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Z.S. Huseynova[1]
Azerbaijan Medical University, Azerbaijan, Baku
[1]Binagadi Medical Center named after A.D. Melikov, Azerbaijan, Baku

CHARACTERISTICS OF REPRODUCTIVE FUNCTION DISORDERS IN PATIENTS WITH ENDOMETRIAL HYPERPLASIA WITHOUT ATYPIA

e-mail: med_avtor@mail.ru

The study involved 118 women who were divided into three groups: Group C – control, practically healthy women (50 women), Group I – women with endometrial hyperplasia and reproductive dysfunction (43 patients), Group II – women with reproductive disorders and endometrial hyperplasia in combination with one of the other benign uterine pathologies (25 patients). Patients with an increased body mass index and advancing age were found to have a higher incidence of endometrial hyperplasia and reproductive dysfunction. In patients with endometrial hyperplasia, menstrual dysfunction was manifested by menometrorrhagia, which was accompanied by posthemorrhagic anemia. Reproductive dysfunction in patients with endometrial hyperplasia is characterized by infertility. In Group I, primary infertility predominates**;** in Group II, secondary infertility is more common, and infertility lasting more than 5 years is more frequent in Group II. Levels of estradiol were higher, and progesterone levels were lower compared to the control group. In the group with endometrial hyperplasia, changes in the hemodynamic parameters of the uterine arteries were observed: the systole-diastolic ratio, resistance index, and pulsation index in both arteries were lower than in the control group. When pregnancy occurred after treatment in patients with endometrial hyperplasia, no significant pathologies were observed during pregnancy, in its outcomes, or in the condition of the newborns. Timely assessment and contribute to pathogenetically based treatment and the realization of reproductive desires.

Key words: endometrial hyperplasia, menstrual dysfunction, reproductive dysfunction, infertility.

З.С. Гусейнова

ОСОБЛИВОСТІ ПОРУШЕНЬ РЕПРОДУКТИВНОЇ ФУНКЦІЇ У ПАЦІЄНТОК З ГІПЕРПЛАЗІЄЮ ЕНДОМЕТРІЮ БЕЗ АТИПІЇ

У дослідженні взяли участь 118 жінок, які були поділені на три групи: група С – контрольна, практично здорові жінки (50 жінок), група І – жінки з гіперплазією ендометрію та репродуктивною дисфункцією (43 пацієнтки), група ІІ – жінки з репродуктивними порушеннями та гіперплазією ендометрію у поєднанні з однією з інших доброякісних патологій матки (25 пацієнток). Було виявлено, що у пацієнток з підвищеним індексом маси тіла та літнім віком частіше зустрічається гіперплазія ендометрію та репродуктивна дисфункція. У пацієнток з гіперплазією ендометрію порушення менструального циклу проявлялося менометрорагією, яка супроводжувалася постгеморагічною анемією. Порушення репродуктивної функції у пацієнток із гіперплазією ендометрію характеризується безпліддям. У І групі переважає первинне безпліддя, у ІІ групі частіше зустрічається вторинне безпліддя, а у ІІ групі частіше зустрічається безпліддя тривалістю понад 5 років. Рівень естрадіолу був вищим, а рівень прогестерону нижчим порівняно з контрольною групою. У групі з гіперплазією ендометрію спостерігалися зміни гемодинамічних показників маткових артерій: співвідношення систола-діастола, індекс резистентності та індекс пульсації в обох артеріях були нижчими, ніж у контрольній групі. Коли після лікування у пацієнток з гіперплазією ендометрію наставала вагітність, жодних суттєвих патологій під час вагітності, її наслідках чи стані новонароджених не спостерігалося. Своєчасна оцінка та діагностика клінічних симптомів у пацієнток з гіперплазією ендометрію та репродуктивними порушеннями сприяють патогенетично обґрунтованому лікуванню та реалізації репродуктивних бажань.

Ключові слова: гіперплазія ендометрію, порушення менструального циклу, репродуктивна дисфункція, безплідність.

Endometrial hyperplasia (EH) is a pathological process of the uterine mucosa characterized by glandular proliferation and an increased glandular-stromal ratio [4]. In the structure of gynecological pathology, endometrial hyperplastic processes occur with a frequency of 15–40 % [3, 8]. The prevalence of EH reaches 133 per 100,000 women and tends to increase with age. Its frequency in women under 30 years of age is relatively low, but after 35–40 years, it increases, peaking in the 50–54 age group [6]. Clinically, this pathology manifests through disturbances in menstrual and reproductive functions. The main clinical determinants of EH include abnormal uterine bleeding (AUB) and/or heavy or intermenstrual bleeding during regular menstrual cycles or oligomenorrhea [10]. EH is generally associated with a progesterone-deficient state and can cause anovulatory infertility [14]. Women who are overweight or obese, experience long anovulatory menstrual cycles, or have increased conversion of androgens to estrogens in adipose tissue are at an elevated risk of developing endometrial hyperplasia and endometrial cancer [1, 13]. The diagnosis of EH is based on ultrasound findings, clinical history, and hysteroscopic evaluation. However, the final diagnosis is confirmed through a morphological study of the endometrium [3, 14].

Despite advances in understanding endometrial hyperplastic processes, the issues surrounding the diagnosis and management of endometrial pathology in infertility remain unresolved [7]. Approximately 40 % of young women with endometrial hyperplasia undergo surgical treatment, which may lead to a loss of reproductive function [5].

The purpose of the study was to analyze the features of endometrial hyperplasia without atypia and its effect on reproductive function.

Materials and methods. The study included women of reproductive age with reproductive dysfunction who sought medical help in the city of Baku at Maternity Hospital No. 5 named after Shamama Alasgarova, Clinical Medical Center No. 1, and Women's Counseling Center No. 5 during the period from 2017 to 2022. To assess the effect of endometrial hyperplasia on reproductive disorders, endometrial hyperplasia without atypia was diagnosed in 68 women aged 18 to 45 years among 200 women with benign uterine pathologies and reproductive disorders. To characterize the effect of endometrial hyperplasia on reproductive dysfunction, study participants were grouped as follows:

– A Control group: 50 fertile women without reproductive disorders.

– B Group I: 43 women with endometrial hyperplasia and reproductive disorders.

– C Group II: 25 women with reproductive disorders and endometrial hyperplasia in combination with one of the other benign uterine pathologies (uterine fibroids, adenomyosis, or endometrial polyps).

Inclusion criteria: Women aged 18 to 45 years; a history of endometrial hyperplasia and reproductive dysfunction (infertility); endometrial hyperplasia combined with one of the other benign uterine pathologies (uterine fibroids, adenomyosis, or endometrial polyps) and reproductive disorders.

Exclusion criteria: Women under 18 or over 45 years of age; a history of benign uterine pathologies and reproductive dysfunction in the absence of endometrial hyperplasia; infertility or fertility disorders of other origins.

Complaints were collected, and anamnesis data were assessed. For all patients, the age of menarche, menstrual function characteristics, reproductive history, and the presence of concomitant extragenital pathology were documented. All patients underwent a physical examination, including determination of body mass index (BMI). Echography was performed using a standard method with a vaginal sensor operating at frequencies of 3.5–7.0 MHz**,** utilizing a SonoAce R7-4D Samsung Madison (Korea) device. The standard method was also applied during Doppler imaging, with the flow imaging mode set at a minimum flow filter level of 50 Hz. The velocity range in 4D color Doppler imaging (CDI) was set to 6 cm/s. To clarify the role of hormones and Doppler indicators in reproductive dysfunction associated with endometrial hyperplasia, a hormonal study was conducted on days 2–3 of the menstrual cycle. The characteristics of echographic signs and Doppler indicators in the uterine arteries were analyzed during the first phase of the menstrual cycle.

Quantitative and qualitative data were analyzed using statistical processing methods, including the Student-Bonferroni t-test, Mann-Whitney U-test, and discriminant analysis (Pearson Chi-Square test), within the SPSS-26 statistical package. The null hypothesis was rejected at $P<0.05$.

Results of the study and their discussion. The mean age of patients with endometrial hyperplasia without atypia and reproductive dysfunction was 31.1±0.5 years. In women with endometrial hyperplasia, overweight was observed in 62.8 % of patients in Group I and in 68.0 % in Group II. Obesity was detected in 11.6 % of patients in Group I and in 16.0 % in Group II. The average body mass index (BMI) in the control group was 25.5±0.4, in Group I – 26.9±0.4, and in Group II – 26.7±0.5. The difference between the groups was Pc-I = 0.010* and Pc-II = 0.032*. When examined for extragenital diseases, iron deficiency anemia was detected in 30 (69.8 %) women in Group I and in 27 (84 %) women in Group II. In the control group, iron deficiency anemia was registered in 13 (26 %) women with degree I anemia; the difference between the control group and groups with endometrial hyperplasia was $p<0.001$. Arterial hypertension was detected in 7 (16.3 %) patients in Group I and in 10 (40.0 %) patients in Group II; the difference between the groups was P I-II = 0.031*. Polycystic ovary syndrome was detected in 16 (41 %) patients in Group I and in 6 (24.0 %) patients in Group II; the difference between the groups was P I-II = 0.043*. In the group with endometrial hyperplasia, menarche began at the age of 13.4±0.2 years; there were no significant differences between the groups. The average duration of menstruation was 7.1±0.3 days in Group I, 7.4±0.4 days in Group II, and 5.7±0.1 days in the control group; the difference between groups was $P<0.001$. A menstrual cycle lasting less than 21 days was observed in 32 % of patients in Group II, while a cycle of more than 35 days occurred in 34.9 % of patients in Group I. The duration of the menstrual cycle within 21–35 days was more often recorded in both groups with endometrial hyperplasia (53.5 % and 64.0 %, respectively).

Menorrhagic disorders of the menstrual cycle were more frequently noted in Group I. A significant difference between Groups I and II was PI-II = 0.004*. (Fig. 1).

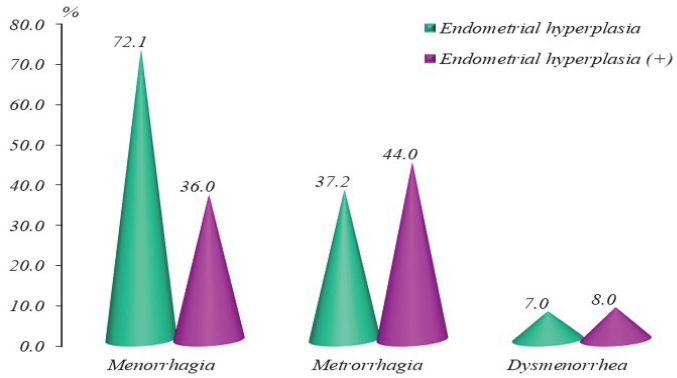

Fig. 1. Comparative characteristics of menstrual function indicators in women with endometrial hyperplasia and reproductive dysfunction.

In patients with endometrial hyperplasia, primary infertility was observed in 25 (58.1 %) patients in Group I and in 11 (44.0 %) patients in Group II. Secondary infertility was detected in 18 (41.9 %) patients in Group I and in 14 (56.0 %) patients in Group II. Patients with infertility lasting 2 years predominated in Group II, accounting for 30.0 % of patients (4.8 % in Group I). The duration of infertility of 3–5 years prevailed in Group I and was observed in 23 (57.5 %) patients, while in Group II – in 3 (14.3 %) patients. The duration of infertility over 5 years prevailed in Group II and was detected in 81.0 % of patients (12.5 % in Group I). There was a significant difference between the groups (PI-II<0.001).

The initial diagnosis of endometrial hyperplasia was established during transvaginal ultrasound examination in the first phase of the menstrual cycle. Ultrasound examination determined the thickness, size, and nature of the endometrium. In patients with endometrial hyperplasia, the thickness of the endometrium was 15.9±0.7 mm in Group I, 15.0±1.0 mm in Group II, while in the control group it was 5.7±0.1 mm. The differences between the groups with endometrial hyperplasia and the control group were statistically significant (p<0.001). To clarify the role of the blood supply to the uterus and study factors that can cause reproductive dysfunction in patients with endometrial hyperplasia, spectral Doppler ultrasound of the uterine artery was performed. The main attention was paid to indicators such as resistance index (RI), pulsatility index (PI), and systolic-diastolic ratio (S/D) (Table 1).

Table 1

Characteristics of Doppler indices in the uterine arteries

Indices	Groups	N	M	±m	Me	Q1	Q3	Pк	PI
S/D right	Control	50	5.76	0.19	5.62	4.94	6.32		
	Group I	43	5.50	0.19	5.32	4.54	6.42	0.245	
	Group II	25	5.16	0.17	5.27	4.75	5.68	0.062	0.423
S/D left	Control	50	6.29	0.20	6.02	5.23	7.24		
	Group I	43	5.89	0.18	5.91	5.05	6.58	0.179	
	Group II	25	5.31	0.23	5.21	4.28	5.81	0.004*	0.034
	Control	50	0.82	0.007	0.82	0.80	0.84		
	Group I	43	0.81	0.006	0.81	0.78	0.84	0.165	
	Group II	25	0.81	0.008	0.81	0.79	0.83	0.065	0.614
RI left	Control	50	0.83	0.005	0.84	0.81	0.80		
	Group I	43	0.82	0.005	0.83	0.80	0.77	0.178	
	Group II	25	0.81	0.008	0.80	0.85	0.83	0.005*	0.052
PI right	Control	50	2.17	0.05	2.20	1.89	2.36		
	Group I	43	2.01	0.06	1.98	1.67	2.32	0.049*	
	Group II	25	1.88	0.08	1.81	1.68	2.16	0.004*	0.370
PI left	Control	50	2.35	0.06	2.33	1.96	2.68		
	Group I	43	2.11	0.05	2.04	1.85	2.34	0.006*	
	Group II	25	2.01	0.09	1.83	1.75	2.31	0.003*	0.224

Note: Statistical significance of differences between indicators: Pc – control group (Wilcoxon/Mann-Whitney test) P I – group with isolated endometrial hyperplasia (Wilcoxon/Mann-Whitney test) * – the null hypothesis is rejected (p<0.05).

The survey was conducted to study the role of hormones in the group with endometrial hyperplasia and reproductive disorders, as well as to identify similarities and differences with other groups in relevant indices. The level of estradiol in the blood was 98.6±0.96 pg/ml in Group I and 97.9±1.64 pg/ml in Group II**,** which was higher than in the control group (70.2±0.68 pg/ml). A statistically significant difference was observed between the control group and the endometrial hyperplasia groups (p<0.001). The follicle-stimulating hormone (FSH) level was 6.27±0.23 mIU/ml in Group I, 6.58±0.28 mIU/ml in Group II, and 5.33±0.04 mIU/ml in the control group. A statistically significant difference was observed between the hyperplasia groups and the control group (Pc-I = 0.006, Pc-II = 0.001**).

The level of luteinizing hormone (LH) was increased in Group I and amounted to 5.30±0.19 mIU/ml, while in Group II it did not differ from the control group (4.89±0.14 and 4.96±0.27, respectively). The level of prolactin in the blood was nearly the same in the groups with endometrial hyperplasia (17.7±0.4 ng/ml and 17.6±0.8 ng/ml), but higher than in the control group (15.5±0.2 ng/ml); the statistical difference between groups was P<0.001.

The level of progesterone in the second phase of the menstrual cycle in the control group was higher and amounted to 18.8±0.3 ng/ml, while in the groups with endometrial hyperplasia, the level of progesterone was 17.7±0.4 and 17.6±0.4 ng/ml. There were no significant differences between the groups in the levels of thyroid hormones and androgens.

When studying a general blood test, the hemoglobin level in the groups with endometrial hyperplasia (10.4±0.16 g/dl and 10.1±0.22 g/dl) differed from the level in the control group (11.9±0.14 g/dL), which was confirmed by a statistically significant difference between the groups (Pc-I<0.001, Pc-II<0.001). Low hemoglobin levels and the predominance of anemia in endometrial hyperplasia were explained by menstrual dysfunction such as polymenorrhea, hyperpolymenorrhea, menorrhagia, and menometrorrhagia.

To restore the menstrual cycle and realize reproductive desires, patients with endometrial hyperplasia were prescribed hestogens: 30 (69.8 %) patients from Group I and 17 (68.0 %) patients from Group II**.** Oral contraceptives were prescribed to 21 (48.8 %) patients from Group I and 13 (52 %) patients from Group II**.** Hemostatic therapy was prescribed to 20.9 % of patients in Group I and 68.0 % of patients in Group II**.** A hormonal intrauterine device (Mirena – levonorgestrel) was used for hemostatic and therapeutic purposes in 9.3 % and 12.0 % of cases, respectively. To improve the rheological properties of blood in women with changes in the hemostatic system, low doses of aspirin were prescribed to 11 (25.6 %) patients in Group I and 14 (56.0 %) patients in Group II.

During treatment, menstrual function was restored in both groups with endometrial hyperplasia, and reproductive goals were achieved in 35 (81.4 %) patients in Group I and in 15 (60.0 %) patients in Group II**.** There were no statistically significant differences between the groups in the course of pregnancy and the condition of the newborns.

Endometrial hyperplasia is often associated with obesity and insulin resistance [1, 6]. The complex of metabolic disorders identified in patients with EH against the background of overweight or obesity creates the preconditions for the development of pathological proliferative changes in the endometrium. In our study, we found that patients with a higher body mass index and advancing age had a higher incidence of endometrial hyperplasia and reproductive function disorders. In the groups with endometrial hyperplasia, abnormal uterine bleeding was manifested by menstrual irregularities such as menorrhagia and metrorrhagia. According to other studies, menorrhagia, which characterizes abnormal uterine bleeding, was the most common symptom and occurred in 71.25 % of cases [15], which is consistent with our results. At the same time, endometrial damage negatively affects embryo implantation, thereby aggravating infertility [2]. In our study, reproductive dysfunction was also characterized by infertility. Primary infertility was more common in the patients of the first group, while secondary infertility was more common in the patients of the second group. Infertility lasting 2 years and 3–5 years was more common in Group I, while infertility lasting more than 5 years predominated in Group II.

The level of estradiol in the group with endometrial hyperplasia in the early proliferative phase was higher than in other groups and differed from the level in healthy women. An assessment of the activity of the pituitary-ovarian system showed that in patients with endometrial hyperplasia, high levels of estradiol and low levels of progesterone are characteristic of the anovulatory cycle and menstrual dysfunction. While estradiol stimulates uterine thickening, progesterone promotes differentiation and secretion of epithelial cells [9].

In patients with endometrial hyperplasia, the level of FSH in the blood in the early proliferative phase was higher than in the control group. At the same time, in groups with endometrial hyperplasia, the level of prolactin in the blood was also higher than in the control group but was within the reference values.

As a result of the study, it was found that Doppler study allows measurement of the direction and speed of blood flow, which can serve as an indicator of tissue hypoxia [11]. For this purpose, our study conducted Doppler ultrasound in patients with endometrial hyperplasia, taking into account the role of the blood supply to the uterus in reproductive function.

In patients with endometrial hyperplasia and reproductive dysfunction, the systolic-diastolic ratio of blood flow velocity in both uterine arteries (S/D-M±m) was lower than in the control group. The use of Doppler indices such as IR and PI permit to quantify vascular changes and determine the nature of the pathology. In our study, both parameters were lower in the endometrial hyperplasia group compared with the healthy group.

Timely diagnosis and adequate treatment of EH without atypia are important, regardless of the presence of abnormal uterine bleeding. In cases of menstrual irregularities in patients with EH, treatment was aimed at restoring menstrual function and achieving reproductive desires.

For patients with EH and reproductive disorders, hormonal drugs (hestagens, combined oral contraceptives (COCs)) were used to normalize hormonal levels and suppress further endometrial proliferation.

Hestagens were prescribed in standard doses for 3–6 months. Dydrogesterone (Duphaston) was used as a hemostatic and therapeutic agent for atypical EH in patients of reproductive age from the 5th to

the 25th day of the cycle at a dose of 10–20 mg/day, and for menometrorrhagia in the second phase of the menstrual cycle from the 14th or 16th to the 25th day. In case of relapse of EH, the patient was fitted with a levonorgestrel-intrauterine system (LNG-IUS), after which observation was carried out for 1–1.5 years.

Clinically, low-dose aspirin is often used to prevent miscarriage. A previous study found that triple therapy with aspirin, prednisone, and a multivitamin may improve pregnancy outcomes for unexplained recurrent miscarriage [12]. Similarly, in our prescription, a low dose of aspirin (75 mg) was prescribed to patients with hemodynamic changes (25.6 % in Group I and 56.0 % in Group II), as well as the prescription of multivitamins at the preconception stage stimulated positive results**.** Patients with EH undergoing treatment may experience pregnancy outcomes similar to those with a normal endometrium [2].

Conclusions

1. The incidence of endometrial hyperplasia and reproductive dysfunction increases with age and is more common with excess body weight.

2. Menstrual irregularities with endometrial hyperplasia often occur in the form of menometrorrhagia, which is accompanied by posthemorrhagic anemia.

3. Reproductive dysfunction in patients with endometrial hyperplasia is characterized by infertility. In Group I, primary infertility predominates; in Group II, secondary infertility is more common, and infertility lasting more than 5 years is more prevalent in Group II.

4. Doppler indices (systolic-diastolic ratio, resistance index, and pulsation index) are lower in women with endometrial hyperplasia compared to healthy women, with even lower values observed in those with endometrial hyperplasia combined with other benign uterine pathologies.

5. Women with endometrial hyperplasia have higher levels of estradiol and lower levels of progesterone compared to healthy women.

6. When pregnancy occurred after treatment in patients with endometrial hyperplasia, no significant pathologies were observed during pregnancy, in its outcomes, or in the condition of the newborns.

Thus, in patients with endometrial hyperplasia and reproductive dysfunction, timely evaluation of clinical and diagnostic criteria enables pathogenetically justified treatment, leading to the normalization of menstrual function and the fulfillment of reproductive desires.

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