Organ preserving method in the management of atypical endometrial hyperplasia

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Summary

The problem of organ preservation in the management of atypical endometrial hyperplasia (AEH) comes about especially in patients of reproductive age. Two hundred and fifty-four women with a diagnosis of AEH were hospitalized in our clinic from the period 1991 to 2000. Of those, atypical endometrial hyperplasia with normal uter and appendages was found in 192 women. The remaining 62 patients had diseases of the cervix, corpus uteri, ovaries and oviducts and were subjected to radical hysterectomy. To define the possible sparing tactics of management, 192 women with AEH were divided into two groups. The patients in Group were administered hormonal therapy during a three month period (17α OPC – 12.5 g, Depo-Provera – 6 g). If a clinical effect and histological pathomorphism were achieved the patients were subjected to an additional three months of hormonotherapy. Of a total of 96 patients in the first group, 36 (37.5%) who were prescribed hormonotherapy were found to also have mastopathy and endocrine pathology dysfunction of the thyroid gland, and were additionally administered iodine-containing preparations. After completion of the effective hormonotherapy three patients had a normal pregnancy and delivery. Conservative management proved to be effective in 96.4% and ineffective in seven (3.6%) cases. These seven patients were subjected to surgical treatment. All patients in Group 2 were subjected to radical hysterectomy.

Key words: Atypical endometrial hyperplasia; Hormonotherapy; Organ preserving method.

Introduction

The method of management of atypical endometrial hyperplasia had undergone a certain evolution. For many years scientists believed that dynamic follow-up of patients with the above pathology undergoing treatment basically limited to repeated diagnostic curettage and administration of drugs for uterine contraction was sufficient.

Over time, data testifying to the fact that endocrine-metabolic disturbances are present in the majority of women with atypical endometrial hyperplasia and endometrial carcinoma has become increasingly convincing. This triggered the idea of a non-surgical conservative management of AEH.

After development of the highly active progestin preparations, conservative hormonotherapy has become feasible to successfully manage AEH in the majority of patients.

Endocrine-metabolic disturbances such as diabetes mellitus and hypertension are often observed in women with atypical endometrial hyperplasia. Endocrine changes deserve special attention since the rupture of one link in the endocrine chain can result in various lesions and pathological shifts due to the fact that the hypothalamohypophysical system controls and is continuously interrelated with the pancreas, thyroid and mammary glands. On the contrary there is a close interrelationship between the ovaries and the cortical substance of the adrenal gland, and between the ovaries and thyroid gland. Hormonal balance impairment can possibly cause development of various pathologies including endometrial hyperplasia [1]. Thus it is quite reasonable to use hormonal prepartions to correct hormonal balance impairment.

Hence our clinic set out to conduct prospective randomized scientific research to develop such method of management of atypical endometrial hyperplasia, which would solve not only the problem of reversing development of the precancerous disease, but would also regulate the endocrine-metabolic processes and hopefully allow the preservation of the uterus, which is particularly important in cases of young women.

Materials and methods

A total of 254 women with a diagnosis of atypical endometrial hyperplasia were admitted to our clinic within the period 1991-2000 (Table 1). Of those, 192 did not have any other pathology of the genitalia. In 62 patients the following diseases were diagnosed in addition to atypical endometrial hyperplasia: uterine fibromyoma – in 46, polycystosis of the ovaries with expressed Stein-Leventhal syndrome – in six, ovarian cystoma – in two, endometrial polyposis – in three, endometriosis – in two, zero stage of cervical carcinoma – in three patients. Due to the presence of accompanying disease those 62 patients were not included in the randomized study and were subjected to radical hysterectomy.

The majority of women with atypical endometrial hyperplasia (Table 2) had the same endocrine-metabolic disturbances (adiposity, diabetes mellitus, hypertension) as the patients with corpus uteri carcinoma.

Table 1. — *Incidence of atypical endometrial hyperplasia at the Gynecological Clinic of the National Oncological Center of Georgia 1991-2000*

Number of patients	Without accompanying gynecological tumors	With accompanying tumors of the uterus and ovaries
254	192	62

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Table 2. — *Endocrine-metabolic disturbances in cases of atypical endometrial hyperplasia and pathogen groups at the Gynecological Clinic of the National Oncological Center of Georgia 1991-2000*

Pathogen Groups	Total	Anovulatory Bleeding	Adiposity	Hypertension	Diabetes Mellitus	Diabetes Insipidus	Thyroid Gland Pathology
I	231 (90.5%)	230	230	230	8	1	36
II	23 (9.4%)	–	–	–	–	–	–
Total	254	90.5%	90.5%	90.5%	3.1%	–	–

Due to this fact the patients were divided into two pathogen variants: 1 – hormone-dependent and 2 – autonomous. The women without endocrine-metabolic disturbances were ascribed to pathogen group 2.

One hundred and ninety-two women with atypical endometrial hyperplasia without accompanying gynecological disease served as the subjects for our study. The patients were randomly (blindly) divided into two groups with 96 women in each group. The women from the first group represented the basic experimental group and were administered conservative treatment. Of those 96 patients who were administered hormonotherapy 36 had mastopathy and thyroid gland pathology in addition to AEH. The second group was a control group and the patients from this group were subjected to surgery – radical hysterectomy.

Results

In 96.4% of patients after a 3-month course of therapy improvement in the general state of health was observed – the bloody discharge disappeared, histological examination of the material of the control curettage of the uteri demonstrated the presence of hormonal pathomorphism, no atypical cells were present any longer and the patients were administered the second course of treatment.

Generally, hormonotherapy in cases of atypical endometrial hyperplasia is considered to be completed after three months of therapy. In 96.4% of patients histological examination of the material of the uterine curettage demonstrated complete hormonopathomorphism. In 3.6% of cases the treatment proved to be ineffective (these women belonged to pathogen group 2). They were subjected to surgery – radical hysterectomy. The woman who had atypical endometrial hyperplasia with universal obesity, hypertonic disease, diabetes mellitus, diabetes insipidus was cured through hormonotherapy. In three cases normal pregnancy and delivery occurred after the cure.

Hence, hormonotherapy causes not only reverse development of atypical endometrial hyperplasia up to complete pathomorphism, but also contributes to the restoration of menstrual and generative function in young women. Moreover, acceleration of reverse development of the hyperplastic processes due to impaired iodine circulation can be attained by adding iodine preparations to the progestins. Through the complex processes at the molecular level the stabilization of the endocrine status in the female organism, as well as complete extermination of atypical endometrial hyperplasia in hormone-dependent patients belonging to pathogen group 1 was achieved.

Discussion

Anovulatory bleeding, adiposity and hypertension were found in 230 (90.5%) patients; diabetes mellitus with adiposity was observed in eight (3.1%) cases. Those patients were ascribed to pathogen group 1. A 48-year-old patient with atypical endometrial hyperplasia who had universal adiposity, hypertension and diabetes insipidus was also in this group. The remaining 24 patients (9.4%) were assigned to pathogen group 2.

The majority of age-matched patients (44.4%) were in the 50-59 age group with few in the age groups under 40 (Table 3).

Table 3. — *Age of patients with atypical endometrial hyperplasia admitted to the Gynecological Clinic of the National Oncological Center of Georgia (1991-2000)*

Total number of the patients	A age-matched patients				
	20-29	30-39	40-49	50-59	>60
254	5.8%	12.3%	33.0%	44.4%	15.5%

Conservative treatment implied horomonotherapy with progestins which continued for three months (Table 4); 12.5% 17α oxyprogesterone capronate was given every third day with a total dose per course of 12.5 g; Medroxyprogesterone (Depo-Provera) was administered in a dose of 500 mg once a week in the form of intramuscular injections together with 500 mg of Farlutal (1 tablet every day).

Table 4. — *Hormonotherapy of atypical endometrial hyperplasia at the Gynecological Clinic of the National Oncological Center of Georgia (1992-2000)*

Preparation	Single dose	Time and way of administration	Duration
17α Oxyprogesterone capronate 12.5%	500 mg	Every third day, deep intramuscular injection	3 months
Medroxyprogesterone (Depo-Provera)	500 mg	Once a week; intramuscular injection	3 months
Farlutal	500 mg	1 tablet/day	3 months

In cases of efficacy of the first course of treatment and histomorphologically confirmed regression of the pathological process, the patients were subjected to a sencond course of treatment: the women in reproductive age were administered steroid birth control (Non-Ovlon, Norcolute, Bysecurine) to regulate the menstrual cycle. The preparations were administered in a cyclical manner (total of 5-6 cycles). A similar treatment was administered to the women in perimenopause. The patients in postmenopause were administered the following androgens to stabilize menopause: 20 mg/day methiltestosterone for two months. If the treatment was ineffective and the uterine curettage material did not reveal any pathomorphism, the patient underwent radical surgical treatment.

Conclusions

1. In 96.4% of patients with atypical endometrial hyperplasia treated with progestins a complete cure was achieved. During the II course of treatment a normal menstrual cycle was restored in the young women of reproductive age, and in postmenopausal patients a stable menopause was achieved.
2. In cases of accompanying endocrine pathology (thyroid gland) the addition of an iodine-containing preparation improved the results of the therapy.
3. Hormonotherapy with progestin should be considered the treatment of choice for women with atypical endometrial hyperplasia without accompanying gynecological diseases. In cases with accompanying gynecological diseases radical surgery – hysterectomy preserving the ovaries of young women – should be performed.

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