REVIEW

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)

Pharmacotherapy of Endometriosis: Balancing of Safety, Efficacy, and Adherence to Treatment

V.I. Petrov[1], I.S. Kulakova[1,2], V.S. Gorbatenko[1], O.V. Shatalova[1], I.D. Bezuglov[1], A.S. Ignatova[1]

[1] Volgograd State Medical University,
1 Pavshikh Bortsov Sq., Volgograd, Russia, 400066
[2] Dochki-materi Clinics,
2 Nevskaya Str., Volgograd, Russia, 400087

E-mail: iraida97@mail.ru

Received 15 Oct 2025 After peer review 03 Dec 2025 Accepted 17 Dec 2025

The aim. To conduct a comprehensive analysis of the clinical and pharmacological efficacy of progestins (dydrogesterone, dienogest, and norethisterone acetate) for the treatment of endometriosis by systematizing data on their pharmacodynamic, pharmacokinetic characteristics, and safety profile to optimize the selection of a personalized therapeutic strategy.

Materials and methods. The search of the literature was conducted regarding randomized controlled trials (RCTs), cohort studies, and meta-analyses for the period from 1958 to 2025 from the PubMed, Cochrane Library, and eLibrary.ru databases.

Results. It was found that dienogest, dydrogesterone, and norethisterone acetate demonsrates comparable efficacy in reducing the intensity of endometriosis-associated pelvic pain. Dienogest showed efficacy comparable to gonadotropin-releasing hormone agonists with a better tolerability profile. Dydrogesterone exhibited the best safety profile with minimal impact on metabolic parameters. Norethisterone acetate showed efficacy comparable to dienogest, but with more pronounced androgenic effects. Key pharmacological features affecting the safety profile of drugs were identified, and the need for a personalized approach to the choice of therapy was justified. The main limitation is the insufficient number of direct comparative studies of various progestins.

Conclusion. All the progestins considered are effective treatments for endometriosis, but have different safety profiles, which determines the need for individual drug selection, taking into account the patient's characteristics and concomitant pathology. Promising areas for future research include conducting large multi-center RCTs, developing algorithms for personalized therapy selection, and studying the long-term effects of treatment.

Keywords: endometriosis; progestins; dienogest; dydrogesterone; norethisterone acetate; gonadotropin-releasing hormone agonists; combined oral contraceptives; chronic pelvic pain; clinical efficacy; safety

Abbreviations: GnRH agonists — gonadotropin-releasing hormone agonists; AUB — abnormal uterine bleeding; VAS — visual analog scale; CGRP — calcitonin gene-related peptide; CYP3A4) — cytochrome P450 enzyme system; ESHRE — European Society of Human Reproduction and Embryology; TNF-α — tumor necrosis factor alpha; FSH — follicle-stimulating hormone; FSFI — Female Sexual Function Index; IL-8 — interleukin-8; IL-1β — interleukin-1 beta; COCs — combined oral contraceptives; LH — luteinizing hormone; MRI — magnetic resonance imaging; NSAIDs — nonsteroidal anti-inflammatory drugs; RCTs — randomized controlled trials; RANTES (Regulated on Activation, Normal T Expressed and Secreted, or CCL5) — chemokine; SF-36 (Short Form-36) — quality of life assessment questionnaire; CPPS — chronic pelvic pain syndrome.

For citation: V.I. Petrov, I.S. Kulakova, V.S. Gorbatenko, O.V. Shatalova, I.D. Bezuglov, A.S. Ignatova. Pharmacotherapy of Endometriosis: Balancing of Safety, Efficacy, and Adherence to Treatment. *Pharmacy & Pharmacology.* 2026;14(1):4-17. **DOI:** 10.19163/2307-9266-2026-14-1-4-17

Для цитирования: В.И. Петров, И.С. Кулакова, В.С. Горбатенко, О.В. Шаталова, И.Д. Безуглов, А.С. Игнатова. Фармакотерапия эндометриоза: баланс безопасности, эффективности и приверженности к лечению. *Фармация и фармакология.* 2026;14(1):4-17. **DOI:** 10.19163/2307-9266-2026-14-1-4-17

Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ
(PHARMACY & PHARMACOLOGY)

ОБЗОР
DOI: 10.19163/2307-9266-2026-14-1-4-17

Фармакотерапия эндометриоза: баланс безопасности, эффективности и приверженности к лечению

В.И. Петров[1], И.С. Кулакова[1,2], В.С. Горбатенко[1], О.В. Шаталова[1], И.Д. Безуглов[1], А.С. Игнатова[1]

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, 400066, г. Волгоград, пл. Павших Борцов, д. 1
[2] Общество с ограниченной ответственностью «ДОЧКИ-МАТЕРИ», Россия, 400087, г Волгоград, ул. Невская, д. 2

E-mail: iraida97@mail.ru

Получена 15.10.2025 После рецензирования 03.12.2025 Принята к печати 17.12.2025

Цель. Проведение комплексного анализа клинико-фармакологической эффективности прогестинов (дидрогестерона, диеногеста и норэтистерона ацетата) для терапии эндометриоза путем систематизации данных об их фармакодинамических, фармакокинетических характеристиках и профиле безопасности для оптимизации выбора персонализированной терапевтической стратегии.

Материалы и методы. Поиск литературы проводили среди рандомизированных контролируемых исследований (РКИ), когортных исследований и метаанализов за период с 1958 по 2025 гг. в базах данных PubMed, Cochrane Library и eLibrary.ru.

Результаты. Установлено, что диеногест, дидрогестерон и норэтистерона ацетат демонстрируют сопоставимую эффективность в снижении интенсивности эндометриоз-ассоциированной тазовой боли. Диеногест показал эффективность, сравнимую с агонистами гонадотропин-рилизинг-гормона, но с лучшим профилем переносимости. Дидрогестерон проявлял наилучший профиль безопасности с минимальным влиянием на метаболические параметры. Норэтистерон ацетат показал сопоставимую с диеногестом эффективность, но с более выраженными андрогенными эффектами. Определены ключевые фармакологические особенности, влияющие на профиль безопасности препаратов, а также обоснована необходимость персонализированного подхода к выбору терапии. Основным ограничением является недостаточное количество прямых сравнительных исследований различных прогестинов.

Заключение. Все рассмотренные прогестины являются эффективными средствами терапии эндометриоза, однако имеют различные профили безопасности, что предопределяет необходимость индивидуального выбора препарата с учетом особенностей пациентки и сопутствующей патологии. Перспективными направлениями будущих исследований являются проведение крупных многоцентровых РКИ, разработка алгоритмов персонализированного выбора терапии и изучение долгосрочных эффектов лечения.

Ключевые слова: эндометриоз; прогестины; диеногест; дидрогестерон; норэтистерона ацетат; агонисты гонадотропин-рилизинг-гормона; комбинированные оральные контрацептивы; хроническая тазовая боль; клиническая эффективность; безопасность

Список сокращений: аГнРГ — агонисты гонадотропин-рилизинг-гормона; АМК — аномальные маточные кровотечения; ВАШ — визуальная аналоговая шкала; CGRP — кальцитонин-ген-связанный пептид; CYP3A4 — фермент системы цитохрома P450; ESHRE — Европейское общество репродукции человека и эмбриологии; ФНО-α — фактор некроза опухоли альфа; ФСГ — фолликулостимулирующий гормон; FSFI — индекс женской сексуальной функции; ИЛ-8 — интерлейкин-8; ИЛ-1β — интерлейкин-1 бета; КОК — комбинированные оральные контрацептивы; ЛГ — лютеинизирующий гормон; МРТ — магнитно-резонансная томография; НПВП — нестероидные противовоспалительные препараты; РКИ — рандомизированные контролируемые исследования; RANTES (Regulated on Activation, Normal T Expressed and Secreted, или CCL5) — хемокин; SF-36 (Short Form-36) — опросник для оценки качества жизни; УЗИ — ультразвуковое исследование, СХТБ — синдром хронической тазовой боли.

INTRODUCTION

Chronic pelvic pain syndrome (CPPS) is one of the most significant problems in gynecological practice. According to global estimates, its prevalence among women of reproductive age reaches 25 %, with 40 % to 87 % of cases associated with endometriosis [1]. According to the World Health Organization (WHO), endometriosis is diagnosed in one in ten women, which corresponds to approximately 190 million (10–15%) individuals aged 15 to 49 years. It is important to note that patients with endometriosis account for 40–50 % of all the cases of female infertility [2].

In 2020, M. Ghiasi et al. conducted a review of the global prevalence of endometriosis from January 1989 to June 2019. Out of 28 scientific works, 17 provided an assessment of endometriosis prevalence among women with infertility, which was 27 % in a sample of 8 172 individuals. Eleven studies examined the prevalence of endometriosis among women with CPPS, which was 29 % in a sample of 5 104 individuals. In the overall cohort, which included over 14 million women, there is a significant variation in endometriosis prevalence estimates across geographical regions: in Africa — from 0.2 % to 48 %, in Australia — from 3.4 % to 3.7 %, in the Americas — from 0.7 % to 70 %, in Asia — from 1 % to 72 %, in Europe — from 0.8 % to 70 %. A significant limitation of this review is the complexity of diagnosing endometriosis, which complicates the determination of the true prevalence of the disease in the population [3].

The increase in registered cases of endometriosis is due to a complex of factors, among which the improvement of diagnostic methods and the increased awareness of medical professionals about the clinical manifestations of the disease play a key role. The significant increase in the number of cases, combined with growing patient awareness of the impact of endometriosis on reproductive function, contributes to the expansion of the global market for the therapy of this pathology. The global market volume for endometriosis treatment is estimated at 1.6 billion US dollars in 2024, and by 2034, it is expected to grow to 5.4 billion US dollars with a compound annual growth rate of 13.3 %[1].

Endometriosis represents a colossal medical problem in the Russian Federation, causing significant demographic and socio-economic damage. One of the most significant complications of this pathology is infertility, leading to an annual decrease in reproductive potential, estimated at approximately 14,365 unborn children. Modern hormonal therapy methods can reduce potential demographic losses by about 2212 cases per year. However, at present, only 536 children are born using this treatment method, indicating partial realization of therapeutic potential. The socio-economic aspect of the disease is characterized by significant losses in the working population, reaching 33.0 million days of temporary disability per year. The use of hormonal therapy could provide a reduction in this indicator by 5.4 million days; however, the actual reduction does not exceed 1.1 million days. Considering the data provided, the economic damage from the pathology reaches 553 billion rubles per year. Potential hormonal therapy can reduce losses by 93.2 billion rubles; however, the actual reduction is only 19.1 billion rubles. Data analysis also shows that the administration of drugs to all patients in need can further reduce economic damage by 15.9 billion rubles [4].

The problem of diagnosing endometriosis is due to the frequent asymptomatic course of the disease, which complicates the assessment of its real prevalence. Given the diversity of clinical manifestations, the pathology remains one of the most socially and demographically significant diseases, which necessitates the application of a multidisciplinary approach to its treatment and diagnosis[2].

Endometriosis is predetermined by the presence of estrogen-dependent, progesterone-resistant endometriotic foci outside the uterine cavity. Despite numerous hypotheses regarding etiology and pathogenesis, key links include systemic and local hyperestrogenemia, progesterone resistance, neoangiogenesis, neurogenesis, and reduced apoptosis. These changes cause a chronic inflammatory reaction, often leading to endometriosis-associated pelvic pain. The nature of the pain varies significantly: menstruating patients experience cyclical and non-cyclical pain, accompanied by dyschesia, dysuria, dysmenorrhea, and dyspareunia [5]. Endometriotic foci have their own vascular structure and are innervated by sensory and autonomic fibers, providing afferent access to peripheral and central pain pathways. However, foci are not the sole cause of pain, as its intensity and duration do not correlate with their number, localization, or disease severity.

It should be noted that endometriosis is a chronic estrogen-dependent inflammatory disease that leads to the chronification of pelvic pain and requires lifelong continuous treatment [6]. Despite many years of research, the diagnosis and

[1] Endometriosis Treatment Market Size, By Disease Type, By Treatment Type, By Drug Class, By Administration Method, By Distribution Channel, 2025–2034; Global Market Insights Inc. – 2024. Available from: https://www. gminsights.com/industry-analysis/endometriosis-treatment-market 2

[2] Clinical Guidelines. Endometriosis. Russian Society of Obstetricians and Gynecologists; Rubricator of clinical recommendations; 2024. 62 p. Available from: https://cr.minzdrav.gov.ru/view-cr/259_2. Russian

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DOI: 10.19163/2307-9266-2026-14-1-4-17

treatment of endometriosis remain complex and relevant for both physicians and patients. Not fully understood pathophysiological mechanisms and the diversity of clinical phenotypes complicate the assessment of published data and the selection of adequate patient management strategies [7]. To date, there is no single treatment method — neither surgical nor medical — that has demonstrated unequivocal superiority in efficacy. Modern therapy for endometriosis-associated pelvic pain is aimed at systemic or local suppression of estrogen production and inflammation, as well as inhibition of proliferation. Treatment should be personalized and consider the severity of the disease, symptoms, and the patient's reproductive plans [8].

THE AIM. To analyze the clinical and pharmacological efficacy of progestins (dydrogesterone, dienogest, and norethisterone acetate) for the therapy of endometriosis based on data on their pharmacodynamic, pharmacokinetic characteristics, and safety profile to optimize the selection of a personalized therapeutic strategy.

MATERIALS AND METHODS

A search for clinical studies was conducted in the PubMed, Cochrane Library, and eLibrary.ru databases. Key search terms used included: dydrogesterone, dienogest, norethisterone, norethindrone, progestins, gestagens, endometriosis, chronic pelvic pain, chronic pelvic pain syndrome, and their combinations, as well as their English equivalents: didrogesterone, dienogest, norethisterone, norethindrone, progestins, gestagens, and endometriosis, chronic pelvic pain. The search conducted across multiple scientific databases identified a total of 726 relevant studies, including original articles and reviews. The search was conducted for the period 1958–2025.

RESULTS AND DISCUSSION

Progestins in the Therapy of Endometriosis-Associated Pain Syndrome

In accordance with current International and Russian Clinical Guidelines, progestins are first-line therapy drugs for endometriosis with mild to moderate pain syndrome[3]. It is reported that they reduce or eliminate painful symptoms in approximately 90 % of patients [9]. Various forms of progestins (oral, injectable, intrauterine, subcutaneous implants) are widely used for the treatment of endometriosis. Progestins therapy is a more preferred option compared to commonly used nonsteroidal anti-inflammatory drugs (NSAIDs), which do not alter the course of the disease and are not ideal for long-term use due to gastrointestinal side effects.

Current Clinical Guidelines "Endometriosis" 2024, among hormonal therapy agents, consider gonadotropin-releasing hormone agonists (GnRH agonists) and combined oral contraceptives (COCs). GnRH agonists play an important role in managing patients with advanced and infiltrative forms of the disease, both after surgical intervention and with a confirmed diagnosis. However, their long-term use is limited by several side effects, including neurovegetative and psychoemotional disorders, as well as negative effects on bone mineral density. Therefore, GnRH agonist therapy lasting longer than six months requires mandatory "add-back therapy"[4].

Regarding COCs [10, 11], their application aims include contraception, empirical treatment, and prevention of recurrence after surgical interventions. Despite an extensive evidence base confirming the therapeutic and prophylactic properties of COCs and their many years of global use in genital endometriosis, the issue of prescribing estrogen-gestagenic agents remains a subject of active discussion. With the development of minimally invasive surgery techniques, allowing for earlier and more accurate diagnosis of the pathology, information has emerged about the potentially negative impact of COC use on the course of deep infiltrative and extragenital endometriosis. Adverse effects are linked to several factors: the presence of an estrogen component in COCs, the development of "progesterone resistance" in endometriotic foci, and the traditional cyclic regimen of their administration. It has been noted that pain relief during COC use can lead to delayed diagnosis and reduce the effectiveness of subsequent surgical treatment due to "masking" typical symptoms of the disease [12].

It is proven that progestins suppress estrogen action, slowing the growth of endometriotic tissue, and

[3] ESHRE Endometriosis Guideline Development Group. Endometriosis Guideline; European Society of Human Reproduction and Embryology; 2022. 192 p. Available from: https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Endometriosis-guideline

[4] Clinical Guidelines. Endometriosis. Russian Society of Obstetricians and Gynecologists; Rubricator of clinical recommendations; 2024. 62 p. Russian

also possess anti-inflammatory, antiproliferative, and antiangiogenic effects. Based on available data, it can be concluded that progestins are highly effective and affordable drugs with long-term safety and absence of estrogen-deficiency side effects [8, 13].

A systematic review by M.N. D'Alterio et al. established that progestins effectively relieve pain and improve quality of life; however, treatment should be personalized and consider the patient's condition, the need for surgery, and pregnancy planning [14]. For severe pain or lack of effect from previous methods, second-line therapy — GnRH agonists — may be prescribed, but their use is limited due to potential serious side effects. In clinical practice, the efficacy and side effect profile of all hormonal drugs are individual, and finding suitable therapy is often empirical[5]. Among gestagens registered in Russia for the treatment of endometriosis, dydrogesterone, norethisterone, and dienogest are the most studied, possessing different safety profiles and the possibility of therapy personalization.

These drugs promote regression of endometriotic foci with prolonged use. The high affinity of dienogest, and to a lesser extent norethisterone, not only for progesterone but also for steroid receptors, provokes the risk of adverse reactions. Consequently, due to low patient adherence to the drug regimen because of side effects, treatment becomes clinically ineffective and unsafe, which contributes to disease recurrence. The absence of dydrogesterone's connection to steroid receptors, compared to other progestins, as well as its high selectivity for progesterone receptors, reduces the risk of adverse reactions, increases safety, and improves treatment adherence. This allows for pain relief, improved quality of life, reduced risk of self-discontinuation of medication and subsequent endometriosis recurrence, and improved subjective assessment of clinical effect, which is necessary considering long-term therapy [15].

First-line drug therapy, especially in patients with mild to moderate pain syndrome, is considered to be progestins with a level of evidence 1a. These drugs induce a range of pharmacological effects that influence the pathogenetic links of endometriosis development, and also have systemic and local effects on the endometrium[6]. The interaction between progestins and target tissues occurs through specific gestagen receptors located both on the plasma membrane and within the cell. Binding sites realize rapid, millisecond-lasting, and slow, up to 1-hour-lasting, specific biological effects of gestagens, making this group of drugs the choice for first-line therapy in endometriosis. The main objectives are to induce anovulation and hypoestrogenemia, which promotes decidualization and acyclicity of both normal and ectopic endometrium. These effects are realized through various molecular mechanisms. The mechanism of action of gestagens in endometriosis is complex and occurs at multiple levels (Fig. 1). At the systemic level, they suppress the activity of the hypothalamic-pituitary-ovarian axis, leading to suppression of cyclic hormonal fluctuations and reduced estradiol production. Directly in endometriotic foci, gestagens induce decidualization of the stromal component, followed by atrophy of pathological tissue. Additionally, they cause secretory transformation of the glandular epithelium, which collectively leads to the regression of endometriotic heterotopias. Another mechanism is competitive binding with the estrogen receptor and anti-estrogenic action. Suppression of prostaglandin E2 synthesis leads to apoptosis activation and inhibition of cell proliferation and neovascularization. By activating 17β-hydroxysteroid dehydrogenase type 2, gestagens reduce estradiol activity levels by converting it to the less active estrone [16].

When considering various progestins from the perspective of efficacy and safety in treating endometriosis-associated pelvic pain, differences in molecular structure, receptor affinity, and pharmacokinetic characteristics must be taken into account. The ideal progestin should be a progesterone receptor agonist and not possess activity towards androgen, mineralocorticoid, estrogen, or glucocorticoid receptors. The assessment of progestin activity is usually conducted at the preclinical stage of research using animal models. Next, we will consider the main progestins available for endometriosis treatment in the Russian Federation.

Dydrogesterone has been used since the 1960s for the treatment of menstrual cycle disorders,

[5] ESHRE Endometriosis Guideline Development Group. Endometriosis Guideline; European Society of Human Reproduction and Embryology; 2022. 192 p.

[6] Ibid.

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DOI: 10.19163/2307-9266-2026-14-1-4-17

endometriosis, and threatened miscarriage. It is a retroprogesterone, close in structure and properties to natural progesterone [17]. Its structural features ensure high selectivity for progesterone receptors with practically no agonistic influence on other steroid receptors. The key advantage is a pronounced progestogenic effect without the side effects characteristic of other progestins [18].

On the one hand, dydrogesterone has low bioavailability; on the other hand, the key advantage of this drug is its metabolism without the involvement of the cytochrome P450 system. Dydrogesterone has a short half-life and no active metabolites, which collectively may require dosing twice daily.

Dienogest (or 17α-cyanomethyl-17β-hydroxy-estra-4,9-diene-3,1) is a derivative of 19-nortestosterone, a selective 4-generation progestin [19]. A distinctive feature of the molecule is an additional double bond between carbon atoms 9 and 10, as well as the absence of an ethinyl radical at the 17th atom, replaced by a cyanomethyl radical. Thanks to these structural modifications, dienogest combines the pharmacological properties of 19-norprogestins and progesterone derivatives. It affects key transcription factors such as AEBP1, HOXB6, KLF2, and RORB. The drug's mechanism of action is based on suppressing cytokines in the stroma of endometrial cells, providing a strong progestogenic and moderate estrogen-suppressing effect, as well as anti-inflammatory, antiproliferative, and antiangiogenic properties without significant androgenic, mineralocorticoid, or glucocorticoid effects [20–22].

Other advantages of the drug include high bioavailability when taken orally, a short half-life, selectivity for progesterone receptors, and no interaction with sex hormone-binding globulin. It is noted that dienogest is particularly suitable for patients with delayed reproductive plans, as it does not negatively affect ovarian reserve and protects ovarian tissue [23]. Dienogest is a weak inhibitor of CYP2C19 and CYP3A4 and can slow down the metabolism of other drugs, increasing their concentration and the risk of side effects. Active metabolites of dienogest circulate in plasma for a long time, ensuring high efficacy with a single dose, and are primarily excreted in feces, making it a drug of choice for patients with impaired renal function [19].

Norethisterone acetate is a 2-generation derivative of 19-nortestosterone, a representative of the numerous group of synthetic progestins — testosterone derivatives [24]. Modification of the testosterone molecule reduced androgenic activity, but nevertheless, this drug has a pronounced affinity for androgen receptors [25]. Positive effects of this drug include: reduction of CPPS, dysmenorrhea, and dyspareunia. Among the negative effects are dyslipidemia, weight gain due to metabolic disorders, and hyperinsulinemia with prolonged use of low doses [26]. Androgenic properties cause a number of adverse clinical manifestations: acne, hirsutism, and fluid retention. With the use of high doses of this progestin, an increase in the atherogenic index and an increased risk of cardiovascular complications occur [27]. Norethisterone acetate is a prodrug; upon absorption, it undergoes primary metabolism in the liver, and the metabolite has high bioavailability. The drug circulates in plasma primarily bound to proteins. The enzyme CYP3A4 is involved in the metabolism of norethisterone acetate, so drug interactions with inducers and inhibitors of this enzyme are possible. The elimination half-life of 8 to 12 hours allows for once-daily administration. It is mainly excreted in urine as conjugates. A comparative pharmacological profile of progestins is presented in Table 1.

Clinical Efficacy of Progestins

Long-term therapy is necessary to prevent endometriosis recurrence in women not planning pregnancy. Progestins vary significantly in cost, and inexpensive options should also be used as first-line therapy [28, 29].

Dydrogesterone is widely used in endometriosis therapy due to its safety profile and its unique ability not to suppress ovulation. However, its use is accompanied by several issues in the evidence base that limit definitive conclusions about its efficacy. These issues include an insufficient number of large randomized trials, a limited number of studies comparing the efficacy of different progestins, and their inconsistency, which adds uncertainty to the conclusions. To date, there are no reliable predictors of individual patient response and the effectiveness of a particular progestin, leading to misinterpretation of the drug's overall ineffectiveness.

One of the latest meta-analyses included 14 studies comparing dydrogesterone with placebo, letrozole, gestrinone, GnRH-α leuprolide, danazol, norethisterone acetate, and depot medroxyprogesterone acetate, as well as coagulation of endometriotic foci; and with no treatment after surgery. It was found that comparative analysis was not performed for dydrogesterone in 5 studies. There is minimal evidence of the efficacy and safety of dydrogesterone in endometriosis treatment due to a limited number of randomized controlled trials. Based on the available data, it is concluded that dydrogesterone may have some advantages over gestrinone, GnRH agonists, and other therapeutic interventions in endometriosis treatment. However, this conclusion should be approached with caution [30].

The efficacy of dydrogesterone in endometriosis-associated pelvic pain has been evaluated in several studies. Results from a prospective Russian study conducted in 2018–2021 at the gynecological department of the clinic of obstetrics and gynecology of Pavlov First Saint Petersburg State Medical University indicate the efficacy of dydrogesterone in CPPS therapy. Within the study, the effectiveness of various conservative treatment methods for endometriosis-associated pain syndrome was assessed before laparoscopic verification of the diagnosis. In the study group of 115 patients, a high rate of disease recurrence was recorded — 52 % (61 cases), which was associated with irrational drug use and low treatment adherence. Analysis of previous therapy also showed that 24 % of patients (28 individuals) received COCs without appropriate indications, 35 % (40 individuals) received nonsteroidal anti-inflammatory drugs, and 25 % (29 individuals) received other drugs prescribed by specialists from related fields. 20 patients (17 %) had no therapy, which led to disease progression and required surgical intervention. The study itself was conducted in three stages. In the first stage, after obtaining informed voluntary consent, preoperative examination was performed, including assessment of pain intensity using the Visual Analog Scale (VAS), clinical and instrumental diagnostics, and laparoscopic intervention. In the second stage, morphological and immunohistochemical examination of the surgical material was carried out to confirm the diagnosis. The third stage included dynamic observation in the postoperative period with assessment of long-term results at 6 and 12 months. The monitoring program included analysis of pain syndrome dynamics, quality of life indicators (SF-36, Short Form-36 quality of life assessment questionnaire), sexual function (FSFI, Female Sexual Function Index), registration of complications, disease recurrences, and cases of pregnancy in patients with infertility. The use of a combined approach, including surgical treatment followed by long-term anti-relapse therapy with dydrogesterone, demonstrated a statistically significant reduction in endometriosis symptoms ($p < 0.0001$) and improvement in quality of life indicators ($p < 0.05$) after 12 months [31].

A similar study conducted in India, involving 98 patients, also demonstrates the high clinical efficacy of the drug. Patients were prescribed dydrogesterone 10 mg or 20 mg per day in severe cases orally from day 5 to day 25 of the menstrual cycle for 3–6 months, with assessments every 3 months. CPPS significantly decreased ($p = 0.05$) from a mean baseline score of 1.24 ± 1.01 to 0.87 ± 0.86 (a 29 % reduction) after the first month of treatment. By the end of the sixth treatment cycle, the reduction in CPPS compared to baseline was 95 %, 87 %, and 85 %, respectively; improvement in endometriosis-associated pelvic pain symptoms was observed in 71% of patients [32].

Thanks to the widespread and prolonged use of dydrogesterone in global practice, as well as its market availability, extensive clinical experience has been accumulated. The question of comparative efficacy between continuous therapy at doses from 10 to 30 mg/day and prolonged cyclic therapy (from day 5 to day 25 of the menstrual cycle) in relieving endometriosis-associated pelvic pain and improving patients' quality of life remained open for a long time. Within the prospective observational multicenter study "ORCHIDEYA," involving 350 women and conducted in real clinical practice settings in Russian medical centers, the clinical effects of dydrogesterone therapy in patients with endometriosis were studied depending on the administration regimen. Participants received the drug according to one of two standard regimens: 10 mg — 2–3 times daily continuously or in a prolonged cyclic regimen from day 5 to day 25 of the menstrual cycle. The study included three visits: baseline, 3 months, and 6 months of therapy. It was found that both administration regimens — prolonged cyclic and continuous — led to a significant reduction

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DOI: 10.19163/2307-9266-2026-14-1-4-17

in CPPS intensity, improvement in quality of life, and enhancement of sexual well-being. The mean change in pain indicators was -3.3 (standard deviation [SD] = ±2.2; $p < 0.0001$ compared to baseline) for patients receiving the prolonged cyclic therapy regimen, and -3.0 (SD = ±2.2; $p < 0.0001$ compared to baseline) for patients receiving the continuous therapy regimen, with no statistically significant differences between the groups [33]. The study results demonstrate the effectiveness of therapy in treating endometriosis.

Dienogest is of particular interest with a well-studied evidence base. The drug is an effective agent for the long-term treatment of all endometriosis phenotypes, as well as for postoperative therapy. Dienogest's advantages include minimal impact on metabolic parameters. This progestin has minimal effects on protein, lipid, and carbohydrate metabolism. L.V. Adamyan's demonstrated that dienogest administration allows for the discontinuation of NSAIDы use for endometriosis-associated pelvic pain. In a group of 24 patients aged 18 to 45 years with histologically confirmed endometriosis between 2021 and 2022, they were divided into subgroups of 12 people each. The first group received the progestin at a dosage of 2 mg per day; the second group received NSAIDs — ibuprofen. All women underwent minimally invasive surgery, the choice of which depended on the location of endometriotic foci. Further patient follow-up revealed a significant reduction in pelvic pain intensity on the VAS scale in the 1 group: mild — in 2 (16.67 %), moderate — in 7 (58.33 %), severe — in 3 (25 %), as well as improvement in sexual quality of life. In the 2 group, women taking NSAIDs for pain syndrome did not report positive changes during treatment; the intensity of pain syndrome on the VAS scale was: mild — in 3 (25 %), moderate — in 5 (41.67 %), severe — in 4 (33.3 %) [34].

In a systematic review by A. Samy et al., 36 RCTs were analyzed. The authors concluded that dienogest (0.94), COCs (0.782), and elagolix (0.38) showed the best results in reducing CPPS after 3 months. For reducing CPPS after 6 months of therapy, GnRH agonists (0.75), the levonorgestrel-releasing intrauterine system (0.73), and dienogest (0.65) were the most suitable medications. However, when ranking drugs by p-score, GnRH agonists (0.63) and elagolix (0.54) showed the best results in reducing CPPS after 3 months, and desogestrel (0.94) and COCs (0.91) after 6 months [35].

In a randomized study of COCs containing 2 mg of dienogest or 1.5 mg of 17b-estradiol and 2.5 mg of nomegestrol acetate, women receiving COCs with dienogest showed a more pronounced improvement in quality of life and sexual function on the SF-36 ($p < 0.01$) and FSFI ($p < 0.006$) scales [36]. In a study comparing norethisterone acetate and dienogest, the latter showed higher efficacy and a lower risk of side effects [37]. Studies evaluating the efficacy between progestins and GnRH agonists have demonstrated comparable efficacy in CPPS therapy [22, 38].

Comparing side effects between dienogest and GnRH agonists, treatment with the former significantly increases the frequency of spotting ($p = 0.0007$) and weight gain ($p = 0.03$); however, a lower frequency of estrogen-deficiency states in the form of hot flashes and vaginal dryness ($p = 0.0006$) was noted [39]. It is worth noting that with approximately comparable levels of CPPS relief, progestins provide significantly less hypoestrogenemia and demineralization.

While dienogest demonstrates high efficacy and a favorable safety profile, another synthetic progestin, norethisterone acetate, also holds an important place in endometriosis therapy. Analysis of studies dedicated to the use of this drug allows for a comparative assessment of its therapeutic value.

P. Vercellini et al. study involved 190 patients, standard doses of norethisterone acetate 2.5 mg once daily and dienogest 2 mg once daily were compared. Progestins were administered from day 1 of the menstrual cycle continuously, and results were analyzed after 6 months of use. Efficacy was assessed using a developed scale for non-menstrual pelvic pain. The drugs showed comparable efficacy in reducing pain intensity. The proportion of satisfied and very satisfied women was 71 % in the norethisterone acetate group and 72 % in the dienogest group. The use of the latter was not associated with a statistically significant improvement in overall pain relief, psychological state, sexual function, or health-related quality of life. Treatment was well tolerated by 58% of women in the norethisterone acetate group compared to 80 % of participants in the dienogest group. The study authors suggest that certain advantages of dienogest over norethisterone acetate in their study were due to the low dosage of the latter [26].

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)

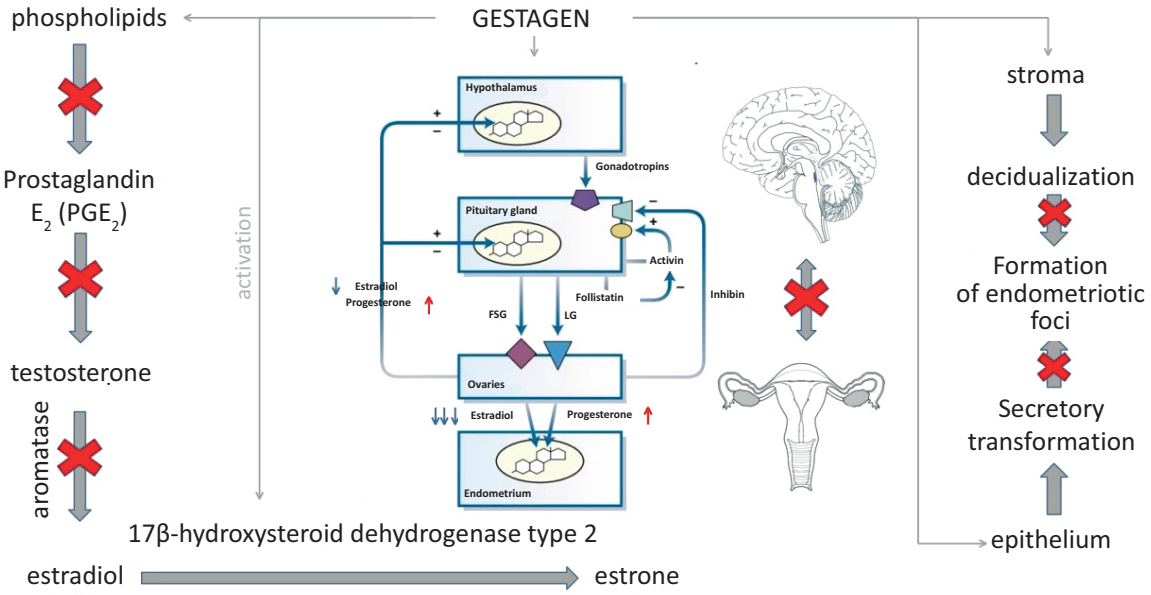

Figure 1 – Mechanism of Action of Progestins.

Table 1 – Pharmacokinetics and pharmacological effects of progestins

Parameter	Dydrogesterone	Dienogest	Norethisterone acetate
Pharmacokinetics*			
Chemical classification	Synthetic progesterone analog	Nortestosterone derivative	19-nortestosterone derivative
Prodrug	No	No	Yes
Bioavailability	Low 28 %	High 91 %	High 60 %
Metabolism involving P450 *(CYP450)*	No	Yes	Yes
Active metabolites	No	Yes	Yes
Half-life, h	5–7	9–10	8–12
Excretion	Urine 70 %	Primarily feces	Urine — 60 %, feces — 40 %
Pharmacological effects [24]			
Anti-estrogenic activity	Effective	Moderately effective	Effective
Anti-androgenic activity	Moderately effective	Effective	Ineffective
Anti-mineralocorticoid activity	Moderately effective	Ineffective	Ineffective
Estrogenic activity	Ineffective	Moderately effective	Effective
Androgenic activity	Ineffective	Ineffective	Effective
Glucocorticoid activity	Ineffective	Ineffective	Ineffective

Note: * — data on pharmacokinetic parameters are taken from official drug instructions available on the grls.minzdrav.gov.ru website.

Table 2 – Side effects of progestins*

Parameter	Dydrogesterone	Dienogest	Norethisterone acetate
Reproductive system			
Ovulation suppression	Yes	Yes	Yes
Abnormal uterine bleeding	No	Yes	Yes
Amenorrhea	No	Moderate frequency	No
Functional ovarian cysts	Yes	Yes	Yes
Mastalgia	Low frequency	Low frequency	Moderate frequency
Metabolism			
Effect on lipid profile	Minimal/neutral	Moderate	Significant
Effect on carbohydrate metabolism	Minimal	Minimal	Moderate
Risk of weight gain, fluid retention	Minimal	Moderate	Moderate/High
Nervous system			
Headaches	Minimal	Yes	Yes
Mood swings	Minimal	Yes	Yes
Decreased libido	Minimal	Minimal	Moderate
Skin reactions			
Acne	No	Minimal	Moderate
Hirsutism	No	Minimal	Minimal

Note: * — table compiled using sources [20, 26, 33, 35–37, 45].

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DOI: 10.19163/2307-9266-2026-14-1-4-17

In the study by T.B. Gurbuz et al., the efficacy and safety of dienogest and norethisterone acetate were evaluated in patients with endometriosis-associated pelvic pain. The dienogest group (2 mg per day) included 40 patients, and the norethisterone acetate group (5 mg per day) included 30 patients. Pain severity was assessed on the VAS scale before treatment initiation, then at 6 and 12 months. Safety was assessed by the prevalence of side effects and the willingness to continue taking the drug throughout the treatment period. The drugs showed comparable efficacy in reducing pain on the VAS scale. Patients in the dienogest group discontinued treatment significantly more often and earlier than patients in the norethisterone acetate group. At six months, there were 23 patients in the norethisterone acetate group and 21 in the dienogest group; however, 16 patients in the norethisterone acetate group and 18 patients in the dienogest group completed treatment. Side effect profiles were comparable, but the dropout rate from the study after six months was higher in the dienogest group (47.5 % vs. 23.3 %; $p = 0.026$). The study authors concluded that norethisterone acetate may be an effective alternative to dienogest therapy [40].

In a retrospective cohort study by T.B. Gurbuz et al., conducted in Italy, long-term effects of treating rectovaginal endometriosis were studied. 103 women completed norethisterone acetate treatment, with a follow-up period of 5 years; the primary endpoint was treatment satisfaction after 5 years of use. Over 68 % of women who completed the study were satisfied or very satisfied with the drug. Side effects were the reason for discontinuation of treatment in 38.1% (16 women). According to the study authors, norethisterone acetate is an optimal drug for long-term treatment of rectovaginal endometriosis, considering its low cost and favorable pharmacological profile [41].

The study by S. Ferrero et al. included 40 patients with confirmed colorectal endometriosis. A twelve-month course of norethisterone therapy led to a significant reduction in pain syndrome, dyskinesia, and deep dyspareunia. After using the progestin for 12 months, a reduction in pain syndrome severity was noted — 3.5 ± 1.6 points ($p < 0.001$), dyskinesia, and deep dyspareunia. Furthermore, a trend towards a decrease in the frequency of dysmenorrhea and cyclical rectal bleeding was observed [42].

Safety and Side Effects of Progestins

The renaissance of scientific and clinical interest in dydrogesterone occurred after the first expected side effects from progestins with androgenic, glucocorticosteroid, and mineralocorticoid activity were identified. It is precisely such common adverse reactions as weight gain, emotional lability, decreased libido, rash, and hirsutism that cause low patient compliance with treatment and become frequent reasons for non-adherence to the treatment regimen and, consequently, treatment ineffectiveness, as well as endometriosis recurrence. Progestin side effects are presented in Table 2.

It has been established that the high efficacy of dydrogesterone at a relatively low dosage minimizes the adverse reactions characteristic of most progestins. It is also important to remember that to ensure an effect in the context of possible progesterone resistance, the gestagen's binding to receptors must be higher than that of endogenous progesterone [15]. Undoubtedly, dydrogesterone is a metabolically neutral drug that carries minimal side effects. Norethisterone acetate has weak androgenic activity and can cause hirsutism, acne, and negatively affect the lipid profile. The drug reliably suppresses luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion.

In the studies we examined, both with short-term and long-term use of dienogest, patients also experienced adverse reactions. According to the results of a pooled analysis of four studies conducted within the European research program, the most common adverse events with dienogest were headache, breast discomfort, acne, depressed mood, nausea, and weight gain [44].

In the study by B. Cho et al., the most frequent side effects were abnormal uterine bleeding (AUB) in 129 (4.14 %) patients, weight gain in 80 (2.57 %) patients, and headaches in 38 (1.22 %) patients. Analyzing the causes of adverse drug reactions, the authors concluded that patients with a history of allergies had a significantly higher risk of their occurrence with combination therapy or concomitant treatment compared to those without [20].

In the work by F. LaTorre et al., a study of long-term dienogest treatment for 36 months was conducted. At the first follow-up after starting dienogest, after 12 months, 23 % of 114 patients experienced breakthrough bleeding, of which 52 % had spotting, 38 % had light bleeding, and 10 % had moderate bleeding; 22 patients (19 %) discontinued the drug. Among the known reasons for treatment discontinuation were: side effects (36 %), ineffectiveness (27 %), a combination of ineffectiveness and side effects (23 %), desire to become pregnant (9 %), and seeking contraception (5 %). After 36 months of follow-up, among the adverse reactions that led to discontinuation of dienogest treatment, the most frequent were: unsatisfactory contraception, decreased

libido, vaginal dryness, and mood swings. On average, treatment was discontinued after 7.2 months. The most frequently registered side effects were fluid retention (29.3 %), weight gain (26 % with a mean of 2.0 kg), AUB (22.9 %), breast tenderness (20.7 %), abdominal bloating (18.7 %), mood swings (17.4 %), headache (16.3 %), decreased libido (15.2 %), vaginal dryness (15.2 %), hot flashes (10.9 %), acne (10.8 %), hair loss (9.8 %), insomnia (8.7 %), seborrhea (6.6 %), and hirsutism (6.6 %) [45].

R. Vercellini et al. conducted a comparison of standard doses of norethisterone acetate 2.5 mg once daily and dienogest 2 mg once daily in 180 study participants. In terms of adverse drug reactions, both groups had a comparable frequency of occurrence. However, on average, women gained weight twice as often when taking norethisterone acetate—28 patients (n = 89) — than in the dienogest group — 14 women (n = 85) %. Spotting was reported by 22 % of patients in the norethisterone acetate group and 16 % in the dienogest group. After 6 months of treatment, 24 out of 90 women in the norethisterone group were very satisfied with their treatment, 40 were satisfied, 1 was neither satisfied nor dissatisfied, 15 were dissatisfied, and 10 were very dissatisfied. In the dienogest group, the figures were: 45 out of 90 patients — very satisfied, 20 — satisfied, 1 (1 %) — neither satisfied nor dissatisfied, 14 — dissatisfied, and 10 — very dissatisfied [26].

At the present stage, the choice of treatment strategy is complex and should be based on a thorough assessment not only of the clinical status but also of drug tolerability, progesterone sensitization, and safety profile analysis [46, 47]. Clinicians are also advised to consider reversible and irreversible side effects when determining which therapy may be most suitable for specific patient groups [48, 49]. Thus, given the multifactorial nature of endometriosis-associated pelvic pain, a systematic monitoring and management of the progestin therapy safety profile is a critical component of a long-term therapeutic strategy, enabling sustained disease control while maintaining a high quality of life for patients [50].

Review Limitations

The conducted study has several important limitations that may affect the interpretation and generalization of the obtained results.

Limitation of design and methodology. The authors conducted a non-systematic review, which is the main limitation of this study. A systematic review's distinguishing advantage is the reproducibility of results and transparency of methodology. In our case, the choice was made in favor of a narrative review, as the studies included in this work were extremely heterogeneous. Different criteria were used in various articles to establish the diagnosis of endometriosis and evaluate the results of its treatment.

Small studies and retrospective design. A significant number of studies were retrospective and had small sample sizes. Large pharmacoepidemiological studies evaluating the efficacy of a particular drug in the long term are lacking.

Contradictory results. Significant contradictions were found in the results of different studies regarding safety and adherence.

CONCLUSION

Currently, dydrogesterone is one of the strategic options for treating endometriosis-associated pelvic pain, especially in certain population groups with dyslipidemia, diabetes mellitus, and obesity. The drug does not negatively affect the lipid profile as it does not lower high-density lipoprotein levels, which is crucial for patients with an existing risk of cardiovascular diseases; it does not worsen tissue sensitivity to insulin and has minimal impact on carbohydrate metabolism, making it a safe treatment option for women with diabetes mellitus or a high risk of its development. For patients with obesity or those at increased risk of thromboembolic complications, dydrogesterone is a more preferred alternative to progestins with high thrombogenic activity. Thus, dydrogesterone represents a first-line therapy drug for high-risk patients, without worsening metabolic disorders.

As mentioned earlier, its main difference from other progestins lies in its molecular structure, which ensures safety, metabolic neutrality, and minimal side effects necessary for long-term therapy. Dydrogesterone's high safety profile is a key advantage in the long-term treatment of endometriosis. Despite this, all available progestins today hold their rightful place in the symptomatic and pathogenetic treatment of CPPS and other symptoms caused by endometriosis. Large multicenter RCTs are needed to clarify dydrogesterone's administration regimens, dosages, treatment duration, comparisons with other progestins, and the possibility of combination with other drugs effective in endometriosis treatment. It is important to develop an algorithm for more personalized therapy, considering potential side effects.

According to the recommendations of the European Society of Human Reproduction and Embryology (ESHRE), the choice of a specific progestin for endometriosis therapy should be determined precisely by the individual side effect profile of each

drug. This approach represents a key direction for optimizing long-term disease management. The implementation of personalized progestin selection principles in clinical practice can significantly improve patient adherence to treatment and enhance their quality of life. The therapy optimization strategy should include: thorough assessment of individual risk factors for adverse reactions and comorbidities in women, regular monitoring of treatment tolerability throughout the course of therapy, timely correction of the treatment regimen if side effects occur, and consideration of reproductive plans. The implementation of this approach, recommended by ESHRE, contributes to achieving an optimal balance between treatment efficacy and tolerability, which is the key to successful long-term disease control.

FUNDING

This study did not have financial support from third-party organizations.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Petrov V.I. — conceptualization, writing — review & editing; Kulakova I.S., Gorbatenko V.S. — data collection, writing — original draft, writing — review & editing; Bezuglov I.D. — data collection, visualization, writing — original draft, writing — review & editing; Ignatova A.S — data collection, writing — original draft; Shatalova O.V. — supervision, writing — review & editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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AUTHORS

Vladimir I. Petrov — Doctor of Sciences (Medicine), Professor, Head of the Department of Clinical Pharmacology and Intensive Care of the Volgograd State Medical University; Chief freelance specialist — Clinical Pharmacologist of the Ministry of Health of the Russian Federation; Honored Scientist of the Russian Federation; Honored Doctor of the Russian Federation; Academician of the Russian Academy of Sciences. ORCID ID: 0000- 0002-0258-4092. E-mail: brain@sprintnet.ru

Iraida S. Kulakova — applicant of the Department of Clinical Pharmacology and Intensive Care of the Volgograd State Medical University; obstetrician-gynecologist, Dochki-Materi Clinics (Volgograd). ORCID ID: 0000-0002-2717-8218. E-mail: iraida97@mail.ru

Vladislav S. Gorbatenko — Candidate of Sciences (Medicine), Assistant Professor of the Department of Clinical Pharmacology and Intensive Care of the Volgograd State Medical University. ORCID ID: 0000-0002-6565-2566. E-mail: vlad30.03@mail.ru

Olga V. Shatalova — Doctor of Sciences (Medicine), Professor of the Department of Clinical Pharmacology and Intensive Care of the Volgograd State Medical University. ORCID ID: 0000-0002-7311-4549. E-mail: shov_med@mail.ru

Ivan D. Bezuglov — 6th year student of the Faculty of Medicine of the Volgograd State Medical University. ORCID ID: 0009-0007-1579-5765. E-mail: i.bezuglov.d@bk.ru

Anastasia S. Ignatova — 6th year student of the Faculty of Medicine of the Volgograd State Medical University. ORCID ID: 0009-0000-1140-5124. E-mail: 9281459863@mail.ru