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PHARMACEUTICAL SAFETY OF THE USE OF COMBINED ORAL CONTRACEPTIVES (LITERATURE REVIEW)

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Combined oral contraceptives (COCs) are currently the most common method of contraception among women of the reproductive age. However, many factors must be considered and analyzed when prescribing these drugs to women. The assessment of the benefit/risk ratio, i.e. the pharmacosafety of drugs, is an integral part of the analysis of the feasibility of prescribing combined oral contraceptives to certain patients.
***The purpose of the work** – to carry out an analysis of literature data regarding the assessment of the pharmacological safety of the use of combined oral contraceptives.*
***Conclusions.** The analysis of literature data on the pharmacosafety of the COCs'use made it possible to establish that the use of these drugs is directly related to the following side effects: the development of venous thromboembolism, depression, migraine, arterial hypertension, and the development of oncopathology. It is also necessary to take into account the metabolism of COCs in the woman's body and, accordingly, the possible interaction with other drugs, especially when their metabolic pathways cross.*

Key words:
combined oral contraceptives, pharmacosafety.

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ФАРМАЦЕВТИЧНА БЕЗПЕКА ЗАСТОСУВАННЯ КОМБІНОВАНИХ ОРАЛЬНИХ КОНТРАЦЕПТИВІВ (ОГЛЯД ЛІТЕРАТУРИ)

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Комбіновані оральні контрацептиви (КОК) на сьогодні є найпоширенішим методом контрацепції серед жінок репродуктивного віку. Однак при призначенні цих препаратів жінкам необхідно враховувати та аналізувати багато факторів. Оцінка співвідношення користь/ризик, тобто фармакологічна безпека лікарських засобів, є невід'ємною частиною аналізу доцільності призначення комбінованих оральних контрацептивів певним пацієнтам.
***Мета роботи –** здійснити аналіз даних літератури щодо оцінки фармакологічної безпеки застосування комбінованих оральних контрацептивів.*
***Висновки.** Аналіз даних літератури щодо фармакобезпеки застосування КОК дав змогу встановити, що застосування цих препаратів безпосередньо пов'язане з такими побічними ефектами: розвитком венозної тромбоемболії, депресією, мігренню, артеріальною гіпертензією, розвитком онкопатології. Необхідно також враховувати метаболізм КОК в організмі жінки і, відповідно, можливу взаємодію з іншими препаратами, особливо при перетині їх метаболічних шляхів.*

Ключові слова:
комбіновані оральні контрацептиви, фармакологічна безпека.

Клінічна та експериментальна патологія 2024. Т.23, №3 (89). С. 47-52.

Introduction

Combined oral contraceptives (COCs) are currently the most common method of contraception among women of reproductive age worldwide [1, 2, 3]. Despite the sufficiently safe profile of the use of COCs, many factors must be considered and analyzed when prescribing these drugs to women. Thus, in particular, venous thromboembolism (VTE) is rare in young women of the reproductive age, but COCs increase its risk [4, 5]. Dosing of estrogen, i.e. ethinyl estradiol, is identified as the main risk factor for VTE [6]. Also, it should be taken into account that according to WHO recommendations [7] there are a number of contraindications to prescribing COCs, including women with hereditary thrombophilia (antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden and prothrombin-G20210A mutation).

The purpose of the work

To carry out an analysis of literature data regarding the assessment of the pharmacological safety of the use of combined oral contraceptives.

Main part

Women who use transdermal contraceptive patches and combined oral contraceptives (COCs) have an approximately eightfold greater risk of VTE than those who do not use hormonal contraceptives (HCs), corresponding to 9.7 cases per 10,000 women/year. Vaginal rings increase the risk of VTE by a factor of 6.5 compared with no use of GCs, corresponding to 7.8 events per 10,000 women/year. Several studies have demonstrated an increased risk of VTE in transgender people receiving hormone therapy (HT). Hormonal therapy during menopause approximately doubles the risk of VTE, and this risk increases with obesity, thrombophilia, age over 60 years, surgery, and immobilization. The route of estrogen administration, dosage, and type of estrogen-related progestogen may influence the risk of VTE in the menopausal period. Combined estrogen-progesterone therapy increases the risk of VTE compared with estrogen monotherapy. Postmenopausal HT increases the risk of thrombosis in atypical sites [2, 3].

Combined estrogen-progesterone therapy increases the risk of VTE compared with estrogen monotherapy. Postmenopausal HT increases the risk of thrombosis in atypical sites.

A meta-analysis showed that COCs containing certain progestins may cause an increased risk of VTE compared with COCs containing levonorgestrel. This finding should be considered in the context of the overall risk of VTE among women of reproductive age. Any small increase in relative risk accounts for the small number of population-level events. Assuming a risk of 9-10 VTE events per 10,000 woman-years among women using COCs containing levonorgestrel in this meta-analysis suggests that women using COCs containing other progestogens may have an increased risk of 1.5-2.0 times, resulting in an absolute risk of approximately 14-20 VTE events per 10,000 woman-years, or an additional 5-10 events per 10,000 woman-years [8].

Based on the results of the analysis of the pharmacosafety of the COCs' use, it was established that the use of these drugs is directly related to the following side effects: the development of venous thromboembolism, depression, migraine, arterial hypertension, and the development of oncopathology. Also, the simultaneous use of COCs with other drugs taken by a woman should be taken into account. Another study found that an increased risk of VTE was associated with COCs containing ethinyl estradiol. The use of combined estradiol-containing products only slightly increases the risk, possibly due to cyproterone-containing COCs, whereas the use of progestin-only contraceptives is not associated with venous thromboembolism [9].

Data on the relationship between the use of COCs and symptoms of depression and low mood are ambiguous. It has been reliably established that COCs with antiandrogenic progestogens, such as drospirenone and desogestrel, are more favorable to mood symptoms than progestogens with a higher androgenic profile. Available evidence suggests that lower doses of ethinyl estradiol may be beneficial in female patients with adverse mood symptoms [10].

The results of a pairwise meta-analysis indicated that COCs were more effective than placebo in the treatment of general premenstrual symptoms (PMS) (standardized mean difference, 0.41; 95 % confidence interval, 0.17-0.67), but not specifically of premenstrual symptoms, in particular depression (standardized mean difference, 0.22; 95 % CI, –0.06 to 0.47). In terms of comparative characteristics among COCs, none of the drugs under study was superior to the other in reducing premenstrual depression (PMD) symptoms and general premenstrual symptoms. That is, these results suggest that COCs can improve general premenstrual symptoms in women with PMS or PMD, but not PMD symptoms [11].

Studies documenting long-term cumulative use of COCs continue to demonstrate a significant association between duration of use and risk of hypertension. In a case-control study in China that reported more than 20 years of COC use, each additional 5 years of use was associated with higher odds of hypertension [12]. Similarly, those who had stopped taking COCs more than 15 to 20 years before the start of the study were about 60 % less likely to have hypertension than those who were currently using COCs [13].

A pooled meta-analysis of 24 studies including 270,284 participants from Asia, Europe, North America, and Oceania reported similar results, describing a 13 % higher risk of hypertension for every 5 years of COC use [14]. However, between-study heterogeneity was high, as data from the included studies were collected from the 1970s to the 2000s. Although doses and formulations of COCs were not recorded, they likely varied significantly given the range of years for which data were available.

According to WHO eligibility criteria, hypertensive women taking COCs may have an increased risk of cardiovascular diseases. The risk-benefit ratio depends on the severity of the condition. Although moderate elevations in blood pressure (BP) are common in COC users, the potential for high BP exists with COC use. Therefore, there is a possibility of an increased cardiovascular risk, as the available data on this issue are limited.

Several cross-sectional and prospective studies have established that the estrogenic component is primarily responsible for changes in the blood pressure in individuals taking COCs. Some researchers have hypothesized that progestins may enhance the effects of estrogen on BP through off-target effects on androgen and estrogen receptors [13].

The findings of the researchers indicate a clinically significant result associated with an increase in blood pressure in users of ethinyl estradiol in combination with gestodene in a cyclic scheme for 6 months. Conversely, a decrease in the blood pressure was observed among users of ethinyl estradiol in combination with chlormadinone during 24 months of use. Although this study found slight variations in BP among different forms of COC, these differences are not significant enough to warrant specific clinical recommendations [15]. However, the results suggest that people with hypertension should be cautious with ethinyl estradiol, especially when cycled with gestodene, because of the potential risk of BP elevation. In addition, the use of COCs containing ethinyl estradiol

in combination with chlormadinone acetate or ethinyl estradiol in combination with drospirenone may be more suitable for individuals at high risk of developing hypertension [16].

Regarding the relationship between the use of COCs and the development of oncology, in 2012, the International Agency for Research on Cancer published data that the use of COCs can increase the risk of developing some types of cancer and protect against others. Thus, it was established that in endometrial cancer, COCs had a protective effect that increased with duration of use and remained at least 20 years after discontinuation. For ovarian cancer, a more significant reduction in risk was observed with duration of use and was sustained for at least 30 years after cessation. It has also been suggested that COCs may reduce the risk of colorectal cancer and have an unlikely potential to alter the risk of thyroid, lung, stomach, urinary tract, gall bladder, pancreas, lymph node, skin and central nervous system cancers [17].

Ocular morbidity associated with COC use is estimated to be 1 in 230,000, including dry eye symptoms, corneal edema, lens opacities, and neuro-ophthalmologic or retinal vascular complications. Serious ocular complications of COC can be prevented by canceling the dosage of estrogens and choosing third-generation progestins. In any case, before choosing any method of contraception, doctors should take into account the patient's systemic and ophthalmological history [18].

Taking into consideration that metabolism plays an important role in the elimination of estrogens and progestins contained in COCs, the possible interaction in a woman's body should be taken into account during the simultaneous use of COCs and other drugs. If the simultaneously used drug induces the enzymes responsible for the metabolism of progestins and/or estrogens, an unwanted pregnancy or irregular bleeding may occur [19, 20].

Migraine is common among women of the reproductive age and is associated with an increased risk of ischemic stroke. COC use is also associated with an increased risk of ischemic stroke [21]. The use of COCs by women with migraine may further increase the risk of stroke among women of reproductive age [22, 23]. However, according to the results of a randomized controlled trial, it was established that the long-term use of ethinyl estradiol/levonorgestrel (30/150 mcg/day) in women with menstrual migraine as a preventive measure against menstrual migraine confirmed the effectiveness and safety of such use [24]. Another study found that ultra-low-dose COCs, those containing less than 20 mcg of ethinyl estradiol, may help to prevent menstrual migraines and reduce the frequency of auras [25].

Conclusions

The analysis of literature data on the pharmacosafety of the use of COCs made it possible to establish that the use of these drugs is directly related to the following side effects: the development of venous thromboembolism, depression, migraine, arterial hypertension, and the development of oncopathology. It is also necessary to take into account the metabolism of COCs in the woman's body and, accordingly, the possible interaction with other drugs, especially when their metabolic pathways cross.

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