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GENETIC POLYMORPHISM AND AGE OF MANIFESTATION GENITAL ENDOMETRIOSIS

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ABSTRACT

Background: Endometriosis is one of the most common gynecological diseases, which reflects the medical and social significance of the problem of effective diagnosis and treatment. To date, the causes, diagnosis and treatment of this disease remain the subject of controversy. The pathogenesis of the disease is multifactorial and has not been sufficiently studied; non-invasive examination methods have relative diagnostic value, therefore modern therapeutic approaches often do not provide a complete cure.

Purpose: Improving the diagnosis of genital endometriosis based on apoptosis markers and angiogenesis regulators.

Methods: Clinical and laboratory examination of patients was carried out on the basis of the gynecological department of the perinatal center of the Bukhara Regional Perinatal Center. Patients with genital endometriosis underwent ultrasound examination of the pelvic organs, hysteroscopy, followed by targeted diagnostic curettage of the uterine cavity and histological examination of the scraping, and general clinical and laboratory research methods were used.

Conclusion: Early age of manifestation of genital endometriosis is associated with genetic variants -308 AA, -308 GA tumor necrosis factor a and +36 GG, +36 AG tumor necrosis factor receptor type 1.

KEYWORDS: genital endometriosis, genetic polymorphism, endometrium, hyperplastic process.

INTRODUCTION

Currently, many aspects of the etiopathogenesis of endometriosis are controversial and continue to be the focus of attention of domestic and foreign researchers [11]. There are a significant number of hypotheses for the occurrence of endometriosis, however, none of them

has become definitively proven and generally accepted [3]. According to experimental and clinical data, tumor necrosis factors play a significant role in the development of endometriosis [12]. These cytokines, having pro-inflammatory, apoptotic, proliferative mechanisms of action [], influence the development and progression of endometrioid lesions [14]. Genetic factors are important in the etiopathogenesis of endometriosis. A number of works are devoted to the study of the genetic basis of endometriosis [15]. However, it should be noted that most of these studies were carried out abroad, and the results obtained by different groups of researchers are contradictory and do not give a clear answer about the role of genetic factors in the pathogenesis and clinical features of endometriosis. Clinical genetic works devoted to the molecular genetic aspects of genital endometriosis are few in Uzbekistan and mainly affect the genes of detoxification [16], the major histocompatibility complex [9], aromatase [10], integrins [8], and interleukins [7]. The role of polymorphic markers of tumor necrosis factor genes and their receptors in relation to genital endometriosis in our country has been studied extremely poorly, which dictates the need to conduct these studies in the Bukhara region.

The purpose of the study. Improving the diagnosis of genital endometriosis based on apoptosis markers and angiogenesis regulators.

MATERIALS AND METHODS

The results of observations of 116 patients with genital endometriosis and 31 population control women were analyzed. The samples of patients and population controls included individuals of Uzbek nationality who were natives of the Bukhara region and were not related to each other. Genomic DNA was isolated from peripheral blood using the phenol-chloroform extraction method (Mathew C.G., 2015). Genotyping of DNA markers was carried out by analysis of restriction fragment length polymorphism (RFLP) of PCR amplification products of specific genome regions using the appropriate restriction enzymes produced by Sibenzym LLC (Moscow) and allele discrimination based on Tag Man probes using software - Standard Edition Version 2.0 (Bio-Rad).

RESULTS AND DISCUSSION

Due to the particular importance for practical gynecology of the problem of developing individual tactics for managing patients with genital endometriosis, which largely depends on the reproductive plans of patients and the age of diagnosis [13], we analyzed the associations of the studied

polymorphic genetic markers with age of disease manifestation at various stages of the pathological process. Significant associations of two (-308 G/A TNFa and +36 A/G TNFR1) of the four analyzed molecular genetic markers with the age of manifestation of genital endometriosis were established. It was revealed that in patients with the 1st stage of the spread of the pathological process, having genotypes +36 AG and +36 GG TNFR1, an earlier onset of the disease is observed (median 26.0 years, lower quartile - 22.0 years, upper quartile - 33.0 years) in comparison with patients with the +36 AA TNFR1 genotype (median 33.3 years, lower quartile - 24.9 years, upper quartile - 40.1 years, $p = 0.02$).

In the group of patients with genital endometriosis with stage 5 of the prevalence of the process, associations between the age of onset of cyclic pain and the polymorphic marker -308 G/A TNFa were identified. Women with the highly productive -308 A TNFa allele (genotypes -308 AA and -308 GA) are characterized by early onset of cyclic pain (median - 24.0 years, interquartile range 25.0 - 31.0 years) compared to individuals with the - genotype - 308 GG TNFa (median - 33.0 years, lower quartile - 26.0 years, upper quartile - 41.4 years, $p = 0.02$).

In patients with PMU stages of the disease, the age of onset of genital endometriosis is associated with the genetic polymorphism -308 G/A tumor necrosis factor a: in patients with genotypes -308 AA and -308 GA, the age of manifestation of the first symptoms of genital endometriosis is 21.0 years (lower quartile - 14.0 years, upper quartile - 23.0 years), which is significantly less than the same indicator for patients with the -308 GG TNFa genotype (median age of onset of first symptoms is 28.0 years, with an interquartile range of 24.0 - 41. 0 years, p =0.015).

Thus, the data obtained indicate the important role of genetic markers associated with pro-inflammatory effects [6] in the early manifestation of genital endometriosis.

Among the 116 women examined with genital endometriosis, 53 patients (45.7%) complained of pelvic pain, infertility was detected in 71 women (61.2%), perimenstrual bleeding was observed in 31 women (26.7%), dysmenorrhea was registered in 85 patients (75.3%), hypermenorrhea - in 57 (49.1%), dyspareunia - in 75 (64.6%) patients.

It was found that in patients with perimenstrual bleeding, the concentration of the +250 GG Lta genotype was 11.79% and was 2.5 times higher compared to women in the control group (4.45%, x^2=4.89, p=0, 01, taking into account the Bonfferoni correction Pcog=0.046, OR=2.71, 96%C1 1.19-6.10). In women with infertility due to genital endometriosis, a high frequency of the -308 A TNFa allele (15.29%) was detected compared with the control group (10.08%, p = 0.05, 0R = 1.61, 95%C1 1.02 -2.59) and patients with genital endometriosis without infertility (8.91%, p=0.05).

Thus, genetic polymorphisms -308 G/A TNFa and +250 A/G Lta have important clinical significance in genital endometriosis. Their associations with the formation of infertility and the appearance of perimenstrual bleeding in genital endometriosis may be based on pro-inflammatory mechanisms of action of tumor necrosis factor a and lymphotoxin a [7].

Modern ideas about the pathogenesis of genital endometriosis and endometrial hyperplastic processes indicate the presence of common mechanisms for the development of these pathological processes: decreased apoptosis in endometrial cells, increased proliferative activity of the endometrium, hyperproduction of growth factors and cytokines, etc. [4]. In this regard, we analyzed the distribution of the studied molecular genetic markers in women with genital endometriosis depending on its combination with endometrial hyperplastic processes. Among 116 patients with endometriosis, endometrial hyperplastic processes occurred in 31.03% of patients (n=36).

It was found that in patients with genital endometriosis and endometrial hyperplasia, the frequency of the -308 A TNFa allele is 19.05%, which is 1.9 times higher than the same figure in the control group (11.07%, x^2= 3.99, p= 0.03, 0R = 2.21 96% CI 1.09-3.09).

So, the molecular genetic risk factor for the development of endometrial hyperplasia in women suffering from genital endometriosis is the highly productive allele -308 A of tumor necrosis factor α. Our results are consistent with literature data on the important role of this genetic marker in the development of endometrial hyperplastic processes combined with uterine fibroids [1,15]. Having a pro-inflammatory effect, tumor necrosis factor a enhances proliferative changes in the endometrium, which can lead to its hyperplasia [5,19,20].

According to the literature, genital endometriosis is considered a hormone-dependent pathology [5,7,9]. The development of genital endometriosis occurs against the background of dysfunction of the hypothalamic-pituitary-ovarian system, which can lead to pathological conditions in the mammary glands in patients with endometriosis [3]. Among the 116 patients with genital endometriosis we examined, mastopathy occurred in 23 women (22.0%).

In a comparative analysis of the distribution of genetic polymorphisms of tumor necrosis factors and their receptors in groups of patients with endometriosis, depending on the presence of mastopathy, it was found that patients with genital endometriosis with mastopathy are

characterized by a significantly lower (more than 2.5 times) frequency of the +36 CO genotype of the necrosis factor receptor type 1 tumors (10.20%) compared with both women with endometriosis without mastopathy (27.98%, x2 =5.4, p=0.01, Pcor =0.02) and with population controls (25.79%, =4.5, p = 0.015, Pcog = 0.039, OK = 0.29, 95% C1 0.11-0.79).

According to the literature (Bazzoni F. et al, 2016), the tumor necrosis factor type 1 receptor is involved in TNF-dependent apoptosis. In accordance with this, a low level of TNFR1 production (characteristic of individuals with genotypes +36 AA and +36 AG TNFR1) may cause a decrease in TNF-dependent apoptosis, which is clinically will be manifested by the development, along with genital endometriosis, of proliferative processes in the mammary gland. We recorded this phenotypic effect in our study.

An analysis of the relationships between genetic polymorphisms and clinical features of genital endometriosis combined with mastopathy was carried out. It was shown that among patients with mastopathy who have pain, the concentration of the +250 GG Lta genotype (20.69%) is 4 times higher compared to women in the control group (4.09%, =5.69, p = 0.01 , Pcog = 0.02, OR = 4.00, 95%C1 1.29-16.39). It has been established that in patients with genital endometriosis with mastopathy who have perimenstrual discharge, the highest frequency of the genotype +250 GG Lta (17.97%) is observed, which significantly exceeds the corresponding indicator in the control group (4.99%, =5.12, p=0 .01, peor =0.03, OR = 3.18, 95%CI 1.19-12.08).

In the etiology of genital endometriosis, an important role is played by hereditary predisposition (Tikhomirov A.L., 2017, Adamyan L.V., 2016). A study was carried out of the relationship between genetic polymorphisms of tumor necrosis factors and their receptors with the formation and clinical characteristics of endometriosis, depending on the hereditary burden of hyperplastic processes of the uterus. In the study sample of patients (n=116), 26.7% (n=39) had a hereditary history of hyperplastic processes of the genitals; in 71.1% (n=170), the heredity was not burdened.

Associations of genetic markers with the formation and clinical signs of endometriosis were identified only among women without a hereditary burden of genital hyperplastic processes. It has been established that the risk factor for the formation of genital endometriosis in cases of uncomplicated heredity due to hyperplastic processes of the uterus is the genotype +250 GG Lta, the concentration of which in this group (11.98%) was 3.5 times higher than among patients with a hereditary burden (3, 23%, x2 =3.21, p=0.06) and was 2 times higher than in the control group (4.98%, =4.79, p=0.014, Pcog=0.039, OR=2.69, 95% CI 1.16-4.99).

A detailed analysis of the associations of molecular genetic markers with clinical symptoms of genital endometriosis among patients without a hereditary history of genital hyperplastic processes showed that in women of this group with dysmenorrhea, the frequency of the +250 GG Lta genotype was 16.45% and was more than 3 times higher compared to the control group (5.27%, x2 = 8.3, p = 0.005, Pcog = 0.015, OR = 3.44, 95% CI 1, 42-8.35). The highest frequency of the +250 G Lta allele was found in the study group of patients (31.22%) in comparison with women in the control group (25.1%, x2=3.78, p=0.05, OR=l.49, 95% CI 1.02-2.01). The concentration of the genotype - 308 GG TNFa in women without hereditary burden of hyperplastic processes of the uterus and with infertility was 66.04% and was significantly less than the same indicator in the control group (79.89%, x2 = 5.04, p = 0.01, Pcog=0.02, OK=0.48, 95% C1 0.26-0.78). A high prevalence of the +250 CC Ltα genotype was also revealed in the group of patients with perimenstrual discharge (14.29%) compared to the control group (4.29%, =7.18, p = 0.005, Pcog = 0.014, OK = 3.29 , 95% C11.28-6.59).

The results of our study showed that the proportion of morphologically verified endometriosis in women who underwent laparoscopy for infertility was 60.8%. At the same time, other clinical manifestations of endometriosis (pelvic pain, bleeding) were absent in 58.7% of women. Pelvic pain with an average severity of 7.0 points according to VAS was registered in

41.3% of women with endometriosis-associated infertility, 29.3% suffered from dysmenorrhea, 31.3% suffered from dyspareunia, and 12.7% of women suffered from abnormal uterine bleeding. The main localizations of endometriosis were the uterosacral ligaments (80%), pelvic peritoneum (60%), and ovaries (40.7%). More than half of the patients with infertility had stage I-II endometriosis. At the same time, during laparoscopy, it was found that the minimum preserved function (Least function score, LF) in patients of group III averaged 12.4 ± 4.4 points, in patients of group IY 12.8 ± 4.8 points (p = 0.765). The fertility index (EFI) in patients of group III was on average 6.1 ± 3.6 points, in patients of group I–V 6.2 ± 2.4 points (p = 0.860).

Previous studies also indicated the frequent diagnosis of minor forms of endometriosis in patients with infertility and the detection of pain syndrome not in all patients with endometriosis and infertility [1,17,18].

We did not find an association between the polymorphism of genes for estrogen metabolism enzymes: CYP1A1 (T → 264 C), CYP1A2 (C → 734 A), CYP19 (C → 10 T), SULT1A1 (G → 638 A) in infertile women with endometriosis in comparison with patients with tubo-peritoneal infertility. The absence of this relationship may indicate the absence of a significant role of hyperestrogenism in the pathogenesis of endometriosis-associated infertility, which may determine approaches to combination therapy of the disease that exclude the prescription of drugs that have a significant anti-estrogenic effect.

It should be noted that earlier Zotova O.A. et al. (2016) showed the relationship between these polymorphisms and the presence of adenomyosis [2]. On the contrary, Kublinsky K.S. (2015, 2017, 2019) studied other polymorphisms of the same genes CYP1A1 (A-4889G), CYP1A2 (C-734A), SULT1A1 (G-638A) and SULT1E1 (C-174T) and did not reveal their relationship with the effectiveness of treatment of endometriosis. associated infertility in women [12].

The results of our study showed that clinical and anamnestic factors are fundamental in the preoperative diagnosis of endometriosis. Thus, the most significant factors in the preoperative diagnosis of endometriosis in infertile patients are the presence of chronic pelvic pain syndrome ($\chi2=21.677$, $p<0.001$), age ($\chi2=14.172$, $p<0.001$) and the presence of concomitant gynecological diseases ($\chi2=11.185$, $p= 0.001$), living in the city ($\chi2=6.788$, $p=0.009$), presence of dyspareunia ($\chi2=6.954$, $p=0.008$), AUB ($\chi2=3.848$, $p=0.050$), age of sexual debut ($\chi2=4.271$, $p=0.039$), a history of salpingectomy ($\chi2=1.126$, $p=0.04$). Using logistic regression, a computer program “Clinical and anamnestic prognosis of NGE in patients with infertility” was developed, which has a predictive probability of 91.2%.

Currently, all professional medical societies, based on clinical trial data, do not support drug treatment to improve fertility in patients with endometriosis [1,6,8]. However, the results of our study showed that combined treatment of endometriosis-associated infertility using a surgical method (coagulation and excision of endometriosis foci) followed by the administration of GnRH or dienogest is highly effective in reducing both the clinical manifestations of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, bleeding), and in cases of endometriosis-associated infertility. Spontaneous pregnancy occurs in more than half of patients, regardless of the type of drug therapy: in patients in the GnRHa group - in 53.3%, in the dienogest group - in 54.7% (p = 0.870). This approach is significantly more effective than surgical treatment alone. Thus, according to G. David Adamson (2010), with a fertility index of 6 points, the frequency of spontaneous pregnancy within a year is 29.5%, within two years - 48.0%, and within three years - 54.5 % [39]. Patients treated with GnRHa had a significantly higher rate of side effects that affected quality of life (92%), a trend towards a higher rate of pregnancy failure (17.3%) and a lower rate of live births (82.7%) than patients treated with GnRHa. who received dienogest. Among the side effects of GnRH, the most frequently reported were hot flashes (82.7%), decreased libido (74.2%), sweating (60.0%), mood changes (44.0%), and palpitations (42.7%). In women receiving dienogest, a decrease in libido was most often diagnosed (30.0%),

which, however, did not have a significant impact on the quality of life, since the pain syndrome in these patients was practically relieved.

A high incidence of side effects of GnRH agonists has also been reported in previous studies [1]. To eliminate vasomotor manifestations while taking GnRH, it is recommended to prescribe add-back therapy, however, the effectiveness of such a combined approach in relation to the symptoms of endometriosis remains unclear, since the administration of estrogens may neutralize the therapeutic effect of GnRH on endometrioid heterotopias [1,5]. It is believed that further expanded randomized multicenter studies are required to confirm the benefits of prescribing gestagens in combination therapy for patients with endometriosis-associated infertility and pelvic pain [10].

Thus, as a result of the study, it was established that in women who underwent laparoscopy for infertility, the frequency of morphologically verified endometriosis is 60.8%. Despite a significant decrease in fertility according to laparoscopic examination (minimal preserved function minimal preserved function - 12.8 12.8 ± 5.6 points and fertility index ± 5.6 points and fertility index - 6.7 ± 2.6 points), d6.7 ± 2.6 points), other clinical manifestations of endometriosis are absent in more than half of the patients. In endometriosis-associated infertility, the main sites of endometriosis are the uterosacral ligaments, the pelvic peritoneum and the ovaries. It has been proven that there is no relationship between the polymorphism of genes for estrogen metabolism enzymes: CYP1A1, CYP1A2, CYP19, SULT1A1 and endometriosis-associated infertility, which indicates the absence of the role of hyperestrogenism in the pathogenesis of impaired fertility in these patients. The determining factor in the preoperative diagnosis of endometriosis is the assessment of clinical and anamnestic factors: the presence of typical clinical manifestations of the disease (chronic pelvic pain syndrome, dyspareunia, AUB), the patient's age and coitarchal age, the presence of concomitant gynecological diseases, and residence in the city. Preoperative diagnosis of endometriosis for the purpose of selecting patients for surgical treatment can be carried out using the computer program "Clinical and anamnestic prognosis of NGE in patients with infertility," developed using binary logistic regression and including nine clinical and anamnestic factors, which has high sensitivity and specificity. A combined approach to the treatment of patients with endometriosis-associated infertility is highly effective in relieving pain; pregnancy occurs in more than half of women within a year. The effectiveness of treatment does not depend on the type of drug therapy (a-GnRH or dienogest), however, when prescribing a-GnRH, adverse neurovegetative symptoms are much more common, and there is a tendency to increase the incidence of non-developing pregnancy.

The results of the study showed that almost half of women with endometriosis-associated infertility have stage III-IV endometriosis. The predominant localization of endometriosis foci in infertile patients of both groups was the pelvic peritoneum, uterosacral ligaments and ovary. A previous study by Meuleman C. showed that 37% of infertile patients without a prior surgical diagnosis of endometriosis who underwent diagnostic

laparoscopy, III IV stage of endometriosis is detected. Despite the randomization, patients of group III had a statistically significantly higher incidence of damage to the uterosacral ligaments 88% (66) ($p = 0.014$), and patients of group IV had a greater number of women with a history of spontaneous pregnancy and a greater number of pregnancies and births per 1 patient. The groups were similar in other characteristics.

It is now generally accepted that surgical and medical treatments for endometriosis should not be opposed. The advantages and disadvantages of each method must be carefully weighed before starting treatment, taking into account the individual characteristics of the case. This will minimize the negative features of the case. This will make it possible to minimize negative results, and, on the contrary, to maximize positive ones, and, on the contrary, to maximize positive results [1,9]. It is generally accepted that drug treatment after surgery does

not improve It is generally accepted that drug treatment after surgery does not improve fertility, however, all patients included in the study had manifestations of pain (intermenstrual pelvic pain, dysmenorrhea, dyspareunia), and therefore a decision was made to prescribing drug therapy after surgical treatment.

After a combined approach, including surgical treatment (ablation and/or excision) of endometriotic lesions followed by drug therapy with GnRHa or dienogest, pregnancy occurred spontaneously in more than half of the cases in both groups (53.3-54.7% (40-41)). A previous retrospective cohort study demonstrated a significantly lower 3-year pregnancy rate in patients with endometriosis-related infertility compared with patients with unexplained infertility (36% (27) vs. 56% (42), $p < 0.05$) [9].

The issue of a combined approach to the treatment of endometriosis-associated infertility has not yet been clearly resolved and associated infertility has not yet been clearly resolved and is widely discussed in the literature. The study conducted in China is widely discussed in the literature. In a study conducted in China, He L.Q. (2018), showed that therapy (2018), showed that GnRH therapy after conservative laparoscopic surgery can significantly increase pregnancy rates in infertile women with moderate to severe endometriosis. However, it has been proven that in patients with mild forms of endometriosis, GnRH therapy does not improve the prognosis. The first 6 months after months after laparoscopic surgery or after stopping treatment or after stopping GnRH treatment is the optimal time interval for pregnancy, and a longer time from stopping therapy is associated with pregnancy, and a longer time from stopping therapy is associated with a lower likelihood of spontaneous pregnancy. pregnancy [7].

A case-control study conducted by Yang Y. (2019) on 116 patients demonstrated the benefits of the combined approach in terms of overall efficacy, pregnancy rate, relapse rate, and levels of serum markers IL-17, IL-6 and TNF- α. There was no statistically significant difference in the incidence of adverse reactions between the two groups ($p = 0.730$) [6].

In the study Artymuk N.V. et al. (2016, 2017) shows a similar study by Artymuk N.V. et al. (2016, 2017) showed similar effectiveness of a combined approach to the treatment of endometriosis; the effectiveness of a combined approach to the treatment of endometriosis-associated infertility with the use of dienogest and GnRH agonists after associated infertility with the use of dienogest and GnRH agonists after surgical treatment. Frequency of spontaneous pregnancy during surgical treatment. The spontaneous pregnancy rate within a year was about 30.7% (23) in both groups, but in patients receiving GnRHa agonists, there were significant side effects. , as well as statistically, GnRH, and also statistically significantly more often non-developing pregnancy was registered, which was significantly more often registered non-developing pregnancy, which was probably due to the hypoestrogenic effect of the drug on the endometrium [endometrium [11, 12,13,17].

In a study by Muller V. (2017), similar results were obtained in 144 patients after cystectomy for endometrioma who were planned for IVF. After surgical treatment, the patients were divided into 3 groups: in one group dienogest was prescribed, in the other - GnRHa, the third group of women did not receive treatment. As a result, in patients receiving dienogest, pregnancy was registered 2.5 times more often (44.7% versus 16.7%, $p = 0.012$), and the birth rate was three times higher (36.8% versus 11.1 %, $p = 0.013$) compared with patients receiving GnRHa [8]. In contrast, a study conducted by Xue H. (2019) showed benefits in a combination approach of triptorelin over gestrinone and mifepristone. Patients receiving triptorelin had a higher pregnancy rate, a lower relapse rate, and a similar incidence of side effects [6]. However, hormonal therapy with antigonadotropins, most professional associations do not recommend antigonadotropin therapy for patients with endometriosis and infertility to increase the chances of spontaneous pregnancy, including after surgery, the chances of spontaneous pregnancy, including including after surgery [1, 5, 8,9, 16].

Treatment of endometriosis-associated infertility should be interdisciplinary and take into account the presence of pain, duration of infertility, general assessment of the infertile couple, various phenotypes of endometrioid lesions, and the desire to use “aggressive” treatment methods [11, 14, 15].

Summary. Thus, the results of the study showed that combined treatment of endometriosis-associated infertility using a surgical method (coagulation and excision of endometriosis foci) followed by the administration of GnRH-a or dienogest is highly effective in reducing the clinical manifestations of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, bleeding). Spontaneous pregnancy occurs in more than half of the patients. Combined treatment of endometriosis-associated infertility in patients with a fertility index of 6.1 ± 3.6 points, 6.1 ± 3.6 points and 6.2 ± 2.4 points in and 6.2 ± 2.4 points using a surgical approach (coagulation and excision of endometriosis foci) followed by drug therapy using dienogest or gonadotropin-releasing hormone agonists leads to similar pregnancy rates within a year in both groups - 53.3% and 54.7%. Patients treated with GnRH-α had a significantly higher rate of side effects that affected quality of life (92%), a trend towards a higher rate of pregnancy failure (17.3%) and a lower rate of live births (82.7%) than in patients receiving dienogest. Among the side effects of GnRH a, the most frequently reported were hot flashes (82.7%), decreased libido (74.2%), sweating (60.0%), mood changes (44.0%), and palpitations (42.7%). In women receiving dienogest, decreased libido was most often diagnosed (30.0%). Further expanded randomized multicenter studies are required to confirm the benefits of prescribing gestagens in combination therapy for patients with endometriosis-associated infertility and pelvic pain.

Summarizing the results obtained, it should be noted that the relationship of genetic polymorphisms with the formation and clinical features of genital endometriosis are significant among patients without a hereditary burden of genital hyperplastic processes and are absent in the group of women with a hereditary burden. These data may indicate that there are other genetic factors that determine, to a greater extent than genetic polymorphisms of tumor necrosis factors and their receptors, the features of inheritance of hyperplastic processes of the uterus (including endometriosis) in the group of patients with genital endometriosis we studied (these genetic factors, according to the literature, include polymorphisms of factor genes growth [1], estrogen and progesterone receptors [2], cynpeccopob oncogenes [4], detoxification of xenobiotics [5], the major histocompatibility complex [3].

CONCLUSION

When using genetic polymorphisms of tumor necrosis factors and their receptors for individual prognosis of the clinical manifestations of genital endometriosis, the presence of a hereditary burden of hyperplastic processes of the uterus should be taken into account.

The prevalence of the -308 A TNFa allele in women with genital endometriosis combined with endometrial hyperplasia is 1.8 times higher compared to population controls. The protective factor for the development of genital endometriosis combined with mastopathy is +36 GG TNFR1 (OR=0.2), and the formation of pain and perimenstrual discharge in women of this group is associated with the +250 GG Lta marker (OR=4.9 and OR= 4.3 respectively).

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