DOI: https://doi.org/10.17816/aog631635

Long-term pharmacotherapy in patients with uterine myoma: assessment of effectiveness

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ABSTRACT

BACKGROUND: Uterine myoma is one of the most prevalent gynecological diseases. Data concerning the effects of the medicinal agents used in patients with uterine leyomyomas, are both scientifically and practically important.

AIM: This study aims to assess the clinical, laboratory, and instrumental effectiveness of 5-year use of micronized oral contraceptive containing estrogen and progestogen, intrauterine levonorgestrel-releasing system and progesterone receptor modulator in patients with uterine myoma.

MATERIAL AND METHODS: Patients aged from 21 to 40 years old were assigned to 3 arms in accordance with the treatment regimen. Group 1 included 42 women with myomas ⩽2 cm in diameter. These patients received combined oral contraceptive pills containing ethinylestradiol 20 mcg and desogestrel 150 mg according to the conventional contraceptive regimen, i.e. one pill daily, 21-day courses with following 7-day pauses. Group 2 included 34 women with uterine myoma and concomitant uterine endometriosis. In this group, the intrauterine devices containing levonorgestrel were inserted. Group 3 included 33 patients treated with the progesterone receptor modulator in order to reduce the diameter of uterine myomas. They received oral mifepristone at a dose of 50 mg daily for three months, followed by a 3-month pause and subsequent 3-month course of treatment. During the year, two cycles that included 3-month treatment course and 3-month treatment-free period, were repeated. All patients underwent standard clinical, laboratory and instrumental gynecological examination. Statistical processing was performed in the basis of Statistica 12.0 software.

RESULTS: In Group 1, 80.9% of patients exhibited unchanged mean diameters of uterine myomas all over the course of treatment with contraceptive drugs, 16.7% of patients demonstrated growth of myoma (by 15%), while in 2.4% of patients myoma reduction (by 5%) was observed. In Group 2, the increase in the diameter of leiomyoma ranged from 20 to 30 percent was observed following the insertion of intrauterine levonorgestrel-releasing system in 58.8 percent of patients. In contrast, 35.3 percent of patients exhibited no change in myoma size, while a decrease by 15 percent was observed in only 5.9 percent of patients. In Group 3, 10 intermittent 3-month courses of mifepristone (50 mg) resulted in the reduction of uterine myoma by 40%–50% of the baseline diameter in 97.0% of patients. In general, the study drugs demonstrated beneficial effects and safety in patients with leiomyoma.

CONCLUSION: The long-term use of low-dose oral contraceptives generally leads in the stabilization of the size of uterine myomas, while intrauterine levonergestrel-releasing system prevents their intensive growth. Nevertheless, the use of a drug belonging to the progesterone receptor modulator class, has proven to be the most effective approach to reducing the size of myomas.

Keywords: uterine myoma; mifepristone; intrauterine levonorgestrel-releasing system; micronized combined oral contraceptives.

To cite this article:
Sinchikhin SP, Magakyan OG, Sinchikhina ES. Long-term pharmacotherapy in patients with uterine myoma: assessment of effectiveness. *V.F. Snegirev Archives of Obstetrics and Gynecology.* 2024;11(4):470–479. DOI: https://doi.org/10.17816/aog631635

Received: 04.05.2024 **Accepted:** 27.08.2024 **Published online:** 12.12.2024

DOI: https://doi.org/10.17816/aog631635

Оценка эффективности пролонгированного применения медикаментозных средств у пациенток с миомой матки

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АННОТАЦИЯ

Обоснование. Миома матки относится к наиболее часто встречающимся гинекологическим заболеваниям. Научно-практический интерес представляют сведения о действии лекарственных препаратов, которые используются у пациенток с лейомиомой.

Цель. Провести клинико-лабораторно-инструментальную оценку 5-летнего применения у пациенток с миомой матки микронизированного орального контрацептива, содержащего эстроген-гестаген, внутриматочной левоноргестрел-высвобождающей системы и модулятора прогестероновых рецепторов.

Материал и методы. Пациентки от 21 года до 40 лет были разделены на 3 группы в зависимости от предложенной терапии. В 1-ю группу вошли 42 женщины с размерами узлов миомы матки, не превышающими 2 см. Пациенткам был рекомендован комбинированный оральный контрацептив, состоящий из этинэстрадиола (20 мкг) и дезогестрела (150 мг), который они принимали в обычном режиме контрацепции: ежедневно по 1 таблетке в течение 21 дня с последующим 7-дневным перерывом. Во 2-ю группу были включены 34 женщины, у которых миома матки сочеталась с аденомиозом, им была поставлена внутриматочная спираль, содержащая левоноргестрел. В 3-ю группу вошли 33 пациентки, у которых для уменьшения размеров узлов миомы матки использовали модулятор прогестероновых рецепторов: мифепристон в дозе 50 мг принимали ежедневно *per os* по 1 таблетке в день в течение трёх месяцев, затем — перерыв на три месяца, далее — повторный приём препарата в указанном режиме ещё три месяца. В течение года дважды применяли 3-месячный курс терапии указанным препаратом с двукратным перерывом. Пациенткам всех групп выполняли стандартный комплекс гинекологического клинико-лабораторно-инструментального обследования. При статистической обработке использовали программу Statistica 12.0.

Результаты. В 1-й группе у 80,9% пациенток отмечалось сохранение средних размеров узлов миомы матки на уровне начала приёма контрацептивных препаратов, у 16,7% — наблюдался рост (на 15%) миоматозных узлов, а их уменьшение (на 5%) — у 2,4% наблюдаемых. Во 2-й группе на фоне внутриматочной левоноргестрел-высвобождающей системы увеличение (на 20–30%) размеров узлов лейомимы через 5 лет произошло у 58,8% пациенток, сохранились стабильные размеры — у 35,3%, уменьшение (на 15%) размеров узлов наблюдалось только у 5,9% пациенток. В 3-й группе после 10 периодически повторяющихся 3-месячных курсов терапии мифепристоном (50 мг) уменьшение на 40–50% от первоначальных размеров узлов миомы матки произошло у 97,0% пациенток. В целом отмечены положительные эффекты и безопасность применения указанных препаратов у пациенток с лейомиомой.

Заключение. При длительном применении в большинстве случаев микродозированные пероральные контрацептивные средства стабилизируют размеры узлов миомы матки, а внутриматочная левонергестрел-высвобождающая система предупреждает их интенсивный рост. Вместе с тем наилучший эффект, направленный на уменьшение размеров миоматозных узлов, наблюдался при применении препарата, относящегося к модуляторам прогестероновых рецепторов.

Ключевые слова: миома матки; мифепристон; внутриматочная левоноргестрел-высвобождающая система; микронизированные комбинированные оральные контрацептивы.

Как цитировать:
Синчихин С.П., Магакян О.Г., Синчихина Е.С. Оценка эффективности пролонгированного применения медикаментозных средств у пациенток с миомой матки // Архив акушерства и гинекологии им. В.Ф. Снегирёва. 2024. Т. 11, № 4. С. 470–479. DOI: https://doi.org/10.17816/aog631635

Рукопись получена: 04.05.2024 **Рукопись одобрена:** 27.08.2024 **Опубликована online:** 12.12.2024

DOI: https://doi.org/10.17816/aog631635

对子宫肌瘤患者长期使用药物的疗效评估

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摘要

背景。子宫肌瘤是最常见的妇科疾病之一。研究治疗子宫平滑肌瘤患者所使用药物的作用具有重要的科学和实践意义。

研究目的。对使用含雌激素-孕激素的微粉化复方口服避孕药、左炔诺孕酮释放宫内系统及孕激素受体调节剂治疗子宫肌瘤患者的5年疗效进行临床、实验室及仪器评估。

材料与方法。研究对象为21至40岁的患者，根据推荐的治疗方案分为三组：1. 第一组（42名患者）：子宫肌瘤结节直径不超过2厘米，服用含炔雌醇（20 μg）和去氧孕烯（150 μg）的复方口服避孕药，每天服用1片，连续21天，之后停药7天，按照避孕常规使用；2. 第二组（34名患者）：患有子宫腺肌症和子宫肌瘤，使用含左炔诺孕酮的宫内节育器；3. 第三组（33名患者）：为缩小子宫肌瘤结节，使用孕激素受体调节剂米非司酮，每天口服50 mg，连续服用3个月后停药3个月，再次进行两轮同样方案的治疗，每年完成两个周期。所有患者均接受标准的妇科临床、实验室及仪器检查。数据统计分析采用Statistica 12.0软件。

结果。第一组：80.9%的患者结节大小保持稳定，16.7%的患者出现结节增长（平均增长15%），2.4%的患者结节缩小（平均缩小5%）。第二组：使用左炔诺孕酮释放宫内系统后，58.8%的患者结节增长（20–30%），35.3%的患者结节大小保持稳定，仅5.9%的患者结节缩小（15%）。第三组：经过10个3个月周期的米非司酮治疗后，97.0%的患者结节大小减少40–50%。总的来说，这些药物在治疗子宫平滑肌瘤患者中显示出良好的效果和安全性。

结论。长期使用微剂量口服避孕药在大多数情况下可稳定子宫肌瘤结节大小，左炔诺孕酮释放宫内系统可预防结节的快速生长。然而，最佳效果体现在使用孕激素受体调节剂（米非司酮）时，显著缩小了结节大小。

关键词：子宫肌瘤；米非司酮；左炔诺孕酮释放宫内系统；微粉化复方口服避孕药。

引用本文:
Sinchikhin SP, Magakyan OG, Sinchikhina ES. 对子宫肌瘤患者长期使用药物的疗效评估. *V.F. Snegirev Archives of Obstetrics and Gynecology.* 2024;11(4):470–479. DOI: https://doi.org/10.17816/aog631635

收到: 04.05.2024 **接受:** 27.08.2024 **发布日期:** 12.12.2024

BACKGROUND

Uterine fibroids (UF) are one of the most common gynecological diseases, which, according to our data, affect 4% of women under 21 years of age, 31% of women between 21 and 40 years of age, and 65% of women between 40 and 50 years of age. In addition, in mid-reproductive age, uterine leiomyomas may be associated with infertility in 21% of cases, pregnancy loss in 27%, and ovarian dysfunction in 29% [1].

It is currently accepted that UF is a benign monoclonal tumor originating from the smooth muscle cells of the cervix or body of the uterus [2]. Monoclonality means that UF nodules originate from a single primary transformed mutant cell (myocyte) of the myometrium [3].

Given the absence of malignancy potential, UFs are biologically destined to undergo involution. The life cycle of a myomatous nodule can be divided into four phases. The first is the proliferative phase, during which the nodule experiences growth due to excessive extracellular matrix synthesis in comparison to the intensity of angiogenesis. The second phase is characterized by a progressive increase in the distance between myocytes and blood vessels, leading to interstitial ischemia. The third phase is marked by the progression of cellular degeneration and the subsequent atrophy of myocytes. The fourth phase is the result of dystrophic collapse, leading to the death of the transformed cell. In this case, the term "inanosis" is used to describe the cell death of the primary altered uterine leiomyoma myocyte [3, 4].

The etiology of the UF development remains elusive, despite the extensive research in the specialized scientific literature addressing its epidemiology, genetics, hormonal aspects, and molecular biology of this benign tumor [1–4]. However, elucidating the etiology and pathogenesis of uterine leiomyoma is crucial for comprehending not only the formation but also the progression of this neoplasm.

The growth of UFs was observed during both pregnancy and the luteal phase of the menstrual cycle [5]. Furthermore, it was demonstrated that 90% of proliferating UF cells have active progesterone receptors [6]. In leiomyoma tissue, progesterone was shown to enhance proliferation, inhibit apoptosis, and induce angiogenesis [3]. Consequently, clinical observations and scientific studies suggest that endogenous progesterone may be an important stimulator of UF growth [1, 3, 5, 6].

The widespread use of ultrasound allows detecting UF nodules before the pronounced clinical manifestations of the disease, including in women planning to have children in the future. However, during the entire reproductive period, there will be a tendency to increase the size of UF nodules with different intensity in certain periods of life under the influence of epigenetic factors [1–3].

According to foreign authors, the fastest growth is observed in intramural nodules up to 20 mm in size, whereas submucosal nodules of medium size grow the slowest [7]. However, the adoption of a waiting strategy may lead to the development of such myomatous nodules, which will result in infertility and complicated pregnancy and childbirth [1–4]. Therefore, the current trends include active strategies of patient management, which involve the use of medications and organ-preserving surgeries.

The choice of management strategy for patients with UF who wish to preserve their childbearing function should be strictly individual and take into account not only the size, location, and number of nodules, but also age, reproductive history, parity of childbirth, and concomitant gynecological and somatic pathologies [1–3].

It is hypothesized that for patients under 35 years of age with nodule sizes of 20 mm or less, microdosed combined oral contraceptives (COCs) with an estrogenic component of 20 μg will be the preferred method to stabilize UF growth [1–3, 8].

In cases of previously parous patients with concomitant adenomyosis, heavy menstruation, and myoma nodules that do not deform the uterine cavity, the use of an intrauterine levonorgestrel-releasing system was demonstrated to reduce clinical symptoms and stabilize leiomyoma growth [1–3, 8].

For patients of a more complicated category, characterized by multiple and relatively large (up to 6.5 cm) nodules, as well as for those who postpone childbearing for an indefinite time, it is reasonable and pathogenetically justified to prescribe mifepristone, an agent belonging to the modulators of progesterone receptors, in a prolonged mode. A notable pharmacological action of this pharmaceutical group is the inhibition of progesterone receptors in UF nodules. This hormone, as previously mentioned, was shown to enhance proliferation, inhibit apoptosis, and induce angiogenesis in uterine tissue [1, 3, 5, 9].

Among progesterone receptor modulators, the preparation containing 50 mg mifepristone in a tablet is currently approved for practical use in our country for conservative and long-term treatment of patients with UF.

In particular, in contrast to endogenous progesterone, mifepristone has a 10-fold greater ability to bind to progesterone receptors on the uterus [5, 8]. The primary mechanism of action of mifepristone is the formation of stable progesterone receptor dimers at the level of the endometrium and myometrium, which do not possess progestagenic activity [2, 3, 8]. Importantly, mifepristone does not affect bone mineral density or induce vascular reactions, as serum estradiol levels are consistent with those observed during the follicular phase [1, 3, 9].

Several studies have demonstrated the antiproliferative, proapoptotic, and antifibrinolytic effects of mifepristone on myomas, as well as its ability to reduce the expression of vascular endothelial growth factor in UMs [5, 6, 9].

The aim of the study was to conduct a clinical, laboratory, and instrumental evaluation of the five-year use of a micronized oral contraceptive containing estrogen-gestagen

DOI: https://doi.org/10.17816/aog631635

combination, as well as an intrauterine levonorgestrel-releasing system and a progesterone receptor modulator in patients with UMs.

MATERIALS AND METHODS

A total of 108 women with UFs were included in the prospective study. The age of the patients ranged from 21 to 40 years, with a mean age of 28.2 ± 2.9 years.

Exclusion criteria: patients under the age of 21 or over 40; those with indications for surgical treatment; those with contraindications for conservative therapy of UFs; and those without the possibility of regular and long-term gynecological medical supervision.

Inclusion criteria: reproductive age from 21 to 40 years; absence of indications for surgical treatment of leiomyoma; absence of contraindications and informed consent of the patient for the prescription of recommended drugs; plans to have children in the future; and regular periodic ultrasound examinations and gynecological consultations.

Patients were divided into three groups according to the proposed use of medications.

Group 1 comprised 42 women with myomatous nodules measuring no larger than 2 cm in size. These patients were prescribed a micronized COC containing ethinyl estradiol (20 μg) and desogestrel (150 mg) for the purpose of contraception and the prevention of progressive growth of myomatous nodules. The patients took the drug in the usual contraceptive regimen: 1 tablet daily for 21 days, followed by a 7-day break.

Group 2 comprised 34 women diagnosed with UF and adenomyosis, who were administered an intrauterine device containing levonorgestrel.

Group 3 included 33 women in whom a progesterone receptor modulator—a preparation containing 50 mg mifepristone—was used as conservative therapy to reduce the size and stabilize the growth of UF nodules. The patient took one tablet daily *per os* for three months, then took a 3-month break, and then took the drug again in the specified regimen for another three months. During the 12-month period, there were two 3-month courses of the indicated drug with a 2-month break.

The patients were followed for five years. The time period was determined by the allowable duration of intrauterine contraceptive use and the comparability of the specified follow-up time in relation to all patients. Mandatory routine consultations were performed at 1, 3, 6, and 12 months in the first year and then at 2, 3, 4, and 5 years from the start of follow-up.

A comprehensive clinical and laboratory evaluation was conducted, encompassing transvaginal ultrasound imaging of the pelvic organs. The primary focus of this evaluation was the measurement of the linear dimensions (largest diameter) of UFs, with particular attention directed toward the dominant nodule. Additionally, the uterine volume was determined for all patients, employing the Brunn's formula for calculation: (length × width × height) × 0.457.

The data obtained were then subjected to statistical processing using the Statistica 12.0 and SPSS Statistics software package. The mean value, standard error of the mean, and 95% confidence interval (CI) were calculated for the indicators. The CI of the relative frequency of binary signs was calculated using the Student's t-test. Differences were considered significant at $p < 0.05$.

RESULTS

Group 1 patients were younger and had a more favorable reproductive history and significantly fewer somatic pathologies that were not contraindications to contraceptive use (Table 1).

A significant proportion of patients in Group 2 had a history of instrumental scraping of the uterine mucosa for various reasons, including artificial abortion, miscarriage, undeveloped pregnancy, or intrauterine gynecological pathology (e.g., polyp, hyperplasia). The development of adenomyosis in this group of patients was probably precipitated by mechanical trauma to the endometrium during previous intrauterine surgical procedures (see Table 1).

The distinguishing characteristic of Group 3 patients was their older age and the prevalence of uncomplicated chronic extragenital diseases. Additionally, the proportion of women who had previously experienced pregnancy and childbirth was comparable to those who had not, with the latter group intending to have children in the future (see Table 1).

Notably, patients with menstrual dysfunctions were identified with equivalent frequency across all groups (see Table 1). However, the nature of the dysfunction varied. Thus, Group 1 patients exhibited a higher prevalence of menstrual dysfunction characterized by prolongation (*opsomenorrhea*) or shortening (*proiomenorrhea*) of the menstrual cycle. In contrast, patients in Groups 2 and 3 demonstrated a higher incidence of heavy (*hypermenorrhoea*) and prolonged (*polymenorrhea*) menstrual discharge. Patients experiencing painful menstruation (*algodysmenorrhea*) exhibited comparable prevalence across Groups 1 and 2.

For Group 1 patients, UF nodules were a sonographic (ultrasound) diagnostic finding in most cases. Patients in the other groups were aware of the UFs. However, no prophylactic therapeutic actions aimed at preventing an increase in the size of UFs were performed. The longest period of passive monitoring of UFs was observed in Group 3 patients (see Table 1).

For 30.9% of Group 1 patients, a certain time (ranging from one to three months) was required for the body to adapt to the use of estrogen-gestagen-containing contraceptives, leading to the cessation of adverse effects such as nausea, weakness, and decreased libido (see Fig. 1).

A total of 20.5% of patients in Group 2 reported experiencing more frequent recurrences of vaginal dysbiotic

Table 1. Clinical characteristics of patients assigned to the study groups

Parameter	Group 1 (*n*=42)	Group 2 (*n*=34)	Group 3 (*n*=33)
Age, years (M±m)	27.5±3.5	33.1±3.2	34.3±2.7
Menstrual disorders, abs. (%)	15 (35.7)	14 (41.2)	13 (39.4)
Menstrual disorders, abs. (%):			
– *opsomenorrhoea, proiomenorrhoea*	11 (73.3)	4 (26.7)*	3 (23.1)*
– *hypermenorrhoea, polymenorrhoea*	4 (26.7)	12 (85.7)*	10 (76.9)*
– *algodysmenorrhoea*	13 (86.7)	11 (85.7)	5 (38.5)*
Reproductive history, abs. (%):			
– vaginal delivery/abdominal delivery	12 (28.6)/6 (14.3)	21 (61.8)*/13 (38.2)*	13 (39.4)/3 (9.1)
– nulligravida	—	—	—
– invasive intrauterine intervention due to the obstetric or gynecological disorders	24 (57.1) 8 (19.0)	32 (94.1)*	17 (51.5) 11 (33.3)
Chronic extragenital diseases, abs. (%)	7 (16.7)	11 (32.4)	21 (63.6)*
Duration of disease (uterine leiomyoma), years (M±m)	Unknown	6.2±2.6	9.1±3.1

* Statistically significant difference (p <0.05) vs. Group 1.

disorders following the insertion of the intrauterine hormonal system (see Fig. 1).

A small proportion of Group 3 patients (15.2%) exhibited symptoms such as weakness and rapid fluctuations in psycho-emotional mood at the start of antigestagen therapy (see Fig. 1). However, additional use of herbal preparations affecting the psychoemotional sphere on days of mifepristone intake (50 mg) effectively eliminated the above symptoms. Importantly, the symptoms listed above and those that could be phytocorrected were not a reason for the patient to refuse the recommended conservative therapy with a progesterone receptor modulator.

Patients in all groups who were initially iron deficient showed a gradual increase in hemoglobin level during therapy (within 3–6 months) without additional use of antianemic drugs. This was undoubtedly due to a decrease in blood loss with a decrease in the volume of menstrual-like discharge.

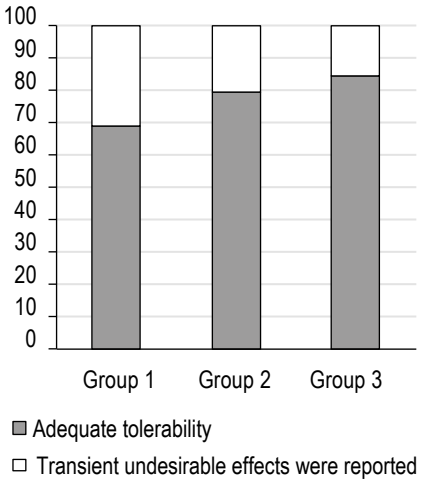

Fig. 1. Study drug tolerability in patients with uterine myoma, %.

No changes in blood biochemistry were observed in patients of all groups during the use of the above drugs.

In a small number (14.2%) of patients in Group 1, the hemogram values changed slightly within physiologically acceptable limits during the first 1–3 months of taking COCs. Later, no changes in this laboratory analysis were observed in these patients.

Patients in Groups 1 and 2 responded positively to the reduction in the volume of menstrual-like discharge and the elimination of dysmenorrhea.

Patients in Group 3 were warned before starting therapy that taking the progesterone receptor modulator may cause scanty bleeding or complete cessation of menstrual-like discharge. Therefore, they were calm about the development of opsomenorrhea or amenorrhea. In addition, therapy with the drug containing 50 mg mifepristone at the beginning of the menstrual cycle prevented the development of endometrial hyperplastic processes in all patients during the follow-up period.

Two (4.8%) patients in Group 1 had to discontinue microdosed COCs because of a 2- to 2.5-fold increase in myoma nodule size at 6 and 12 months. A slight (10–15%) increase in the size of UMs while taking microdosed COCs was observed in another five (11.9%) women with initially small nodules. Only one patient (2.4%) in this group experienced a 5% decrease in the size of the nodule. However, in the majority (80.9%) of patients in Group 1, the average size of the nodules remained at the same level as at the start of the contraceptive regimen (Fig. 2).

Despite the overall positive clinical changes observed during the use of the levonorgestrel-releasing intrauterine system, the tendency for myoma nodules to increase in size persisted in the majority (58.8%) of patients. The size of myomas in this group increased by an average of 20–30% from baseline by the end of the 5-year follow-up period.

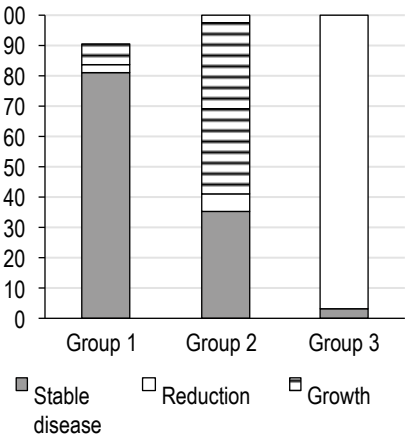

Fig. 2. Change in the diameter of myomas in the study patients, %.

Stable nodule sizes were observed in 12 (35.3%) patients in Group 2, whereas an insignificant (15.0%) decrease in nodule size was observed in only two (5.9%) women (see Fig. 2).

In the overwhelming majority of patients in Group 3, there was a decrease in the size of the nodules during the 3-month course of taking the drug containing 50 mg mifepristone, with stabilization of UF growth observed during the next three months of drug interruption. However, in one patient (3.0%) from this group, no reduction in myoma size was observed during the first three months of taking the indicated drug, and therefore this patient was withdrawn from the prospective study. In general, the patients in this group exhibited a 40–50% reduction in the size of UF nodules following repeated courses of mifepristone therapy (50 mg) over a period of five years (see Fig. 2). Moreover, the reduction of myomatous nodules to a clinically insignificant size reduced the risk of adverse conditions for future obstetric complications in this group of patients.

Due to the withdrawal of some patients from the study for the aforementioned reasons, the overall assessment of the effect of 5-year curative and preventive treatment was performed in 40, 34, and 32 patients of Groups 1, 2, and 3, respectively (see Table 2).

DISCUSSION

Our data confirm the information of other authors that the long-term use of hormonal contraceptives containing 20 μg of ethinyl estradiol and 150 mg of desogestrel in UF nodules up to 2 cm in size does not promote their growth in most cases [9].

Despite the significant improvement in the clinical condition of patients with UF and adenomyosis due to the use of intrauterine hormonal system, this conservative therapy does not prevent the growth of myomatous nodules.

The present study demonstrates that the long-term administration of the preparation containing 50 mg mifepristone (in ten 3-month courses) is both safe and

Table 2. Uterine ultrasound data in the course of 5-year follow-up in patients with myoma, M±m; 95% CI

Follow-up period	Maximum linear diameter of the dominant myoma (cm)			Uterine volume (cm^3)		
	Group 1 (*n*=40)	Group 2 (*n*=34)	Group 3 (*n*=32)	Group 1 (*n*=40)	Group 2 (*n*=34)	Group 3 (*n*=32)
Before treatment	1.70±0.25; 1.2–2.0	3.70±0.60; 3.1–5.1	4.80±0.40*; 3.7–6.5	4.30±0.30; 4.1–4.5	5.50±0.25*; 4.8–6.9	7.10±0.30*; 6.2–9.2
Month 1	1.60±0.32; 1.1–2.0	3.70±0.60; 3.2–5.1	4.70±0.30; 3.7–6.5	4.30±0.50; 4.1–4.5	5.50±0.30; 4.8–6.9	7.00±0.40; 6.1–9.1
Month 3	1.65±0.28; 1.1–2.1	3.70±0.40; 3.2–5.1	4.50±0.55; 3.4–6.2	4.40±0.40; 4.1–4.6	5.60±0.50; 4.9–6.9	6.70±0.52; 5.8–8.3
Month 6	1.69±0.21; 1.1–2.0	3.69±0.45; 3.2–5.2	4.50±0.60; 3.4–6.2	4.41±0.30; 4.1–4.6	5.70±0.30; 4.9–7.0	6.70±0.28; 5.8–8.3
Year 1	1.70±0.31; 1.2–2.0	4.20±0.35; 3.3–5.3	4.20±0.45; 3.2–6.0	4.42±0.52; 4.1–4.7	6.10±0.55; 5.1–7.1	6.30±0.41; 5.5–7.9
Year 2	1.68±0.29; 1.1–2.1	4.30±0.58; 3.3–5.3	3.90±0.50; 3.1–5.9	4.45±0.43; 4.1–4.7	6.40±0.40; 5.2–7.1	5.90±0.26; 5.3–7.6
Year 3	1.66±0.32; 1.1–2.1	4.40±0.39; 3.4–5.3	3.70±0.35; 3.0–5.6	4.50±0.36; 4.1–4.7	6.50±0.25; 5.2–7.2	5.50±0.45; 5.2–7.5
Year 4	1.67±0.30; 1.2–2.0	4.50±0.60; 3.6–5.4	3.50±0.40; 3.0–5.6	4.50±0.38; 4.1–4.7	6.70±0.36; 5.3–7.2	5.30±0.25; 5.2–7.5
Year 5	1.75±0.15; 1.1–2.0	4.60±0.45; 3.7–5.4	3.20±0.25*; 2.9–5.3	4.50±0.40; 4.1–4.8	6.90±0.30*; 5.4–7.3	5.20±0.30*; 5.0–7.4

Note: M, arithmetic mean; m, standard error; CI, confidence interval; * statistically significant difference ($p < 0.05$) for comparison of the data before treatment vs. 5-year follow-up data.

effective in promoting a permanent course (annual) reduction in the size of UF nodules. However, the necessary clinical effect of conservative therapy can be expected only if the size of myomas does not exceed 6–6.5 cm [1, 10, 11].

CONCLUSION

Analysis of the data from this prospective study demonstrated the feasibility of the personalized approach presented for the treatment of patients with UFs who have postponed childbearing for a relatively long period of time. In most cases, microdosed COCs stabilize the size of UF nodules, and the intrauterine levonorgestrel-releasing system prevents their intensive growth. The best therapeutic effect aimed at reducing the size of myomas is observed when using a drug belonging to progesterone receptor modulators.

ADDITIONAL INFO

Authors' contribution. S.P. Sinchikhin provided patient supervision, analyzed clinical data, wrote and edited the manuscript; O.G. Magakyan provided patient supervision, collected clinical data; E.S. Sinchikhina performed search and analysis of literature sources. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before publication).

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declares that there are no obvious and potential conflicts of interest associated with the publication of this article.

Publication informed consent. All patients enrolled into the study signed the necessary voluntary informed consent forms, confirming their willing to participate in the study and allowing to publish their medical data.

Ethical Statement. The study was performed as a part of a teamwork at the Department of Obstetrics and Gynecology, Department of Medicine, Astrakhan State Medical University. The study was approved by the expert committee of this institution (extract from the protocol No. 131 dated by 26 July 2021).

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