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ESTIMATION OF OVARIAN RESERVE IN FEMALES WITH UNREALIZED FERTILITY WITH ENDOMETRIOMAS

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ANNOTATION

We have observed 71 female patients aged from 19 to 45 with endometrioid ovarian cysts (EOC) up to 3 cm. Functional ovarian state has been evaluated (antral follicle count, folliculogenesis in both affected and collateral ovaries, intraovarian blood flow). Effectiveness of hormonal treatment has been assessed in case of small endometrioid cysts (up to 3 cm) in females of reproductive age. Anti-Mullerian Hormone (AMH) level was measured before and after the treatment.

Key words: ovarian functioning, ovarian reserve, endometrioid ovarian cysts, hormonal treatment, dienogest.

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ОЦЕНКА ОВАРИАЛЬНОГО РЕЗЕРВА ПРИ ЭНДОМЕТРИОИДНЫХ КИСТАХ ЯИЧНИКОВ У ЖЕНЩИН С НЕРЕАЛИЗОВАННОЙ РЕПРОДУКТИВНОЙ ФУНКЦИЕЙ

АННОТАЦИЯ

Под нашим наблюдением находились 54 пациентки в возрасте от 19 до 45 лет с эндометриоидными кистами яичников (ЭКЯ) размерами до 3 см. Изучали функциональное состояние яичников (число антральных фолликулов в одном эхосрезе, оценивали фолликулогенез в пораженном и коллатеральном яичниках, показатели интраовариального кровотока). Провели оценку эффективности гормонального лечения при эндометриоидных кистах небольших размеров (до 3 см) у женщин репродуктивного возраста. До и после лечения в крови определялся уровень антимюллеровского гормона (АМГ).

Ключевые слова: функциональное состояние яичников, овариальный резерв, эндометриоидные кисты яичников, гормональное лечение, диеногест.

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ТУХУМДОН ЭНДОМЕТРИОДЛИ КИСТАСИ САБАБЛИ РЕПРОДУКТИВ ФУНКЦИЯСИ АМАЛГА ОШМАГАН АЁЛЛАРНИНГ ОВАРИАЛ ЗАХИРАСИГА БАХО БЕРИШ

АННОТАЦИЯ

Bizning nazoratimiz ostida 19 yoshdan 45 yoshgacha boʻlgan tuxumdon endometrioid kistasi 3sm gacha boʻlgan 54 ta bemor kuzatildi. Tuxumdonlarning funksional xolati oʻrganildi (bitta EXO kesimida antral follikulalar soni, zararlangan va kollateral tuxumdonlarda follikulogenez xolatiga, tuxumdon ichki qon aylanishiga baho berildi). Reproduktiv yoshdagi unchalik katta boʻlmagan (3 sm gacha) endometriod kista kuzatilgan ayollarda gormonal davolash samaradorligiga baho berildi. Davolashdan oldin va keyin qonda antimyuller gormon (AMG) darajasi aniqlandi.

Kalit soʻzlari: tuxumdonlarning funksional xolati, ovarial zaxirasi, tuxumdonlar endometriod kistalari, gormonal davolash, dienogest.

Ovarian tumors are one of the most important and difficult diagnostic and therapeutic areas of modern gynecology [2]. The frequency of ovarian tumors is increasing and, according to various authors, has increased over the past 10 years, amounting to 19-25% of all tumors of the genital organs [4]

The pronounced ability of ovarian tumors to relapse, rapid growth, malignancy, the lack of a clear understanding of the etiology and pathogenesis and poor diagnosis at early stages dictate the introduction of additional research methods and rehabilitation treatment options for patients to prevent recurrence of ovarian formation, restore fertility and improve the quality of life [3].

Risk factors for ovarian tumors are: early menarche, late menopause, menstrual disorders, high-calorie food with a high content of saturated fatty acids, genetic predisposition, infertility, especially hormonal, stimulating therapy, chronic inflammatory diseases of the uterine appendages, smoking, etc. [1-6].

Endometrioid ovarian cysts firmly occupy the third place among the pathologies of the female reproductive system and belong to the most frequent localization in endometriosis [10]. (L.V. Adamyan et al., 2012, S.A. Levakova, M.B. Khamoshina, 2012, A.V. Shiring, 2013, T.V. Tretyakova, 2013, I.A. Lapina et al., 2015). According to L.V. Adamyan, the prevalence of endometrioid ovarian cysts is 5-50% in women of reproductive age. Recently, there has been a clear tendency towards the rejuvenation of this disease, while an increasing number of women postpone pregnancy planning and childbirth to a later reproductive age [8]. Often, in the years when a woman finishes her studies, thinks about a career and creates a family, the emerging symptoms of the disease impede the implementation of existing plans (V.N. Prilepskaya et al., 2012).

Studies by Kitajima M. and Maneschi (2014) showed that even with a small size of the endometrioma in the affected ovary, there is a significant decrease in ovarian reserve. The duration and severity of inflammation affecting the remaining healthy ovarian tissue directly correlates with the size of the cyst [5,6].

The explanation of the mechanisms of ovarian reserve decrease in endometrioid ovarian cysts was based on the burnout theory (Kitajima M., 2014). Oxidative stress is the cause of apoptosis and necrosis of primordial follicles and, as a consequence, a decrease in ovarian reserve (X. Zhang et all, 2006).

In addition to the local inflammatory response, oxidative stress is the cause of ovarian depletion, which has been shown in studies conducted in vitro (J.L. Tilly, J.K.Pru, B.R. Rueda, 2004). According to Somigliana et al (2006), in ovaries containing endometriomas, early activation of follicular development and an increase in follicular atresia, oocyte apoptosis and, as a consequence, accelerated depletion of the ovarian reserve occur, and a more pronounced decrease in ovarian reserve is observed in bilateral ovarian damage.

After the surgical method of treatment, a decrease in the ovarian reserve is associated, among other things, with a violation of intraovarian blood flow as a result of the development of local inflammation, structural changes in ovarian tissue, and protein coagulation [11,12]. Relapses and reoperations on the ovaries lead to the loss of the time interval for the restoration of fertility and a decrease in the ovarian reserve (Shchukina N.A., Buyanova S.N., 2014). At the first European Congress on Endometriosis in 2012 in Siena, it was clearly declared that verified endometrioid ovarian cysts up to 3 cm in diameter are not subject to surgical treatment and pregnancy can be safely tolerated with them [7].

According to the President of the WES (World Society for Endometriosis) R. Vercellini (2014) "the general belief that preliminary laparoscopy should always be performed in order to accurately diagnose the disease must be challenged, since non-surgical diagnosis of endometriosis has demonstrated its high reliability" [4,11].

The tactics of managing women of reproductive age with endometrioid ovarian cysts should be long-term, personified depending on the clinical manifestations of the disease, the size of the education and the woman's reproductive plans [9].

Since 2012, the drug Dienogest 2 mg has been registered in Uzbekistan for the treatment of endometriosis. The drug has an antiproliferative and anti-inflammatory effect on endometrial and endometrioid stromal cells, an anti-oncogenic effect (in experimental studies). Dienogest is the only progestin that has shown similar efficacy to aH-RH at a low dose. The drug effectively relieves pain caused by endometriosis: dysmenorrhea, dyspareunia, chronic pelvic pain due to atrophy of endometrioid foci (Kohler G. Faustmann T.A., Gerlinger C., 2010, Strowitzki T., Marr J. Gerlinger C. et al., 2010).

Objective of the study: to study the functional state of the ovaries, as well as to evaluate the effectiveness of hormonal treatment for endometrioid cysts of small size (up to 3 cm) in women of reproductive age planning pregnancy. Under our supervision (from 2012 to 2016), there were 54 patients aged 19 to 45 years with endometrioid ovarian cysts (ECC) up to 3 cm in size, who, according to international and domestic clinical guidelines, were prescribed Dienogest at a dose of 2 mg.

After collecting anamnesis, all patients underwent clinical and laboratory examination according to generally accepted methods. During ultrasound, special attention was paid to the study of data on the state of the ovaries, the size of the ovaries and the internal echostructure of the endometrioid cyst, the criteria of folliculogenesis in the affected and collateral ovaries (counting the number of antral follicles in one echo section, assessment of the echogenicity of the stroma), indicators of intraovarian blood flow, pulse index of resistance , blood flow in the cyst wall. The level of anti-Müllerian hormone (AMH) was also determined in the blood dynamics.

The average age of women was 32.8 ± 0.7 years. The most frequent complaints in the majority of patients (87.3%) with ECF were pain in the lower abdomen, not associated with menstruation and sexual activity, dysmenorrhea was noted in every fourth (25.4%), dyspareunia in 12.7% of women.

The average duration of infertility in the patients was 2.7 ± 0.1 years, with a predominance of primary infertility in 40 (74.1%) of the examined women.

The ECF diameter varied from 9.7 to 28.3 mm, averaged 20.2 \pm 4.4 mm, Vav = 9.1 mm.

During transvaginal ultrasound examination, the following signs were revealed: rounded shape was the most typical for the majority of patients - 84.5%. The internal structure of the cyst was represented by a finely dispersed suspension in all cases of observation (100%); double contour of the cyst was observed in 20.4% (11) women, single and / or multiple inclusions of increased echogenicity were visualized in 63% (34) women. In 14.8% (8) of the examined women, the only sign of an endometriotic cyst was only a finely dispersed suspension.

Just like the double ECL contour, the echo sign of the presence of single and / or multiple inclusions, increased echogenicity indicates the age of the process and is confirmed by the literature data. They were found in 63% (34) of patients

The study of the functional state of the affected ovary in patients showed that the majority (80.3%) of patients had echo signs of

folliculogenesis disturbance before the start of therapy, the number of antral follicles in one echo cut averaged 2.5 follicles. Almost every second (48.2%) patient experienced luteinization of the non-ovulated follicle.

Hemodynamic study of intraovarial blood flow before the start of treatment showed an increase in the resistance index in the second phase of the menstrual cycle (cf. IR was 0.75, pulsation index cf. PI 1.15).

Ovarian intraovarial blood flow showed lower IR and PI (0.58 and 0.89, respectively). The ovarian stroma was comparable to the echogenicity of the myometrium. The number of antral follicles averaged 5-7 in one echo cut.

The data obtained showed that with an endometrioid cyst, the blood supply to the ovarian stroma is disturbed, the number of antral follicles in both the affected and collateral ovaries decreases, which leads to a decrease in the ovarian reserve.

After the examination, the patients were prescribed Dienogest in a dose of 2 mg for a period of 6 to 12 months according to the generally accepted scheme, from the first day of the menstrual cycle. Dynamic observation in the period after a month, 3.6 months and a year against the background of treatment showed that a decrease in the ECF diameter by an average of 9.7 mm in every second patient (44.4%) was observed after 3 months, while the average ECF diameter was 12.6 + -0.9 mm.

In 11.1% (6) patients in the CDC mode, blood flow was observed in the wall of the endometrioid cyst. In the course of dynamic observation, these patients showed the following feature: a faster regression of the cyst size was noted.

Against the background of hormonal treatment, the structure of the collateral ovary and the unchanged tissue of the affected ovary were characterized by the presence of antral follicles in the amount of 7-10 and 1-2 in one echo cut, respectively. The average diameter of the antral follicles in the collateral ovary was 10.7 mm, and in the affected ovary 5.2 mm. The study of intraovarial blood flow showed that moderate vascularization of the stroma of both ovaries was visualized, the mean RI and PI were 0.56 and 0.87, respectively.

In this case, the echo signs of ECF: fine suspension, double cyst contour, hyperechoic inclusions, rounded form of education, as well as echogenicity of the ovarian stroma, were not changed during the entire treatment period.

After 6 months, against the background of treatment, the diameter of the endometrioid cyst decreased by an average of 10 mm in 14.8% (8) patients. The internal echo structure of the cyst was unchanged after 6 months. The number of visualized antral follicles in one echo section in the collateral and affected ovaries decreased to 35 and 1, respectively. Their average diameter averaged 6 mm and 4.2 mm, respectively. In the CDC mode, insignificant blood flow in the stroma of both ovaries was visualized, the mean IR and PI were 0.50 and 0.70, respectively, which indicates an improvement in blood flow.

After 12 months of treatment, the diameter of endometrioid cysts in 59.3% (32) of patients decreased on average by 5 mm. In 40.7% (22) patients, the cyst diameter remained unchanged throughout the entire period. In these patients, the structure of the collateral and unchanged part of the affected ovary by the end of the observation period was characterized by the presence of 3-5 antral follicles with an average diameter of 3 mm, in the CDC and energy Doppler (ED) mode, insignificant blood flow with highly resistant indices, IR and PI 0 was determined in the stroma. 68 and 0.96, respectively, indicating an improvement in blood flow.

The l evel of AMH in the blood serum on the 3rd day of the menstrual cycle before treatment and after 1,3,6 and 12 months after treatment of the examined patients did not depend on the localization of the endometrioid cyst and before treatment averaged $3.02 \text{ ng}/\text{ml} \pm 2.0 \dots$ In 44 women (81.5%) with unilateral lesion of the ovary, the mean ECF diameter was $21.8 \pm 1.9 \text{ mm}$ and the AMH level was 3.22 ng/ml. With bilateral localization of ECF - 13 patients, the average diameter of the ECF was 21.5 ± 2.0 , the level of AMH was 2.96 ng/ml.

One month after the start of the rapy, the patients showed a slight decrease in the AMH level from $2.78~{\rm ng}$ / ml to $2.26~{\rm ng}$ / ml after 12 months.

A decrease in the level of AMH during therapy with Dienogest is associated with the effect on the granulosa cells of the growing follicle and is due to drug hypoestrogenism, which is necessary for effective treatment of endometriosis.

In 53 patients, we were able to evaluate the effectiveness of treatment with Dienogest 2 mg 12 months after the end of treatment. The menstrual cycle in patients recovered after 1 month in most patients - 55.6% (30) of patients with unilateral ECF localization, and 5.5% (3) of patients with bilateral ECF. The rest of the menstruation resumed after 2 months.

Before the start of therapy, 40.7% (22) of the patients complained of dysmenorrhea, 33.3% (18) of the patient complained of dyspareunia; pain not related to sexual activity was disturbed by 87.0% (47) of the patients. While taking Dienogest after 3 months, complaints of dyspareunia were noted by 9.3% (5) of patients, pains not related to sexual activity persisted in 77.8% (42) of patients. 6 months after the start of therapy, complaints of dyspareunia were noted by 4.2% (2) of patients, 48.2% (26) of patients with pain not related to sexual activity. After 12 months, dyspareunia persisted in less than 1.9% (1) of patients, pain not associated with sexual activity was noted by 22.2% (12) of patients. One of the criteria for the effectiveness of treatment in patients was the assessment of the restoration of reproductive function, which showed the following. Pregnancy occurred in 13% of patients. The average gestational age after the end of treatment was 3.5 months. The maximum number of pregnancies occurred within 6 months after the end of the therapy.

Based on the results obtained, the following conclusions were drawn: Prescription of Dienogest at a dose of 2 mg in monotherapy in the treatment of small size ECL is justified due to the proven clinical efficacy: a decrease in the diameter of the endometrioid cyst by half in 59.3% of patients within 6 months from the moment initiation of therapy. Decrease in the severity of dysmenorrhea in 20%, dyspareunia in 29.1% of patients, pain not associated with sexual activity in 38.8%.

In the presence of echographic signs (irregular form of formation, double contour of the cyst, single and / or multiple inclusions of increased echogenicity), despite the small size of the ECF (up to 3 cm in diameter), there is a decrease in the effectiveness of conservative treatment, which is characterized by the lack of dynamics of reduction of ECF and recovery fertile function. In this regard, these patients in the period after 3-6 months should revise further treatment tactics in favor of combined (laparoscopy with further prescription of anti-relapse therapy).

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