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Research Article

OVARIAN ENDOMETRIOSIS: NEW ASPECTS OF TREATMENT

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ABSTRACT

The results of the assessment of ovarian reserve before and after the use of various methods of treatment based on ultrasound (counting the number of antral follicles) and biochemical methods showed that the levels of anti-Müllerian hormones and the number of antral follicles were lower in patients with bilateral ovarian disease, and were significantly lower in the group with combined treatment. Pregnancy occurred within a year after the end of treatment in 9 (12,7%) women of the first group and in 21 (22,6%) of the second group.

KEYWORDS

Ovarian cysts, hormonal and combined treatment, AMH, dienogest, endometrium.

INTRODUCTION

Endometriosis is one of the most common diseases of the female genital area. Although its true prevalence in the general population of women of reproductive age is not clearly defined, according to the latest epidemiological data, the detectability of the disease in the group of women of reproductive age is 30%, while the detection rate on sectional material approaches 53.7% [1]. In patients suffering from pelvic pain syndrome, endometriosis is detected in 38.8%, and in case of infertility — in 50% of cases [13,15,17,19,21,23]. An important fact is the financial costs necessary for the treatment of this pathology. Thus, according to the

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American Fertility Society, over the past 10 years, the cost of treating patients with endometriosis has increased by 61% [1].

Ovarian damage is considered one of the most common manifestations of endometriosis. It occurs as a result of the growth of the ectopic endometrium in the ovary [3]. Being detected in 17-44% of the total number of patients with endometriosis [89,160], ovarian endometriosis (OE) ranks second among all localizations of this pathology and first in the group of external genital endometriosis (OGE) [1,3,5,7,9,11].

There is not a single epidemiological study showing the frequency of the spread of ED in different periods of a woman's life. It has recently been shown that EYA can develop in adolescent girls before menarche [5]. This supports the opinion that the early onset of endometriosis, including ovarian damage, may develop as a result of the casting of endometrial stem cells during neonatal uterine bleeding in newborn girls [1].

ED has a negative effect on reproductive function, often accompanied by generalization of the pathological process [21]. The frequency of infertility in patients with NGE reaches 50%, ranking third in the structure of infertility, and has no tendency to decrease [25]. An important feature of the course of the disease is its recurrent nature. Relapses occur both after surgical treatment and against the background of hormone therapy and after its cancellation [4]. Repeated surgical interventions can cause irreversible changes in the ovaries, leading to depletion of the follicular reserve [2,4,6,8,10,12].

The facts described above suggest that the problem of studying endometrioid ovarian cysts (ECTS) continues to remain relevant because ECTS account for up to 59% in the structure of genital endometriosis [14,16,18,20,22,25].

Despite numerous studies of various aspects of endometriosis, there is currently no consensus on the pathogenetic mechanisms and treatment regimens for endometriosis. To date, the most promising areas in the study of endometriosis are the study of molecular biological characteristics of cells of the eutopic and ectopic endometrium, markers of proliferation and apoptosis, adhesion, angiogenesis and cell invasion, analysis of genetic features in endometriosis and the influence of epigenetic factors on the development of this disease, which can contribute to further understanding of etiopathogenesis to substantiate new approaches to diagnosis and effective treatment.

The purpose of the study. Improvement of methods of diagnosis and prevention of external genital endometriosis based on the study of the pathogenesis of relapses of endometriodic ovarian cysts.

MATERIAL AND METHODS

In accordance with the set goals and objectives, we examined and treated 164 patients of reproductive age with ovarian endometrioid formations. Depending on the individually selected tactics and the treatment performed, the patients were divided into two groups. The first group included 71 women with endometrioid ovarian cysts, who, according to international and domestic clinical recommendations, underwent empirical hormonal treatment with Dienogest at a dose of 2 mg (the drug is officially registered in the Russian Federation for the treatment of endometriosis). The duration of therapy is from 3 to 12 months. The second group consisted of 93 patients who underwent combined treatment. In this group, therapeutic and diagnostic laparoscopy with cystectomy was performed at the first stage, hormone therapy was performed at the second stage. The main indications for therapeutic diagnostic laparoscopy were: severe pain syndrome; the presence of

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endometrioid ovarian cysts more than 3 cm (according to examination and ultrasound of the pelvic organs); infertility in combination with late reproductive age (over 35 years). The criteria for inclusion in the study were: reproductive age up to 35 years; primary and recurrent ECI confirmed by ultrasound examination (patients with cysts up to 3 cm were included in group 1 and more than 3 cm in group 2); clinical manifestations of external genital endometriosis: menstrual cycle disorders (meno- and metrorrhagia), pain in the lower abdomen and lumbar region of varying intensity, dyspareunia, endometriosis-associated infertility. Exclusion criteria from the study: absence of ovarian endometriosis; the presence of combined infertility factors (tuboperitoneal, uterine, male); the patient's refusal to participate in the study. A comprehensive examination of the patients included the results of anamnestic and clinical data assessment; ultrasound examination of the pelvic organs (on the 5th-7th day from the beginning of menstruation), performed in 2D modes using devices "Madison X 8" (Korea), "Fucuda Denshi" (Japan), related to the contact scanning system using transabdominal and transvaginal sensors with a frequency of 3.5 and 5.0 MHz; studies of the level of anti-Muller hormone (AMH) in the blood serum (on the 3rd day of the menstrual cycle) by enzyme immunoassay performed before surgical treatment. To determine the level of AMH, the Vector-BEST test system (Russia) was used; the results obtained were compared with the reference values of hormones for women of reproductive age in the follicular phase of the menstrual cycle: AMH - 1.00–10.60 ng/ml (regardless of age). A study of the concentration of cancer markers CA-12 was conducted using the test system "Vector-BEST" (Russia); the obtained data were compared with reference values of CA 125-0.0-35.0 IU/ml. Biometric analysis was carried out using the Statistica 6 package and the Microsoft Excel program. In all statistical analysis procedures, the critical significance level p was assumed to be 0.05. When studying menstrual function, it was found that in all patients the average age of menarche was 13.1 +1.2 years. The vast majority of women – 134 (81.7%) - had menstruation with menarche. The analysis of reproductive function showed that 98 (59.6%) patients had one or more pregnancies, primary infertility was diagnosed in 66 (40.2%) patients, secondary infertility in 98 (59.6%). Among the gynecological diseases previously suffered, 106 (64.6%) patients had inflammatory processes of the uterine appendages, for which inpatient and/or outpatient treatment was carried out, 64 (39.0%) had abnormal uterine bleeding. The duration of endometriosis in patients varied in the first group 2.4 ± 0.1 years, in the second – 3.1 ± 0.1 years. The main clinical manifestations of the disease were pelvic pain of varying intensity in 62 (87.3%) patients of the first group and 87 (93.5%) of the second; dysmenorrhea in 18 (25.4%) of the first group and 28 (30.1%) of the second; dyspareunia in 9 (12.7%) patients of the first group and 14(15.1%) – the second group. In 128 (78.1%) women, the ovarian lesion was unilateral, in 36 (21.9%) a bilateral pathological process was diagnosed. The study of the results of clinical examination of patients with endometrioid ovarian cysts did not reveal a correlation of clinical manifestations of the disease with the size of cysts. In patients of both groups, complaints of pain in the lower abdomen, unrelated to menstruation and sexual intercourse, and primary infertility prevailed. All patients before and after surgery were evaluated ovarian reserve, using ultrasound and biochemical methods. During transvaginal echography, antral follicles were counted in real time, and the volume of the ovary was calculated using sonograph software ("Madison X 8" (Korea) and "Fucuda Denshi" (Japan). In addition, resistance indices (IR) in the arteries feeding the ovaries were evaluated in the mode of color Doppler mapping

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(CDK). To assess the blood supply to the ovaries using ultrasound Dopplerometry, three different vascular regions were used in which blood flow velocity curves were recorded: ovarian artery; ovarian gate; ovarian parenchyma; ovarian cyst wall. Ultrasound diagnosis of endometrioid ovarian cysts was established by visualization of the following echo signs: – single–chamber formation of a rounded or oval shape; - unevenly thickened wall from 1.0-6.0 mm; – wall hyperechoic inclusions of a homogeneous structure with a diameter of 5-10 mm; – hypo-, iso-, hyperechoic contents with a non-displaced fine suspension; – with CDK – single vessels in the wall with an IR of 0.5-0.6; – no changes in the echostructure during dynamic observation in different phases of the menstrual cycle. In order to determine the ovarian reserve, we used the determination of the level of anti-muller hormone (AMH) in the blood serum on the 3rd day of the menstrual cycle before treatment and 1,3,6 and 12 months after treatment. Results and discussion In the majority of observations in 128 (78.1%) patients, endometrioid cysts were single-chamber, rounded in shape. The average diameter varied from 9.7 to 159 mm (on average – 42.7± 1.6 mm). In 36 patients, endometrioid cysts were found in both ovaries, in 79 cases they were localized on the left, in 49 – in the right ovary. There were no fundamental differences in the microstructure according to ultrasound of endometrioid implants in patients with different clinical course of endometriosis. In order to assess the effectiveness of the treatment, patients of both groups underwent dynamic ultrasound monitoring and hormonal status study before the start of treatment and in terms of 1, 3, 6 and 12 months after the start of therapy.

The analysis of the results indicates both the presence of a certain pattern of variations in the ovarian reserve, and the absence of significant differences in a number of parameters of the compared groups. Thus, the volume of ovaries in the group of patients who underwent surgical treatment was lower than in patients after conservative treatment. Of course, the volume of the ovaries is one of the reliable markers of their functional ability: it is quite logical that with a decrease in the volume of the ovaries, the number of antral follicles decreases. This postulate is reflected in our research. Along with a decrease in ovarian volume, there was a significant decrease in the number of antral follicles in patients after surgical treatment: 2.9±0.4 versus 3.9±0.2 in the 1st group of women. In a study by C.M. Ercan et al. (2010), when assessing blood flow in the ovaries, a significant decrease in dopplerometric parameters of peripheral vascular resistance (IR) was found in patients after surgical treatment of endometrioid ovarian cysts [24]. In particular, by the 3rd month of follow-up, PI decreased from 2.22±0.46 to 1.76±0.51; IR increased from 0.81±0.06 to 0.88±0.13. In a similar study, G.Pados et al. no such pattern was found [21]. We also have not established a reliable probability of differences in the so-called carbon-independent indices of peripheral vascular resistance. In our opinion, this is due to the relatively small diameter of the ovarian vessels, the identification of which is difficult and therefore differs in a certain subjectivity. To date, the assessment of the level of AMH is rightfully considered the leading criterion of ovarian reserve. According to many researchers, in this regard, the assessment of the secretion of AMH level has the greatest sensitivity. The results of our study showed that the level of AMH in women of group 1 before treatment was 3.02± 0.3 ng/ml, group 2 - 2.4±0.1 ng/ml.

It is known that the level of AMH correlates with the number of antral follicles, which is explained by the fact that, unlike other hormonal markers of the ovarian reserve, AMH expression is less affected by FSH than

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E2 expression. It is believed that this is caused by the fact that AMH is secreted not only by antral, but also by primary and preantral follicles that are not affected by FSH [20,23,25]. As can be seen from Table 2, in our studies, the values of AMH varied in both groups. Thus, the minimum values of AMH in patients of the compared groups were 2.26 and 0.98 ng/ml after 12 months, and the maximum values of AMH – 3.02 and 2.4 ng/ml in groups 1 and 2, respectively, were at the beginning of the study. In general, according to the main indicators (ovarian volume, number of antral follicles, AMH concentrations), the ovarian reserve in group 1 patients was significantly higher than in women after combined treatment. The problem of surgical treatment of patients with ovarian endometriosis is quite acutely discussed in the modern literature [12,11,23,25]. Most authors have a negative attitude to "traditional" cystectomy (complete hatching of an ovarian cyst) in women interested in preserving reproductive function, since the consequences of such operations are partial (less often complete) loss of primordial follicles. Thus, in the study of N.G. Mishieva et al. it is stated that any ovarian resection negatively affects the ovarian reserve [14]. A.V. Morozova and A.I. Ishchenko, studying the results of the use of assisted reproductive technologies (ART) in patients after endosurgical treatment for endometrioid ovarian cysts, came to the conclusion that the frequency of pregnancy in women who underwent surgery on the ovaries was 2 times lower compared to that in women who did not have operations on the appendages of the uterus, – 21 and 42%, respectively [15]. According to a number of authors, in patients with endometriodic cysts of relatively small size (up to 3 cm in diameter), it is advisable to refrain from surgical intervention either before pregnancy [15], or to carry out treatment after receiving a woman's own genetic material in an ART program. A decrease in ovarian reserve during surgical treatment of ovarian endometrosis is shown in studies by G. Pados et al. (2010). In their work, as markers of ovarian reserve, they relied on ultrasound parameters – the number of antral follicles, ovarian volume, parameters of peripheral vascular resistance (IR), which were studied 6 months after surgery. If, according to the last three indicators, it was not possible to detect significant differences in the compared groups, the number of antral follicles was significantly higher in the group of women who were treated with endometrioid ovarian cysts using a three-stage method: 4.36±0.8 and 2.38±0.78 ($p = 0.002$), respectively [25]. Conclusion Our studies confirm the ambiguity of approaches to the choice of treatment method for patients with endometriodic ovarian cysts. This is especially important for patients with unrealized reproductive function, since surgical treatment of endometriosis can worsen the fertility problem. In this regard, surgical principles of treatment of patients with endometriodic ovarian cysts should be based on the most careful attitude to the ovaries. In certain situations (relapses of endometrioid cysts, single ovarian cyst), it may be more appropriate to use less traumatic methods of aspiration treatment of cysts under the control of transvaginal echography. This issue requires further study.

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