ABSTRACT

The use of contraception prevents an unwanted pregnancy, and also reduces the risk of developing diseases associated with premature pregnancy for women, especially for teenage girls. The main criteria for choosing a hormonal contraceptive are its effectiveness and safety. Correct assessment of risk factors, indications and contraindications will allow the use of hormonal contraceptives with maximum effect. For most women, oral contraception is safe, convenient and effective, but you should consult about the possible side effects and the importance of strict adherence to the regimen of oral contraceptives. This review discusses the side effects of combined contraceptives.

Keywords: Combined oral contraceptives; depression; cancer; obesity; thromboembolism.

1. INTRODUCTION

To date, according to WHO, problems with the use of contraception in family planning are still relevant. However, there is an increase in the level of contraceptive use in Latin America and Asia, but unfortunately in the African continent, namely south of the Sahara, indicators are still low [1]. In Fig. 1, we can see how the use of modern contraceptive methods has increased when comparing 1990 and 2015.
As the figure shows, indicators rose slightly from 54.0 to 57.4%.

Also, according to WHO, today we are witnessing global dissatisfaction with contraception among women. As the results show, “214 million women in developing countries would like to delay or exclude pregnancy, but do not use any method of contraception,” for the following reasons.

- Limited choice of methods
- Limited access to contraception
- Concern for side effects or related experience
- Cultural or religious factors
- Poor quality of available services
- Bias of consumers and suppliers
- Gender barriers.

But, nevertheless, as an instrument of family planning, prevention and treatment of gynecological diseases, more than 150 million women use hormonal contraceptives [2].

Studies show that there is no comprehensive evidence of the harmfulness of taking oral hormonal contraception. However, we know that the manifestation of side effects at the beginning of taking oral contraceptives is the highest, and decreases in subsequent cycles [3].

According to studies, hormonal contraceptives themselves have a wide range of actions that favorably affect a woman’s organism. For example, Lene Hee et al. in their review, Continuous Use of Oral Contraceptives: An Overview of Effects and Side-Effects, argue that the endometrium is inactive with prolonged use of oral contraceptives and the risk of endometrial hyperplasia does not increase [4]. Also, it became clear that the number of days of bleeding is halved with the constant use of combined oral contraceptives; however, irregular bleeding is observed at the beginning of oral contraceptive use, decreasing over time and much more.

For most women, oral contraception is safe, convenient and effective, but you should consult about the possible side effects and the importance of strict adherence to the regimen of oral contraceptives. This review discusses the effectiveness, advantages, and disadvantages of combined contraceptives.

1.1 What are Oral Contraceptives?

Combined oral birth control pills are a type of oral medication that is intended for daily use at the same time of the day to prevent pregnancy. There are many different formulations or brands, but the average packaging is for a 28-day period. During the first 21 days of the cycle, users take daily tablets containing hormones (estrogen and progestogen) [5,6,7]. The last 7 days of the cycle are hormone-free days.

Some brands are available with only 21 tablets, and users are advised not to take the tablets for the next week. Other brands produce 7 additional placebo tablets or biologically inactive tablets.

When oral contraceptives used in accordance with the instructions, the estimated risk of becoming pregnant is 0.3% [1]. Or about 3 out of
1,000 women receiving combined oral contraceptive (COC) get pregnant in one year. When taking intermittent tablets, the estimated risk of becoming pregnant is about 9%, or about 9 out of 100 women receiving COCs will become pregnant within one year.

Several factors explain that typical usage efficiency is lower than ideal usage efficiency:
- Errors on the part of those who give instructions on how to use the method
- Errors by the user

For example, a person using oral forms of hormonal birth control may receive incorrect information from their healthcare provider about the frequency of administration, forget to take the pill in one day, or simply don’t go to the pharmacy on time to resume the prescription.

Combined oral contraceptives provide effective contraception from the very first pill if it is started within five days after the start of the menstrual cycle (within five days after the first day of menstruation). If combined oral contraceptives are started at any other time during the menstrual cycle, they provide effective contraception only after using active tablets for 7 days in a row, so you need to use a backup method of contraception (for example, condoms) until the active tablets are taken for 7 days in a row.

Combined oral contraceptives should be taken at approximately the same time each day.

The efficacy of combined oral contraceptive pills seems to be the same regardless of whether the active tablets are taken continuously for long periods of time or if they are taken for 21 active days and 7 days as a placebo.

According to the recommendations of the Centers for Disease Control and Prevention (CDC), a pill is considered to be missed only if 24 hours or more have passed since the last pill was taken [8].

2. SIDE EFFECTS

2.1 Common Side Effects

Various sources report various cases of side effects. The most common side effect is profuse bleeding. A 1992 French review article stated that 50% of new users stop taking birth control pills for the first time before the end of the first year due to annoying side effects such as breakthrough bleeding or amenorrhea [9].

On the other hand, pills can sometimes improve conditions such as pelvic inflammatory diseases, dysmenorrhea, premenstrual syndrome and acne, reduce symptoms of endometriosis and polycystic ovary syndrome, and reduce the risk of anemia. The use of oral contraceptives also reduces the risk of developing ovarian cancer throughout life.

Nausea, vomiting, headache, bloating, chest pain, ankle / foot swelling (due to fluid retention), or weight loss may also occur.

2.2 Heart and Blood Vessels

Combined oral contraceptives increase the risk of venous thromboembolism (including deep vein thrombosis and pulmonary embolism).

Thromboembolism is an acute blockage (embolism) of a blood vessel by a thrombus that has come off from the place of its formation (on the wall of the heart, vessel) and entered the circulating blood. As a result of thromboembolism, the blood flow in the vessel stops, tissue ischemia occurs in the basin of the occluded vessel, often resulting in ischemic infarction.

Combined oral contraceptives with an estrogen content of more than 50 μg increase the risk of ischemic stroke and myocardial infarction, but lower doses are considered safe [10].

These risks are most formidable in women with additional risk factors, such as smoking (which significantly increases the risk of developing thromboembolism) and prolonged use of combined oral contraceptives, especially in women over 35 years of age [11].

The total absolute risk of venous thrombosis per 100,000 women with the current use of combined oral contraceptives is approximately 60 compared to 30 for those who do not use them [12].

The risk of thromboembolism varies depending on the type of birth control pills; in comparison with combined oral contraceptives containing levonorgestrel (LNG) and with the same dose of estrogen and duration of use, the ratio of the frequency of deep vein thrombosis for combined
oral contraceptives with norethisterone is 0.98, with norgestimate 1.19, with desogestrel (DSG) 1.82 with gestodene 1.86, drospirenone (DRSP) 1.64 and cyproterone acetate 1.88. In comparison, venous thromboembolism occurs in 100–200 per 100,000 pregnant women each year [12].

One study showed that the risk of blood clots in women taking combination oral contraceptives with drospirenone is more than 600% higher than women taking birth control pills containing levonorgestrel.

The US Food and Drug Administration (FDA) has initiated studies evaluating the health status of more than 800,000 women taking COCs and found that the risk of thromboembolism was 93% higher for women who took Drospirenone for 3 months or less, and 290% higher in women taking drospirenone for 7–12 months, compared with women taking other types of oral contraceptives [13].

Based on these studies, in 2012, the FDA updated the instructions for drospirenone to include a warning that contraceptives with drospirenone may have a higher risk of dangerous blood clots [14].

Bradykinin lowers blood pressure, causing dilation of blood vessels. Some enzymes can break down bradykinin (an angiotensin converting enzyme, aminopeptidase P). Progesterone can increase the level of aminopeptidase P (AP-P), thereby increasing the breakdown of bradykinin, which increases the risk of hypertension [15].

2.3 Combined Oral Contraceptives and Cancer

A systematic review in 2010 did not confirm an increased overall risk of cancer in women taking combined oral contraceptives, but found a slight increase in the risk of developing breast cancer among women taking combined oral contraceptives, but this relationship disappears 5–10 years after discontinuation [16].

In a study by Polly A. Marchbanks et al. the relative risk of developing breast cancer was 1.0 (95 percent confidence interval, 0.8-1.3) for women who currently used oral contraceptives, and 0.9 (95 percent confidence interval, 0.8 -1.0) for those who have previously used them. The relative risk did not increase sequentially with longer periods of use or with higher doses of estrogen. The use of oral contraceptives in women with a family history of breast cancer was not associated with an increased risk of breast cancer. Among women aged 35 to 64, current or former use of oral contraceptives was not associated with a significantly increased risk of breast cancer [17].

Study by Steven A. Narod et al. The adjusted odds ratio for ovarian cancer associated with past oral contraceptives was shown to be 0.5 (95 percent confidence interval, 0.3–0.8). Risk decreased with increasing duration of use (P for trend <0.001); Use for six or more years has been associated with a 60 percent reduction in risk. The use of oral contraceptives protected against ovarian cancer both for carriers of the Breast cancer type 1 susceptibility protein (BRCA1) mutation (odds ratio 0.5; 95 percent confidence interval, 0.3 to 0.9) and for carriers of the Breast cancer type 2 susceptibility protein (BRCA2) mutation (odds ratio 0.4; 95-percentage confidence interval from 0.2 to 1.1). The use of oral contraceptives can reduce the risk of ovarian cancer in women with pathogenic mutations in the BRCA1 or BRCA2 gene [18].

It should also be noted a large cohort study among women in the UK, in which the results showed the following. When comparing women who had never taken combined oral contraceptives, women who took birth control pills had statistically significant lower rates of colon or rectal cancer, uterus and ovary body, and other malignant neoplasms. Statistically significant trends in increasing the risk of developing cancer of the cervix and central nervous system or pituitary gland, as well as reducing the risk of developing malignant tumors of the uterus and ovaries, were observed with an increase in the duration of oral contraceptives. Reduced estimates of relative risk were observed for ovarian and uterine cancer many years after discontinuing oral contraception, although some were not statistically significant. The estimated absolute decrease in the level of any cancer among regular users was 45 or 10 per 100,000 women per year [19].

2.4 Protective Effects of Combined Oral Contraceptives

COCs reduced the risk of ovarian cancer, endometrial cancer, and colorectal cancer [20].
Two large cohort studies published in 2010 found a significant reduction in the relative risk of mortality from ovarian and endometrial cancer in women who regularly take oral contraceptives compared to those who never took them [21].

The use of oral contraceptives (birth control pills) for five years or more reduces the risk of developing ovarian cancer by 40% and the risk of endometrial cancer by 50% compared to those who have never taken birth control pills [22].

2.5 Combined Oral Contraceptives and Overweight

The most commonly used COCs contain a combination of estrogen and progestin. For some drugs, the distribution volume for a given dose in an obese person is greater than the distribution volume for a thinner person. In addition, in obese patients, drugs that undergo phase II metabolism (or conjugation reactions with glucuronic acid, sulfonates, glutathione, or amino acids) tend to be metabolized faster, which shortens their duration [23].

It was shown that an increase in body weight changes the rate of estradiol metabolism in young women [24]. The time to reach steady levels of levonorgestrel after oral administration in women with obesity is twice as long as in women with normal weight; therefore, the interval to suppression of hypothalamic-pituitary-ovarian activity can be increased, which increases the risk of ovulation in obese women [25].

Recent evidence suggests that obesity may reduce the biological effectiveness of oral contraceptives. A study by Larissa R. Brunner Huber showed a potential link between obesity and oral contraception using data from the 2002 National Family Growth Survey. This population-based study did not reveal a link between obesity and oral contraception. Although, as the authors point out, it is possible that incorrect classification or uncontrolled mixing of birth control pills concealed a true connection [26].

A 2013 Cochrane systematic review showed that studies of combined hormonal contraceptives showed no significant difference in weight compared to placebo groups. The evidence was not convincing enough to be sure that oral contraceptives do not cause any changes in the weight of women. This review also found that “women did not stop taking pills or patches due to weight changes” [27].

2.6 Combined Oral Contraceptives and Sexuality

According to a double-blind, placebo-controlled study in which 340 women participated, the overall sexual function was the same for women in groups of women who took oral contraceptives and women who were given placebo. Orgasm, anxiety, responsiveness, and self-esteem were similar between groups. The average frequency of sexual intercourse satisfaction and personal distress was also the same between the groups. This study did not reveal a negative effect of the use of oral contraceptives containing levonorgestrel on overall sexual function [28].

Combined oral contraceptives may increase the release of natural vaginal lubrication. According to another study, women experience a decrease in libido while taking pills or a decrease in the release of lubricant [29].

Some researchers question the causal relationship between the use of combined oral contraceptives and a decrease in libido. Thus, a study conducted in 2007 among 1,700 women showed that women who took birth control pills did not show any changes in sexual satisfaction [30].

2.7 Combined Oral Contraceptives and Depression

Low levels of serotonin, a neurotransmitter in the brain, is associated with depression. It has been shown that high estrogen levels in some contraceptives containing only progestin lower the level of serotonin in the brain by increasing the concentration of the brain enzyme, which reduces serotonin [31].

More and more scientific evidence suggests that hormonal contraception can have an adverse effect on women's psychological health.

In 2018, the results of a large nationwide Swedish study were published that examined the effect of hormonal contraception on women's mental health, emphasizing the relationship between hormonal contraception and the subsequent use of psychotropic drugs. for women of reproductive age. This relationship was especially great for young women (ages 12–19). The authors call for further research on the
effect of various types of hormonal contraception on the psychological health of young women [32].

A recent study on the relationship of depression and the use of combined oral contraceptives showed that the use of oral contraceptives did not show a relationship with symptoms of depression when combining all age groups. But it is noteworthy that 16-year-old girls reported higher rates of depressive symptoms when using oral contraceptives [33].

In doing so, a study by Charlotte Wessel Skovlund et al. showed that the use of hormonal contraception, especially among adolescents, was associated with the subsequent use of antidepressants and the first diagnosis of depression, which suggests depression as a potential adverse effect from the use of hormonal contraceptives [34].

Monitoring depressive symptoms in adolescents using oral contraceptives is important because using oral contraceptives can affect their quality of life and put them at risk of non-compliance.

It is known that only progestin contraceptives worsen the condition of women who are already depressed. However, current medical contraceptive guides and the WHO agree that current evidence suggests that low-dose combination oral contraceptives are unlikely to increase the risk of depression and it is unlikely that women who are currently depressed and are taking a worsening condition combined oral contraceptives [35].

3. CONCLUSION

Maintaining women’s health and ensuring safe motherhood is the main task of modern medicine. One of the ways to solve it is to prevent unplanned pregnancy, reduce the number of medical and criminal abortions, and maternal mortality after abortions. In the world, abortion occupies a leading place in the structure of the implementation of reproductive function and reproductive losses. The consequences of abortion - high maternal and infant morbidity and mortality, miscarriage, infertility, complications in subsequent pregnancy and childbirth, deterioration in the health of offspring and the nation as a whole - make the use of hormonal contraceptives relevant.

In conclusion, it is worth noting that combined oral contraceptives are today one of the most common methods of contraception. To avoid unwanted side effects, every woman needs specialized advice from a qualified gynecologist or family doctor who must choose the right medicine. The main criteria for choosing a hormonal contraceptive are its effectiveness and safety for women’s health.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/59256