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CLINICAL AND MORPHOLOGICAL FEATURES OF COMBINED HYPERPLASTIC DISEASES OF THE UTERUS AGAINST THE BACKGROUND OF ADENOMYOSIS

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Abstract

To determine clinical and morphological features of combined uterine hyperplastic diseases in premenopausal women at the background of adenomyosis, 62 patients operated on for chronic abnormal uterine bleeding were examined. The control group consisted of 30 premenopausal patients who applied for preventive examination. Anthropometric and ultrasound examinations, assessment of carbohydrate and lipid metabolism, histologic examination were done. It has been established that uterine hyperplasia patients often had lipid metabolism damages (dyslipidemia) and damages of carbohydrate one (alimentary – constitutional obesity, metabolic syndrome) which worsen the clinical course of the main disease. According to histological examination data, the activity of adenomyosis foci in patients with comorbid uterine pathology correlated with the severity of clinical manifestations (abnormal uterine bleeding, pain) and the presence of comorbid lesions (concomitant endometrial hyperplasia, chronic endometriosis, fibroids, endometriosis).

Key words: hyperplastic diseases of the uterus; adenomyosis; endometriosis; dyslipidemia; metabolic syndrome.

Introduction

Increased attention of the clinicians and researches to the problem of the uterus combined hyperplastic processes is due not only to the steady growth in the incidence of this pathology, but also to the fact that these diseases often cause abnormal uterine bleeding, chronic pelvic pain and, ultimately, hysterectomy. In recent years, increasing attention of researchers to the problem of adenomyosis as one of the main causes of chronic abnormal uterine bleeding increases. But in most cases, adenomyosis is combined with such hyperproliferative processes as uterine fibroids, polyps and endometrial hyperplasia, and external endometriosis. This is based on common mechanisms of these estrogen-dependent conditions that are also accompanied by a chronic inflammatory process. Due to comorbidity in such diseases, the frequency of radical surgical treatment increases, especially in premenopausal women with concomitant extragenital pathology and metabolic disorders. The presence of metabolic disorders in women is a significant risk factor for the development of hyperproliferative processes of the uterus, including adenomyosis, uterine fibroids and endometrial hyperplasia [3, 4]. Among the women with benign uterine hyperplastic disease and metabolic syndrome (MS), there is an increase in the incidence of chronic abnormal uterine bleeding. For the current epidemiological situation of all over the world, the population is characterized by a high prevalence of MS, the frequency of which ranges from 10.6% in China to 24% in the United States. It should also be noted that in women it is observed 2.4 times more often [10]. According to the data of US National Institutes of Health, criteria have been proposed for the definition and diagnosis of MS in the confirmation of 3 or more of the following symptoms: abdominal obesity (waist circumference over 80 cm in women; elevated plasma triglycerides over 1.69 mmol/l; reduction of high-density lipoprotein (HDL) cholesterol: in women less than 1.29 mmol/l, hypertension or increased blood pressure over 140/90 mm Hg, fasting hyperglycemia over 6.1 mmol/l) [1].

The objective. To determine the clinical and morphological features of combined hyperplastic diseases of the uterus in premenopausal women on the background of adenomyosis.

Material and methods

The study was conducted on the basis of the Odessa National Medical University Clinic (super specialty medical center, center of reconstructive and restorative medicine). 62 patients with combined hyperproliferative diseases of the endomyometrium have been examined. They all applied for surgical treatment of chronic abnormal uterine bleeding and/or

chronic pelvic pain. The control group consisted of 30 premenopausal patients who appeared for prophylactic examination. The menstrual cycle in all patients was preserved.

The objective condition of patients, gynecological status, special objective examination, general clinical examinations, cytological and bacterioscopic examination of vaginal secretions were evaluated. Ultrasound examination (UE) of the pelvic organs was performed on 6-7 day of the menstrual cycle using transvaginal sensor with a frequency of 7.5 MHz (Sonoline SI-45; Siemens, Germany). Endometrial hyperplasia was diagnosed with an increase in M-echo in the early follicular phase of more than 10 mm, for the diagnosis of endometrial polyps used Doppler blood flow in phase 1 of the menstrual cycle. The FIGO classification (2018) was used to determine the type of uterine fibroids. MUSA criteria (2018) were used for ultrasound diagnosis of adenomyosis.

Morphological verification of endometrial pathology was performed by hysteroscopy or pipette biopsy, followed by histological examination to exclude atypical hyperplasia and endometrial cancer.

Material for histological examination was poured into paraffin and sections were made. The sections obtained were dewaxed and stained with hematoxylin and eosin, picrofuxin according to Van Gizon. The obtained micropreparations were studied using an Olympus CX41LF light microscope, making their digital image.

The state of lipid metabolism was determined by lipid profile (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides). Body-weight index was estimated in all patients as well as anthropometric measures. In the fasted state the level of glucose was measured, and, if necessary, HbA1c, blood pressure was checked. All patients were examined by a physician, and if medically required by endocrinologist.

Statistical processing of the results obtained was performed using Statistica 13.0 software (StatSoft Dell, USA).

Results and their discussion

The age of patients ranged from 36 to 55 years and averaged 44.3 ± 1.5 years. According to preoperative diagnosis, intramural uterine fibroids (FIGO type 4-6) occurred in 33 (53.2%) cases, submucosal uterine fibroids (FIGO type 0-3) was met in 9 (14.5%) cases, endometrial hyperplasia - in 11 (17.7%), polyps – in 10 (16.1%), adenomyosis - in 45 (72.6%) cases. The combination of adenomyosis and deep infiltrative endometriosis occurred in 16 (25.8%) cases, ovarian endometrioma was detected in 11 (17.7%) patients. In the vast majority of the patients under examination (59 or 93.7%) comorbid lesions predominated.

Iron deficiency anemia of varying severity was diagnosed in 16 (25.8%) cases, pain of varying severity - in 35 (56.5%) cases.

According to the reproductive history, 49 (79.7%) patients had childbirth, and one in three (32.7%) - by cesarean section. Artificial and spontaneous abortions were indicated by 22 (35.5%) patients. A history of infertility occurred in 10 (16.1%) patients. Therapeutic and diagnostic scrapings for uterine bleeding occurred in every second patient, conservative treatment with symptomatic and hormonal therapy - in 52 (83.9%). All patients underwent medically indicated surgical treatment, which included laparoscopic total or subtotal hysterectomy in 18 (29.0%), vaginal hysterectomy in 24 (38.7%), with or without appendages, resection of submucosal nodes and polyps in 14 (22,6%), hysteroscopic resection of the endometrium in 6 (9.7%) persons.

Analysis of the lipid profile showed the presence of dislipidemia (combined hyperlipidemia) as well as a tendency to hyperglycemia in the examined patients in comparison with the control group (Table 1).

Table 1.

Indicators of lipid and carbohydrate metabolism in the patients under examination

Indexes	Main group, n=62, M±m	Control, n=30, M±m	P
Total cholesterol, mmol/l	6.1 ± 0.2	4.9 ± 0.3	<0.05
HDL, mmol/l	0.9 ± 0.2	1.5 ± 0.3	> 0.05
Triglycerides, mmol/l	3.4 ± 0.3	1.5 ± 0.2	<0.01
LDL, mmol/l	3.1 ± 0.2	3 ± 0.4	<0.01
Fasting glucose, mmol/l	5.7 ± 0.2	5.3 ± 0.2	> 0.05
Glycated hemoglobin HbA1c,%	5.5 ± 0.2	5.1 ± 0.2	> 0.05
Coefficient of atherogenicity, units	5.8 ± 0.5	3.3 ± 0.2	<0.05

When assessing the alimentary status, it was found that patients with BMI > 25 kg/m² prevailed (96.8%) signs of alimentary-constitutional obesity were in 35.5% of women. The average BMI values were 29.3 ± 1.2 kg/m². Grade I-II hypertension was detected in 15 (24.2%) patients, impaired glucose tolerance and prediabetes - in 9 (14.5%). MS was diagnosed in every second patient (53.2%).

The identified features may indicate the involvement of lipid and carbohydrate metabolism disorders in development of hyperproliferative processes not only at the level of increasing of androgens into estrogens probable conversion against the background of MS, but also by activating lipid peroxidation with oxidative stress formation.

Diagnosis of adenomyosis was based on histological detection in the myometrial tissue of glandular structures of various shapes and sizes, lined with cylindrical epithelium of endometrial type with the surrounding glandular structure of cytogenic stroma and perifocal leiomyomatous hyperplasia. When stained by van Gizon, the stromal component of adenomyosis foci acquired a brighter red color in contrast to the stroma of the normal endometrium of the uterine body (Fig. 1, 2). In chronic abnormal uterine bleeding accompanied by anemia, the activity of adenomyotic foci was most pronounced, which is consistent with the literature [2].

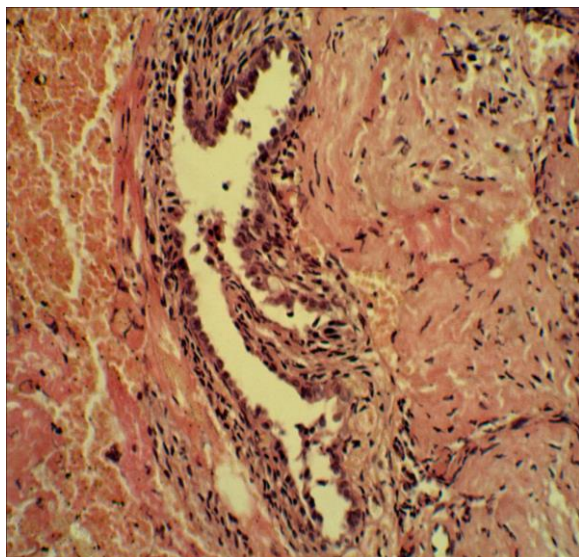


Fig.1. The focus of endometriosis among disordered muscle fibers stained with hematoxylin and eosin.

EP x 10. FL.x 20

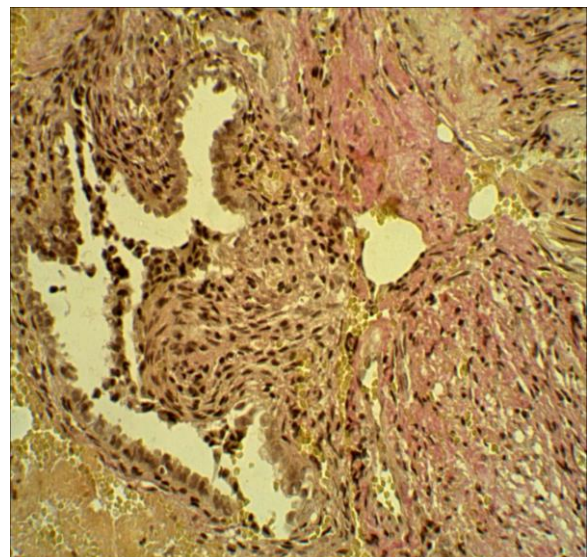


Fig.2. The focus of endometriosis among muscle and collagen fibers.

Van Gizon staining. EP. x 10. FL.x 20

Diagnosis of uterine fibroids was based on the macroscopic detection of fibroids with sizes from 1 to 2.5 cm in diameter, surrounded by a capsule mostly dense and homogeneous structure in section. Histologically, numerous bundles of spindle-shaped smooth muscle cells without atypia were detected, as well as the absence of a pronounced vascular component in

the tumor. Van Gison staining revealed a small amount of connective tissue component in the tumor.

Atypical endometrial hyperplasia was characterized by numerous endometrioid glands of various sizes of oval shape, with a small number of folds distributed unevenly among the normal endometrium. Glandular epithelial cells in the foci of hyperplasia had oval dark-stained nuclei, basophilic cytoplasm and a small amount of mitoses. Also diffuse lymphocytic infiltration with single neutrophils, rod nuclei and segmented leukocytes and necrotic changes around foci were revealed. Vascular component was characterized by plethorical enlarged capillaries and venules with focal thrombosis.

Histological diagnosis of ovarian endometriosis was based on the detection of heterotopic foci of endometrium in ovarian tissue. The study revealed 2 types of the process direction: progression and regression. In the foci of progressive external genital endometriosis (EGE) mostly proliferation of the epithelium of the glands of varying severity, secretory changes, decidualization of the cytogenic stroma was manifested. The foci of regressive EGE were without signs of functional activity and were characterized by cystic transformation of glands, atrophy of the epithelium, fibroplastic rearrangement, hemosiderosis and angiomatosis of the cytogenic stroma. When stained by Van Gison, the stromal component of the foci of endometriosis acquired a brighter red color, both in the cyst walls and in the underdeveloped stroma, which indicates a high amount of collagen.

Histological diagnosis of chronic endometritis on the background of combined hyperplastic processes of the uterus was based on the detected lymphocytic infiltrate with an admixture of leukocytes around the uterine glands and in their lumen.

Given that one of the signs of MS is obesity, it should be noted that adipose tissue is an active endocrine organ, and excess body weight is a group of pathological conditions that cause neuroendocrine regulation of many body functions, including reproductive. The following hormonal changes are observed in MS: increased levels of cortisol in the blood, estrogen, testosterone and androstenedione, decreased levels of progesterone, growth hormone and IGF-1, increased levels of insulin and norepinephrine [10]. Adenomyosis is considered an estrogen-dependent disease, but recent studies have shown progesterone important role. In particular, it is known that progesterone is actively involved in the regulation of gene expression during endometrial differentiation and violations of this regulation are also considered as a pathogenetic factor of the disease [11]. From these data it can be assumed that hyperestrogenemia caused by MS has some influence on the course and

development of adenomyosis and comorbid hyperproliferative pathology of the uterus and is a risk factor for its malignancy.

Conclusions:

1. In patients with combined uterine hyperplastic processes against the background of adenomyosis, disorders of lipid (dyslipidemia) and carbohydrate metabolism (alimentary-constitutional obesity, metabolic syndrome) are frequent, which may worsen the clinical course of the disease.

2. The activity of adenomyosis foci in patients with combined hyperproliferative pathology of the uterus is associated with the severity of clinical manifestations (abnormal uterine bleeding, pain) and the presence of comorbid lesions (concomitant endometrial hyperplasia, chronic endometritis, submucosal myoma, endometriosis).

The prospect of further research is to study the receptor status of the endometrium and myometrium, endometrioid foci in combined hyperplastic processes of the uterus and endometriosis and conduct clinical and morphological comparisons and correlations.

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