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OFF-LABEL USE OF MEDICINES IN GYNECOLOGY

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Abstract

The off-label use of drugs in obstetric and gynecological practice, paradoxically, is a common phenomenon, since it is often difficult for doctors to choose drugs from their limited range in gynecology. Today in gynecology, recommendations are being revised regarding the tactics of managing many pathological processes, for example, endometriosis.

Thus, the off-label use of drugs has its own therapeutic niches in gynecology. The reason for this is the lack of interest of pharmaceutical companies in this segment of the pharmaceutical market due to insufficient funding and difficulties in conducting clinical trials in pregnant women for ethical reasons.

In Ukraine, as elsewhere in the world, there is no regulatory framework for the off-label use of drugs. The legal discussion in European countries regarding the off-label use of drugs in general and in gynecology, in particular, is mainly focused on the risks to the safety of patients taking off label drugs, or on deviations from the methodological official information in pharmacotherapy (for example, in dosage, pharmaceutical form, age, side effects, contraindications, etc.).

Keywords: *gynecology, off-label use, combined oral contraceptives.*

The off-label use of drugs in obstetric and gynecological practice, paradoxically, is a common phenomenon, since it is often difficult for doctors to choose drugs from their limited range in gynecology [23, 14]. It should be borne in mind that pregnant women suffer from the same diseases as all other people, and drugs of most pharmacotherapeutic groups are contraindicated during pregnancy [39, 30]. The use of an officially contraindicated drug can be regarded as a disregard or violation of safety measures, but, on the other hand, there are situations when it is impossible to avoid the use of unlicensed drugs in gynecology. For example, in pregnant women, antibiotics, cytostatics, immunosuppressants, anticonvulsants, warfarin, and many other drugs can be used off-label [24, 43].

Germany has one of the most developed off-label drug regulations in Europe: a 2011 study in 43 German hospitals showed that 65 doctors (91%) prescribed drugs off-label [4, 12, 41, 35]. About half of off-label prescriptions were made in obstetric and gynecological practice. Doctors received most of the information about the off-label use of drugs from their colleagues (66%) or from their own experience (58%), 34% of specialists considered such treatment to be risky [25]. So, hexoprenaline is recommended for the relief of premature birth as an intravenous infusion, the maximum duration of its use is two days. This time is quite enough to carry out the prevention of respiratory distress syndrome in a newborn. However, doctors often use off-label hexoprenaline orally, for a long time, at a dosage of 125-500 μg, which differs from the dosage approved for tocolytic action [13, 36].

It is quite common in obstetrics to use off-label drugs for conditions for which there are no approved treatment standards [28]. For example, in fetal growth retardation syndrome, fetal distress syndrome, oligohydramnios, and polyhydramnios, isoimmune conflict. It is difficult for obstetricians-gynecologists to monitor the development of pathology and not interfere, so they prescribe dipyridamole, antibiotics, glucocorticoids, antihistamines, homeopathic and other drugs that are contraindicated in pregnant, but sometimes are the only alternative in helping pregnant [29]. The main problem with off-label therapy in pregnant women is the lack of conclusive scientific evidence that such treatment can be useful in these conditions. Therefore, the responsibility of an obstetrician-gynecologist for off-label treatment is exclusively in his professional, legal and moral plane [7, 16].

Today in gynecology, recommendations are being revised regarding the tactics of managing many pathological processes, for example, endometriosis. Endometriosis is a dyshormonal, immune-dependent, genetically determined chronic disease characterized by benign proliferation of tissue outside the uterine cavity, which is similar in morphological structure and function to the endometrium [27]. Currently, endometriosis is considered one of the most common and severe gynecological pathologies [8]. Globally, endometriosis is diagnosed in 2-10% of women in the general population and approximately 50% of women with infertility. The cost of treating endometriosis ranges from 0.8 million to 12.5 billion euros per year and is approximately equal to the cost of treating diabetes [11].

In the treatment of this disease, various groups of drugs are used, but none of them, unfortunately, provides either an absolute elimination of symptoms or a stable therapeutic effect and reliable prevention of relapses, which is due to the multifactorial pathogenesis of endometriosis [33]. In addition, long-term use of drugs for the treatment of endometriosis is limited due to the occurrence of possible ARs. In this regard, the search continues for drugs that can act directly on endometrioid heterotopias, and not on the level of sex hormones and ovarian function [21, 19].

Combined oral contraceptives (COCs) are considered to be the first choice (albeit off-label) drugs for endometriosis to relieve pelvic pain in women who do not have contraindications to their use and do not plan to become pregnant at the moment. Potential benefits of COCs are low cost and few side effects. They have been used for many years, but only a few randomized controlled trials have compared them with other therapies (level of evidence Ia). COCs are ineffective in the treatment of relapses, but they are effective as an inhibitory postoperative therapy for the prevention of relapses and the elimination of dysmenorrhea [3, 20].

A distinctive feature of COCs from other methods of endometriosis therapy is the presence of

estrogens in their composition. It is estrogens that play a leading role in the proliferation of endometrioid heterotopias [42]. In addition, it is the estrogens in the composition of COCs that increase the efficiency and compliance with their long-term use due to the high-quality control of the cycle (the absence of irregular bleeding during drug administration).

The presence of certain indications in the instructions, as well as their absence, does not always solve the problem of treatment for this nosology. One of the main indications of COCs in the instructions is to reduce blood loss and restore serum iron levels. Today, the regimens of prescribing COCs for therapeutic and contraceptive purposes have been revised.

Justifying the possibilities of off-label use of COCs with dienogest in endometriosis, the following features can be distinguished:

suppression of cyclic proliferation by reducing the synthesis of estrogens and the peripheral action of dienogest (effect on intracellular signaling systems);

the presence of an anti-inflammatory effect due to dienogest;

initiation of the state of pseudodecidualization followed by atrophy of the foci of endometriosis;

the contraceptive effect, which is especially important with prolonged use, since the termination of pregnancy complicates the course of endometriosis;

dienogest helps prevent the development of cancer in endometriosis (Japanese researchers have classified dienogest as an antineoplastic drug, but clinical experience is needed to confirm this concept);

a continuous regimen of COCs with dienogest has significant advantages in the treatment of endometriosis compared to cyclic, therefore they are the first-line drugs [31, 34, 15].

Consequently, the results of a study of the effects of dienogest in the composition of COCs suggest that they differ from other drugs in this group precisely due to the effect of dienogest on endometrioid heterotopias, and 30 μg of ethinylestradiol provide quality control of the menstrual cycle and create conditions for long-term use [40].

Thus, monophasic COCs occupy an important place in the treatment of endometriosis due to the pathogenetically substantiated inhibitory effect on endometrioid heterotopies, which is achieved by consistently low doses of estrogens and antiproliferative effects of the progestogen component, as well as the large experience and evidence base that demonstrates their clinical efficacy against endometriosis-associated symptoms and relapses after surgery but are used off-label.

Today, the feasibility of expanding the indications for the off-label use of this combination for the treatment of women with endometriosis has been theoretically substantiated and clinically confirmed; 100% of doctors note the effectiveness of using COCs in patients with endometriosis [6].

Along with the main indication for the use of COCs during the treatment of gynecological patients, doctors noted their non-contraceptive advantages, namely:

decrease in menstruation (menstruation is shorter and less profuse);

effectiveness in dysmenorrhea;

establishing a regular menstrual cycle;

positive effect in hyperandrogenic conditions;

reducing the severity of premenstrual symptoms;

positive effect in chronic pelvic pain syndrome [18].

The non-contraceptive benefits of COCs are considered as an important option for their off-label use in the following cases:

for abnormal uterine bleeding (AUB), COCs of 30 μg ethinylestradiol and 150 μg desogestrel can be used as a first-aid step, when surgical methods of treatment, followed by prevention of relapse are not indicated;

in acute AUB, COCs have a high level of evidence - Ia [5].

Monophasic COCs can be used off label in both acute and chronic AUB, when there are no contraindications to their use [38, 26].

COCs have a positive effect on a woman's reproductive and general health, on her quality of life, and have some proven preventive effects. The protective effect of COCs increases with increasing duration of use and persists for more than 20 years after their withdrawal. Also, COCs protects women from developing cancer of the rectum and colon. The presence of positive non-contraceptive effects in COCs allows solving many clinical and preventive

tasks, namely: reducing the risk of developing rheumatoid arthritis by approximately 30% and hospitalizations by 51%, as well as reducing the time of onset of symptoms of multiple sclerosis. COCs are used off-label for polycystic ovary syndrome, acne, seborrhea (30 μg ethinylestradiol and 2 mg chlormadinone acetate), and endometriosis (30 μg ethinylestradiol and 2 mg dienogest). COCs reduce the risk of developing pelvic inflammatory disease by 50-60%. Against the background of the use of COCs, there is a decrease in the likelihood of ovarian cancer, the risk of benign breast diseases. Also, the incidence of fibrocystic mastopathy decreases by 30%, fibroadenoma by 60%, focal breast seals by 40% [6].

An alternative approach in the treatment of endometriosis is the off-label prescription of aromatase inhibitors. The most common third-generation aromatase inhibitors are letrozole and anastrozole, which inhibit this enzyme by competing for the androgen bond. Clinicians have confirmed the efficacy of off-label aromatase inhibitors in combination with hormonal contraceptives, progestogens, or gonadotropin-releasing hormone analogs to reduce pain in women with rectovaginal endometriosis [1].

Examples of the off label use of drugs in gynecology are dexamethasone, drotaverine, letrozole, lindinet, metformin, misoprostol, mifepristone, nifedipine, etc. [9, 10, 17, 32, 37].

Letrozole has been used off-label since 2001 to stimulate ovarian function in fertility. The drug is also prescribed off-label in andrology to stimulate spermatogenesis in men suffering from non-prostitution azoospermia. In 2012, the Indian parliamentary committee on medicines banned the use of letrozole for infertility. However, off-label use of this drug is common in many countries such as the US and UK.

There is ongoing controversy over the regimen for a medical abortion performed with mifepristone and misoprostol. Mifepristone is used for termination of pregnancy in doses of 200 and 600 mg. In addition, there is evidence that the off label use of mifepristone at a dose of 25 mg helps to reduce the size of uterine fibroids [22, 32, 37].

There are long-term clinical observations indicating the high tocolytic efficacy of nifedipine and its safety for the fetus. In Europe, nifedipine is the first choice for reducing the risk of preterm birth, but there is no such indication in the instructions for its medical use [2].

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