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Clinical Efficacy Of Alternative Therapy For Adenomyosis

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Annotation

Relevance: Genital endometriosis is the most common disease of the female reproductive system. Currently, 190 million women and adolescent girls worldwide suffer from this disease. Although many aspects of genital endometriosis have been scientifically studied, there is still a clinical need to improve the methods of diagnosis and treatment of symptoms associated with this disease. These issues are particularly relevant to the management of patients with adenomyosis.
The aim of the study was to evaluate the clinical efficacy of indinol-3-carbinol and epigallocatechin-3-gallate in patients with adenomyosis.
Methods: The study enrolled 72 patients with adenomyosis (mean age 34.1±3.2 years) who received indinol-3-carbinol and epigallocatechin-3-gallate for 6 months. The treatment efficacy was evaluated on the basis of the change in clinical symptoms of the disease and the dynamics of ultrasound criteria of adenomyosis.
Results: After a 6-month course of therapy, there was a significant regression of disease symptoms and positive dynamics of changes in sonographic criteria of adenomyosis. No patient dropped out of the study and no patient experienced any significant side effects.
Conclusion: Therapy with indinol-3-carbinol and epigallocatechin-3 is a promising method of adenomyosis treatment, taking into account a significant improvement in patients' quality of life and the possibility to implement reproductive plans.

Keywords: adenomyosis, therapy, indinol-3-carbinol, epigallocatechin-3-gallate

Introduction:

Currently, genital endometriosis is recognised as the most common and severe gynaecological pathology in women of the reproductive period, significantly worsening the quality of life of patients [1-3]. Most commonly, genital endometriosis affects the uterus, causing adenomyosis (internal endometriosis) [1-6]. The prevalence rate of adenomyosis ranges from 5 to 70%, and this difference is explained by the different diagnostic criteria and instrumental methods used to confirm the diagnosis [3-6].
Adenomyosis is an estrogen-dependent chronic inflammatory disease. It is characterized by the presence of endometrial glands and stroma in the myometrium, resulting in an increase in the size of uterus due to reactive hyperplastic and/or hypertrophic changes in the surrounding myometrium [3,6,7].
Local hyperestrogenism, progesterone resistance and eutopic endometrial proliferation are key to the pathogenesis. These aspects of the pathogenesis have formed the basis of specific hormone therapy for endometriosis. However, hormone therapy of endometriosis is combined with suppression of ovulation or many undesirable side effects, which causes dissatisfaction of patients with this type of therapy [8-11, 27, 28]. In this context, the search for new methods of treating adenomyosis is a very urgent task [12-15].
To date, in the treatment of proliferative processes, particular attention is paid to substances of plant origin with antiproliferative, antiangiogenic and pro-apoptotic properties. In addition, it is necessary to normalise metabolic disorders, eliminate hypoxia characteristic of the pathological process under study. Reconstruction of the metabolic pattern in endometrioid lesions is a critical factor in cell survival and disease progression. A therapeutic strategy to avoid manipulations with hormones, aimed at mitigating the metabolic changes found in the cells and tissues of women with endometriosis, underlies the effectiveness of the drugs indinol-3-carbinol and epigallocatechin-3-gallate [16-18].

The aim of the study was to evaluate the clinical efficacy of indinol-3-carbinol and epigallocatechin-3-gallate in patients with adenomyosis.

Materials and methods: This study was conducted at the Endometriosis Center (Astana, Kazakhstan). In our observations, within 3 months, genital endometriosis was diagnosed in 252 women of the reproductive period, which accounted for 11% of all gynecological patients examined at the Center. The incidence of adenomyosis was 29% (72 patients). Purely isolated forms of adenomyosis accounted for 54.2% (39 of 72), and in 45.8% (33 of 72) of patients adenomyosis was combined with other forms of endometriosis, in particular, with ovarian endometriosis in 36.5% (12 of

33), retrocervical endometriosis in 27.3% (9 of 33), peritoneal endometriosis in 18.1% (6 of 33), and cervical endometriosis also in 18.1% (6 of 33).

The study included 72 patients of reproductive age (18-45 years) with clinically diagnosed adenomyosis (symptomatic adenomyosis). The women's age ranged from 27 to 38 years, with the average age of 34.1±3.2 years. The exclusion criterion was asymptomatic forms of adenomyosis.

All patients with adenomyosis were prescribed indinol-3-carbinol and epigallocatechin-3-gallate for 6 months. The treatment was performed after the patients' informed consent was obtained. The choice of the treatment method was made by open way, the patients were counseled and the treatment method advantages and disadvantages were discussed.

The patients were followed up for 6 months, with mandatory examination, assessment of the dynamics of changes in clinical manifestations of the disease and ultrasound monitoring after 3 and 6 months from the start of treatment.

Pain syndrome intensity was assessed by the visual analogue scale (VAS), where the patient estimated the pain by herself from 0 to 10, where 1-2 points - mild pain; 3-4 points - moderate pain; 5-6 - average pain; 7-8 - severe; 9-10 - intolerable pain.

In order to assess the degree of menstrual blood loss more accurately, a graphical blood loss assessment Scale (Pictorial Blood Loss Assessment Chart (PBAC)) was used (the number of hygiene products used, clot size, duration of bleeding were taken into account). This scale was presented in a form that was given to all patients at the initial examination (Figure1) [19]. After receiving the instructions, on the due date of the next menstruation, women filled out the form on their own. Menorrhagia was defined as a score of more than 100 on the PBAC scale (during the first 8 days of the menstrual cycle), which corresponds to a blood loss of more than 80 ml.

Correct interpretation of the patient's medical history data and the clinical manifestations of the disease allows suspicion of adenomyosis. Therefore, bimanual examination often provides valuable diagnostic and differential diagnostic information in these patients. In order to confirm adenomyosis and exclude oncological pathology, highly informative instrumental examination methods are then used in clinical practice. Currently, ultrasonography is a minimally invasive and accessible method of examination [20-25]. Ultrasound examination of the pelvis was performed on the SonoAce R7 device, the ddiagnostic ultrasound stationary system (Samsung Medison, South Korea), with a contact scanning system using a transabdominal convexic sensor with a frequency of 3.5 MHz and a transvaginal sensor with a frequency of 6.5 and 7 MHz, in 3D/4D mode. The size, shape and thickness of the uterine walls, thickness and structure of the endometrium were determined on this device. Particular attention was paid to the measurement of the transition zone (Figure 2)[12]. Signs of adenomyosis are considered: thickening of the transition zone – 8-12 mm, the ratio of the maximum PZ to the total thickness of he myometrium is more than 40%, the difference between the maximum PZ and the minimum PZ is more than 5 mm. The thickening of the transition zone in the literature is explained by hyperplasia of the transitional epithelium, as well as changes in the angiogenesis of spiral arteries.

To date, it is known that adenomyosis causes a significant increase in blood flow resistance in the uterine arteries, with the blood flow resistance index being the most indicative. In our study, the nature of the blood flow (arterial or venous) was assessed by calculating velocity values and indices in the uterine arteries before the start of treatment and at the 3rd and 6th month of treatment.

All obtained data were statistically processed. This study was conducted according to the international principles of research. All patients who participated in the study gave written informed consent to participate.

Results:

The analysis of the questionnaires of the patients with adenomyosis showed that the majority of the women had normal menstrual cycle - 75% (54 of 72). The patients most frequently associated the disease onset with the intrauterine manipulations or surgeries - 50% (36 of 72), inflammatory diseases of the pelvic organs - 29.2% (21 of 72), in 12.5% of cases (9 of 72) dysmenorrhea was noted with menarche. More than 90% of patients had adenomyosis in women who had given birth, rarely in those who had not. However, half of the patients had only one child. 50% (36) of the patients we observed with internal endometriosis had a history of more than 2 abortions before 5 weeks of gestation, including spontaneous miscarriages with curettage of the uterine cavity - 33.3% (12 of 36). Secondary infertility was observed in 25% of cases (18 of 72).

The main clinical symptoms in the patients were: pain syndrome - 75%, menstrual cycle disorders - 45.8%, infertility - 33.3% (Table 1). The symptoms of the disease were most often combined in various combinations and met with the same frequency at different degrees of lesion. When the sequence of symptoms was analysed, it was found that the first symptom was most often pain, and less often the disease started with menstrual function disorders.

Pain syndrome bothered 54 (75%) patients, while chronic pelvic pain was observed in 20 (37.0%) patients, dysmenorrhea – in 24 (44.4%), dyspareunia – in 10 (18.5%) patients. The average intensity of the pain syndrome according to the VAS was 8 points - severe pain.

Menstrual cycle disorders were noted by 33 patients, 18 of them (25.0%) reported hyperpolymenorrhea, 15 (20.8%) complained of intermenstrual bleeding. All the patients with menstrual cycle disorders noted a blood loss volume of 100 points or more.

Bimanual gynecological examination revealed a slight enlargement of the uterus in 58.3% (42) of patients, tumor-like masses on the appendages in 16.7% (12), tenderness on palpation of the posterior vaginal vault in 8.3% (6), fine-grained formations in the posterior vaginal vault in 4.2% (3). Palpation of the sacro-uterine ligaments was painful in 41.7% (30) cases.

All the patients received therapy for 6 months, against the background of ongoing therapy, not a single patient dropped out of the study. Another feature of this therapy was the good tolerability of the drugs: none of the patients reported any significant side effects.

During 6 months of therapy with indinol-3-carbinol and epigallocatechin-3-gallate, the character of the clinical manifestations of adenomyosis in the patients changed. All the patients noted the regression of clinical manifestations.

After 6 months of the therapy 30 patients (55.6%) out of 54 patients with pain syndrome noted the absence of pain. All the patients noted a decrease in the intensity of pain symptoms from the first month of taking the drugs. By the end of the therapy, 24 of the 54 patients (44.4%) reported mild pain with an average of 2 points, not requiring taking analgesics and did not affect the patient's quality of life (Table 2).

On the background of the conducted therapy 24 (72,7%) out of 33 patients with the symptoms of menstrual function disorders noted the positive dynamics. In particular, 15 patients out of 18 with hyperpolymenorrhea noted the reduction of menstrual blood loss. When the PBAC score was calculated, there was a 30-50% decrease in the points, i.e. if before treatment the PBAC range was between 105 and 200 points (146 on average), after treatment it was 60-80 points (70 on average) (Table 3). The effectiveness of reducing menstrual blood loss contributed to an increase in the level of blood hemoglobin. Thus, the average blood hemoglobin value in these patients was 106 g/L before treatment, and by the end of treatment, the average hemoglobin level reached 115 g/L.

Before treatment, 15 patients complained of intermenstrual metrorrhagia; by the end of treatment, 9 (60%) of them noted the cessation of such menstrual disorders.

Before the start of the study 24 patients reported infertility, by the end of treatment this number remained unchanged.

All the patients underwent ultrasound examination before and after the treatment. The first evaluation criterion was the change in uterine volume. Before treatment, the mean uterine volume was 93.5±2.55 mm^3; after 3 months of treatment, the uterine volume decreased to 92.4±4.84 mm^3; after 6 months of treatment, it was 77.7±3.79 mm^3, which was 15.8 mm^3 less than the initial volume.

The second ultrasound criterion was the measurement of the “junctional area”. Thirty patients (41.7%) had a 5 mm junctional area, 30 patients (41.7%) had an 8 mm junctional area, and 12 patients (16.8%) had a 12 mm junctional area. Thus, a thickening of the junctional area was observed in 42 patients (58.5%). After 6 months of therapy with indinol-3-carbinol and epigallocatechin-3-gallate the junctional area was 5 mm in 60 patients (83.3%) and 8 mm in 12 patients.

The third ultrasound criterion was the change in blood flow resistance index in the uterine arteries. Prior to treatment, the patients showed marked vascularisation and a low uterine artery resistance index (0.47 to 0.69 m/sec, mean 0.54 m/sec) in the area of the adenomyosis foci, indicating increased uterine angiogenesis. In 3 months there were noted changes in blood flow, consisting in decreased vascular pattern at CDI and “mosaic” form of blood flow, but no significant increase in resistance index was detected. After 6 months there was an average increase of the resistance index by 0.16 m/sec. (from 0.65 m/sec to 0.78 m/sec, mean 0.70 m/sec). The increase of the index of vascular resistance testifies to the fact that this therapy leads to a decrease in the number of arteriovenous anastomoses, hence, the uniformity of blood flow distribution improves, which is associated with a decrease in uterine volume and thickness of the junctional area.

Discussion:

In clinical practice, the drugs indinol-3-carbinol and epigallocatechin-3 led to a significant reduction in adenomyosis symptoms, confirming the effectiveness of these drugs on the pathogenetic aspects of adenomyosis development. In particular, patients noted a decrease in the frequency and intensity of the pain syndrome. After 6 months of treatment, 55% of patients noted the absence of the pain syndrome, while 45% noted a significant decrease in the intensity of the pain syndrome, which did not require the use of analgesics and did not affect the patient’s ability to work.

Normalization of the menstrual cycle was noted against the background of the therapy. Almost every patient with hyperpolymenorrhea had a 30-50% decrease in the volume of blood loss. In 60% of the patients with intermenstrual menorrhagias we managed to achieve their cessation. All this led to the increase and normalization of hemoglobin levels in the general blood test.

The results of the ultrasound examination demonstrated a significant improvement in the sonographic picture in the patients after treatment with indinol-3-carbinol and epigallocatechin-3. Thus, the mean uterine volume decreased by 15.8

mm^3; the frequency of junctional area thickening decreased by 25%; and the resistance index in the uterine arteries increased by 0.16 m/s. All this confirms the anti-proliferative, antiangiogenic effect of the described therapy.

Conclusion:

Therapy with indinol-3-carbinol and epigallocatechin-3-gallate is pathogenetically justified because the main mechanisms of action of the drugs are hormone modulating (anti-estrogenic effect, increased sensitivity to progesterone receptors), anti-inflammatory (activation of phagocytosis), anti-proliferative and a pronounced anti-angiogenic effect [10]..
The tolerability of this therapy was satisfactory, with no patients withdrawing from the study due to intolerance and no significant adverse events.
Thus, the therapy with indinol-3-carbinol and epigallocatechin-3 is a promising method of adenomyosis treatment because of the clinical efficacy of the treatment of the disease symptoms and, as a consequence, the improvement of the patients' quality of life. This therapy is of particular interest for patients of reproductive age because it does not interfere with reproductive plans. Probably, the therapy with indinol-3-carbinol and epigallocatechin-3 will show even more significant results of clinical effectiveness with a longer duration of use, which requires more long-term studies, patient observation and analysis of the results.

Figure 1 - Pictorial blood loss assessment chart (PBAC) [19].

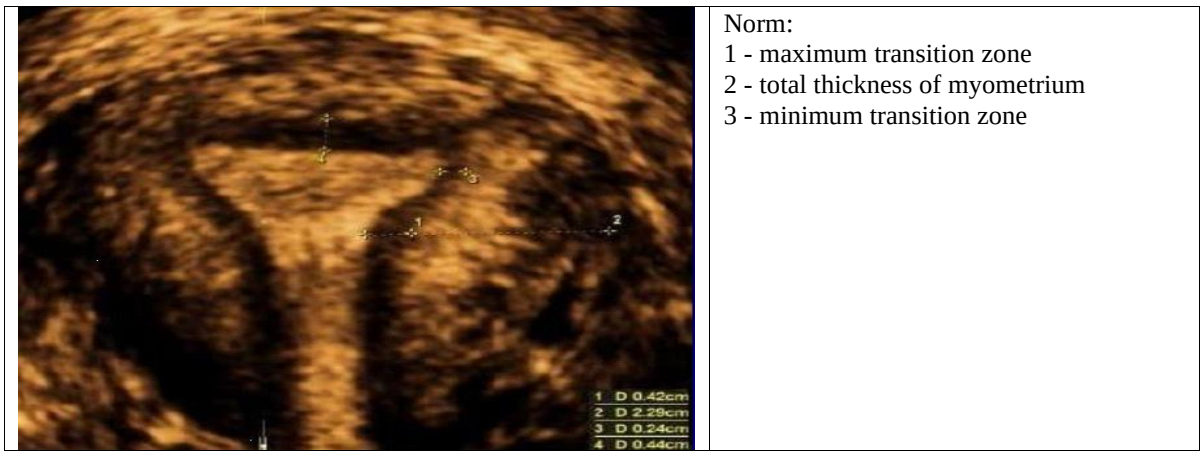

Figure 2 - Measurement of the transition zone of the endometriumarea [12]

Table 1 - Clinical manifestations of adenomyosis

Symptoms		Number of cases	
		Abs.	%
Chronic pelvic pain	Pain syndrome - 54 (75%)	20	37.0
Dysmenorrhea		24	44.4
Dyspareunia		10	18.5
Hyperpolymenorrhea	Menstrual function disorders - 33 (45.8%)	18	25.0
Intermenstrual bleeding - 54 (75%)		15	20.8
Infertility 1-2	Infertility - 24 (33,3%)	6	8.3
Infertility 2-6		18	25.0

Table 2 - Pain Intensity Dynamics according to VAS (Visual Analog Scale)

Symptom	Before treatment	After 6 months	After 6 months
Pain syndrome	8 points (took analgesics)	2 points	No pain
Number of patients (%)	54	24 (44.4%)	30 (55.6%)

Table 3 - PBAC range and hemoglobin content before and after hormone therapy

Parameters	Before treatment	After treatment
PBAC range	105-200	60-80
PBAC mean value (M±m)	146	70
Mean Hb value, g/L (M±m)	106	115

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