2018), the total or partial blockage of blood circulation by a clot that prevents oxygenation of adjacent tissue can be defined as venous thrombosis and can cause pathologies such as myocardial infarction, pulmonary thromboembolism, among other catastrophes. Venous thrombosis (VT) has a high incidence in Brazil, with around 0.6 per 1000 inhabitants annually (SOUSA; ÁLVARES, 2018). Studies on the subject are scarce, which demonstrates the need for research

to understand the risk factors for the female population in order to reduce the incidence or worsening of this important disease.

OBJECTIVE

To describe the association between the use of oral contraceptives and the risk of deep vein thrombosis.

METHODS

This is a bibliographic review, with a survey carried out in the Virtual Health Library (VHL), Latin American Health Sciences Literature (LILACS), U.S. National Library of Medicine (Pubmed) and Scientific Electronic Library Online (Scielo) databases. The publications covered the period from 1968 to 2023. The descriptors used were “oral contraceptives” and “thrombosis”, with the Boolean expression “and” between the terms. Inclusion criteria: full articles in Portuguese, Spanish and English, clinical and randomized controlled trials, case studies and systematic reviews with meta-analysis in the last 10 years, and in the last 12 years on Scielo. Articles on other types of thrombophilia, thrombosis without the use of oral contraceptives and research on children were excluded.

RESULTS

93 articles were found. In *Pubmed*, 48 articles were found, of which 37 reported on other types of thrombophilia and 5 on thrombosis without the use of oral contraceptives, 6 articles were selected. A total of 30 articles were found in the VHL, 26 were excluded because they reported on other types of thrombophilia and 4 were selected. In relation to Scielo, 15 articles were found and 11 were excluded because they dealt with children and other types of thrombophilia, and 4 articles were selected. For the final search, 14 articles were included.

DISCUSSION

The article entitled “A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception”, reports that women using combined oral contraceptives had 8 to 10 events among 10,000 women/year, which shows an increase in the risk factor due to the use of COCs. The article “Combined oral contraceptives: venous thrombosis” states that the size of the effect depended on both the progestogen used and the dose, and that all the COCs investigated in this analysis were associated with an increased risk of VT, as they affect hemostasis in various ways and show indications of increased activity in this system (factor II, factor VII and factor VIII, prothrombin 1/2 and D-Dimer). The research “Hormonal contraception and thrombosis”, corroborates that the estrogenic dominance of contraceptives related to the dose of estrogen and the type of progestin, was evaluated through assays of sex hormone binding globulin (SHBG) levels, thus SHBG was proposed as a marker of the risk of VT, and emphasizes that the use of COCs increases the risk by 4 times when compared to non-users. The paper “Obesity and contraceptive use: impact on cardiovascular risk”, reports that excess weight is an independent risk factor for VT events, since in women aged 40 and under, the risk of deep vein thrombosis (DVT) increases 6.1 times compared to non-obese women in the same age group. The article “The Risk of Venous Thromboembolism with Different Generation of Oral Contraceptives; a Systematic Review and Meta-Analysis”, comments that the likelihood of DVT in women taking COCs was three times higher than in non-users, even when different contraceptives and dosages were taken into account in increasing the risk, concludes that thromboembolic events are multifactorial phenomena, involving acquired and genetic factors. The study “The joint effect of genetic

risk factors and different types of combined oral contraceptives on venous thrombosis risk” found that in women with hereditary thrombophilia, the use of COCs increased the risk of DV, and the presence of a mild mutation in the F5 rs6025 or F2 rs1799963 gene increased the risk of DV in COC users by up to 7 times. The article “Harms of third- and fourth-generation combined oral contraceptives in premenopausal women: A systematic review and meta-analysis” shows that in premenopausal women, the use of third- and fourth-generation oral contraceptives is associated with a lower risk of thrombosis. The study “Epidemiology and 3-year outcomes of combined oral contraceptive-associated distal deep vein thrombosis” concludes that hormones containing estrogen and progestin have a high rate of involvement in cases of DVT. The article “The impact of a male or female thrombotic family history on contraceptive counseling: a cohort study”, reports that hereditary thrombophilia and family history are independent risk factors, and that the initial risk may be further increased in women of reproductive age by the use of COCs. The study “The risk of venous thrombosis in women over 50 years old using oral contraception or postmenopausal hormone therapy” describes that varying doses and types of estrogen and progesterone affect the risk of venous thrombosis differently, however the relative risk of venous thrombosis was especially high in women using COCs with one or more thrombophilic defects. The research “Deep vein thrombosis in an upper limb in a woman taking oral contraceptives and with hereditary thrombophilia: Factor V Leiden”, summarizes that individuals homozygous for factor V Leiden have a 20 to 50 times higher risk of venous thrombosis. The article, “Factores de riesgo de la enfermedad tromboembólica en puerperas” (Risk factors for thromboembolic disease in puerperal women), shows that the

use of COCs increases the risk of thrombosis fourfold, as they block dihydrofolate reductase chromosome 5, an enzyme involved in the synthesis of folic acid, and alter the metabolism of homocysteine, with the consequent creation of states of hyperhomocysteinemia, producing thrombotic effects. The study “Female sex hormones and deep vein thrombosis” concluded that the biological mechanisms involved in oestrogen-related thromboembolism are related to the fact that they increase the procoagulant factors of the coagulation cascade (factor VII, X, XII and XIII) and decrease the anticoagulant factors (Protein S and antithrombin), and that the incidence of thrombosis increases slowly with

age, pregnancy and in users of COCs. The study “*Effect of a low-dose oral contraceptive on venous endothelial function in healthy young women: preliminary results*”, reports that no significant reduction in endothelium-dependent and -independent venodilation was observed after the use of COCs.

FINAL CONSIDERATIONS

Thromboembolic events are multifactorial phenomena and have a high incidence in women using COCs, especially with hereditary thrombophilic genetic alterations, as well as when associated with other acquired risk factors such as pregnancy, the postpartum period, obesity, lack of activity and ageing.

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