

## Receptor Status of Women with Uterine Fibroids and Adenomyosis

Gutikova LV\*, Kukharchyk YV and Pavlovskaya MA

Grodno State Medical University, Grodno, Belarus

\*Corresponding Author: Gutikova LV, Grodno State Medical University, Grodno, Belarus.

Received: April 14, 2020; Published: June 02, 2020

### Abstract

Based on these studies, it was found that in women with uterine fibroids, combined with adenomyosis, there is a pronounced endometrial dysfunction, manifested by a violation of secretory transformations, an increase in fibroblastic changes in stromal cells and its progressive fibrosis, damage to the surface epithelium of the endometrium, a decrease in the level of expression of progesterone receptors and an increase intensities of expression of estrogen receptors both in the nuclei of superficial epithelial cells and gland glandulocytes and in stromal cells. Due to impaired reproductive health in women with myoma uterus and adenomyosis. When choosing therapeutic measures, it is necessary to evaluate two conditions: the morphotype of the node and the presence of adenomyosis. Drug therapy should include the appointment of progestins or antiestrogen drugs.

**Keywords:** Uterine Fibroids; Adenomyosis; Estrogen Receptors; Progesterone Receptors

### Introduction

Uterine fibroids are the most common benign tumor and occur in almost every second woman after 30 years, and among patients of reproductive age its frequency reaches 40% [1,4,5]. Moreover, the percentage of combination of uterine fibroids with adenomyosis is high and is about 55% [2,5].

Along with traditional ideas about the leading role of estrogens in the pathogenesis of hormone-dependent diseases, the attitude to progesterone as a tumor growth stimulator has been revised in recent years [7]. Thickening of the endometrium with a simple form of endometrial hyperplasia occurs mainly due to epithelial hyperplasia and stroma formation, which can be explained by the high sensitivity of the tissue not only to estrogen, but also to progesterone [3]. Estrogens also stimulate hyperplasia of smooth muscle cells, progesterone increases the mitotic activity of cells, initiates the production of growth factors and their receptors, and is involved in the process of differentiation of smooth muscle cells [3,4]. The progesterone effect explains the rapid growth of fibroids during pregnancy [9]. In the literature, the role of tissue receptors of steroid hormones is of great importance in the development of hormone-dependent hyperplastic diseases of the uterus [14]. The synthesis of receptors in the uterus is hormone-dependent in nature and occurs under the influence of many factors: the amount and ratio of sex hormones and growth factors, the phase of the menstrual cycle, the degree of damage to the pathological process of the target organ, metabolic disorders and an imbalance of other hormones [6,10]. The lack of effect of conservative therapy often ends with a hysterectomy in reproductive age with all the consequences of a developing estrogen deficiency.

The results of many studies indicate a negative effect of uterine fibroids on pregnancy rates. It is believed that in patients with infertility and uterine fibroids who do not have signs of tubal peritoneal infertility and ovulatory dysfunction, the cause of infertility may be relative progesterone deficiency, which affects the receptivity of the endometrium [3,5,6]. At the same time, data on endometrial receptivity in

uterine fibroids are few and contradictory, which may be due to the multifactorial nature of infertility in these patients. With a combination of uterine fibroids and adenomyosis, endometrial receptivity is practically not studied, however, adenomyosis, in turn, reduces the reproductive potential of the endometrium, leading to infertility, miscarriage, and failure of assisted reproductive technologies [3,4,6].

Current trends in the increase in the frequency of violations of women's reproductive health, negative demographic processes make it possible to study the receptor status in case of combined uterine pathology in order to improve the diagnosis and increase the efficiency of the developed algorithms for the diagnosis and treatment of infertility in this cohort of patients.

### Objective of the Study

To determine the receptor status of the endometrium in women with uterine fibroids associated with adenomyosis to determine patient management tactics.

### Materials and Methods

We have analyzed the morphological and functional state of the endometrium in 92 women who have been consulted and are being treated at the Grodno Regional Clinical Perinatal Center healthcare institution and the City Clinical Hospital №4 of Grodno healthcare institution. The control group consisted of 25 women who were gynecologically healthy and addressed for pregnancy planning. The first group consisted of 17 patients with uterine fibroids and adenomyosis; the second group - 26 women with uterine fibroids; the third group - 24 patients with adenomyosis.

The main criteria for inclusion in the study: Infertility, reproductive age, regular ovulatory menstrual cycle, normal level of steroid hormones in the blood serum; signed written informed consent of the woman to participate in the study.

Exclusion criteria: External genital endometriosis, taking immunomodulatory, hormonal drugs (participation in ART programs, combined oral contraceptives, progestogens, gonadotropin-releasing hormone agonists/antagonists) during the last 6 months; sub mucous, deforming cavity of the uterine fibroids.

All women participating in the study were examined according to clinical protocols, the scheme included: analysis of complaints, anamnesis, generally accepted clinical laboratory and instrumental methods of investigation (ultrasound of the pelvic organs, histological and immunohistochemical methods for studying the uterine mucosa).

Endometrial sampling was performed on the 7<sup>th</sup> day after ovulation by pip biopsy and was subjected to a comprehensive morphological study. Tissue samples for immunohistochemical studies were prepared according to standard methods. Immunohistochemical study of fragments of remote sites was carried out in a semi-automatic apparatus Thermolabvision 480S according to a standard method using a visualization system. The expression of estrogen receptors (ER) and progesterone receptors (PR) was studied.

Statistical processing of the obtained data was performed using the application package Statistica for Windows 10.0. The equality of the sample means was checked according to nonparametric criteria by the Mann-Whitney U-test. The criteria were considered statistically significant at  $p < 0,05$ .

### Results and Discussion

The average age of the examined patients was: in the I group -  $31,24 \pm 3,61$  years, in the II -  $32,3 \pm 2,93$  years, in the III group -  $30 \pm 5,74$  years ( $p > 0,05$ ).

An analysis of extragenital pathology showed that the most common in the examined women were: thyroid pathology: in 17,6% of women of the first group, in 7,7% of the second, in 29,2% of patients of the third group ( $p_1 - 3, p_2 - 3 < 0,05$ ). Kidney diseases were detected in 11,8% of the examined group one, 3,8% in the second, and 8,3% in the third group ( $p > 0,05$ ). A number of patients revealed diseases of the gastrointestinal tract, which were registered in 5,9% of women in the first group, in 26,9% of the second group, in 8,3% of patients in the third group ( $p > 0,05$ ). It should be noted that in the analysis of comorbidity within the framework of somatic pathology in the examined groups, no significant differences were found, with the exception of thyroid diseases, which were significantly more common in patients with adenomyosis.

When analyzing menstrual function, no significant differences were found in the studied groups, so the average age of the menarche was  $12,15 \pm 0,32$  years in the first group,  $12,51 \pm 0,32$  years in the second group,  $13,01 \pm 0,25$  years - in the third group.

Women with adenomyosis often indicated painful menstruation (29,4%; 26,9%; 41,6%, respectively, in the first, second and third groups) ( $p > 0,05$ ). In the same group, abundant and prolonged menstruation was more often recorded (35,3%; 26,9%; 45,8%, respectively, in the first, second, and third groups) ( $p > 0,05$ ).

The age of onset of sexual activity did not have significant differences in the groups and amounted to  $18,51 \pm 0,67$  years in the first group,  $19,26 \pm 0,76$  years in the second group,  $18,34 \pm 0,54$  years in the third group.

The duration of infertility did not have significant differences in the groups and amounted to  $3,9 \pm 2,67$  years;  $3,24 \pm 2,65$  years;  $4,1 \pm 2,17$  years, respectively, in the first, second and third groups, however, in the presence of adenomyosis, the period of infertility was longer.

Women in the history more often had women of the first group (29,4%), while in the second group they were in every fourth patient (26,9%) and in the third - only in 12,5% ( $p > 0,05$ ).

From the anamnesis, a high frequency of artificial terminations of pregnancy pays special attention. So, medical abortions were registered in 23,5%; 15,4%; 20,8% of women, respectively, in the first, second and third groups, and self-arbitrary miscarriages, respectively - in 29,4%; 30,8%; 25% ( $p > 0,05$ ). The proportion of non-developing pregnancy was revealed in the structure of spontaneous abortions in more than 50% of women in each group.

In all women of groups I and III, chronic inflammatory diseases of the appendages were detected, and significantly more often than in group II ( $p < 0.001$ ), hydrosalpinxes were detected (35,3%, 7,7%, 29,2%, respectively, in the groups), which required a number of them to have a tubectomy.

With a combination of uterine fibroids with adenomyosis, a history of endometrial polyps was more often recorded (35,3%; 15,4%; 4,2%, respectively, in the examined groups;  $p > 0,05$ ); There were no statistically significant differences in the frequency of endometrial hyperplasia in the groups (5,9% in the first group; 3,8% in the second; 12,5% in the third).

Basically, a history of intrauterine interventions was performed in the first group in 47,1% of cases, in the second - in 19,2%, in the third - in 50% of cases. Thus, in the presence of MM associated with adenomyosis (first group) and in adenomyosis (third group), a significantly higher percentage of intrauterine interventions is noted than in the second group ( $p < 0,05$ ).

Analysis of the results of a histological study showed that structural changes in the endometrium of the examined control group corresponded to the middle stage of the phase of secretion of the menstrual cycle, while no morphological signs of the inflammatory process were established. At the same time, the morphological picture of the uterine mucosa of the patients of the first group most often (64,7%) corresponded to the late stage of the proliferation phase, less often (29,4%) to the early stage of the secretion phase. Moreover, the picture of the endometrial structure of patients of the third group in most cases (87,5%) corresponded to the early stage of the phase of secretion

of the menstrual cycle. When examining the mucous membrane of the uterus of women of the second group, morphological signs of the early (61,5%) or middle (38,5%) stage of the phase of secretion of the menstrual cycle were noted, while no structural changes characteristic of the inflammatory process in the endometrium were found.

A morphological study of endometrial biopsy samples of patients of the first and third groups revealed significant dystrophic changes in integumentary epithelial cells and gland glandulocytes with differently expressed polymorphic cell infiltration, fibroblastic rearrangement of the stroma and blood vessels. Often a mild polymorphic cell inflammatory infiltration was found with a predominance of lymphoplasmacytic elements. Lymphocytes were diffusely scattered in the interstitium of the endometrium, their focal accumulations (6 - 7 cells per field of view) without the formation of follicles, which were sometimes located around the vessels and uterine glands, were less common. Also, diffusely scattered single plasmocytes of 4 - 6 in the field of view were often visible. Among the elements of inflammatory cell infiltrate, neutrophilic granulocytes were present, by the number of which they judged the degree of activity of the inflammatory process. Moreover, in the endometrium of patients of the first group, structural changes most characteristic of endometritis of a moderate and minimal degree of activity of the inflammatory process were most often recorded. In endometrial biopsy specimens of the examined third group, inflammatory changes of moderate activity were recorded in 33,3% of cases, and the minimum degree - in 25% ( $p > 0,05$ ).

In endometrial biopsy specimens of women of the first group, the level of fibrotization of the stroma of the uterine mucosa is more pronounced than in tissues from women of the third group ( $p < 0,05$ ). In the interstitium of the uterine mucosa in women with uterine fibroids and adenomyosis, large fields of fibroblasts were identified everywhere among the extensive fuchsinophilic growths of collagen fibers, indicating a pronounced endometrial fibrosis.

An immunohistochemical study showed that the expression of receptors for angiogenesis factors was significantly increased in endometrial biopsies of women of the third group compared to the control group and exceeded the parameters in women with adenomyosis (+ - in the control group, +++ - in the first group and ++ - in the third group) ( $p < 0,05$ ).

To analyze the state of endometrial receptivity on the material of endometrial samples from patients of all examined groups, we studied the number of pinopodia of varying degrees of maturity in the surface epithelium, the level of expression of ER and PR receptors.

In the control group in endometrial biopsies, the number of surface epithelial cells containing pinopodia ranged from 63 to 75%, pinopodia abound; up to 65% of pinopodia had characteristics of mature, about 25% - maturing and only 10% - wilting. The expression level of ER is moderate, PR - expressed. The PR/ER ratio is more than three: for superficial epithelial cells and gland cells -  $3,2 \pm 0,4$ , for stromal cells -  $3,1 \pm 0,3$ .

In the study of endometrial biopsy samples of patients of the first group, the level of ER expression was significantly higher than in women of the control group, both in the nuclei of superficial epithelial cells, gland glandulocytes and in the nuclei of stromal cells. The degree of expression of PR expression was significantly lower than similar parameters in healthy women in gland cells and especially in stromal cells. The PR/ER index was  $1,7 \pm 0,05$  in superficial epithelial cells and  $1,4 \pm 0,07$  in stromal cells. In women of the third group, the total number of epithelial cells containing pinopodia was less pronounced than in the control group, but significantly exceeded the value of this indicator in women of the first group, averaging 27 - 35%. It should be noted that the indicators of ER expression in the surface epithelium and glandulocytes of the glands, as well as in the cells of the stromal component of the endometrium, slightly exceeded the normal parameters, but were significantly lower than the similar values for women of the first group. The intensity of PR expression was also significantly lower than the expression of PR in the control group, but slightly higher than in patients of the first group ( $p > 0,05$ ). The PR/ER ratio for integumentary epithelial cells and gland cells was  $1,7 \pm 0,04$ , for stromal cells -  $1,4 \pm 0,03$ .

As can be seen from table 1, in the tissues of uterine fibroids the estrogen receptor dependence had the following indicators: in 57,3% of cases it was absent, in 27,6% of cases a weak receptor dependence was observed, moderate and strong were 9,2% and 5,9% respec-

tively. Analysis of progesterone expression (Table 1) in the tissues of uterine fibroids showed a predominance of moderate and strong receptor dependence, which amounted to 35,2%; weak receptor dependence was observed in 21,9%, the absence of receptor dependence in 6,6%.

Receptor dependence	Estrogen expression (%)	Progesterone expression (%)
Missing (0 - 2)	57,3	7,7
Weak (3 - 4)	27,6	21,9
Moderate (5 - 6)	9,2	35,2
Strong (7 - 8)	5,9	35,2

**Table 1:** Indicators of receptor dependence of steroid hormones in tissues of uterine fibroids.

A study of the expression of ER and PR receptors in the endometrioid foci of the uterus revealed their differences (Table 2). Strong expression of ER and PR is observed in 60,3% and 49,3%, respectively. Weak expression to ER was found in 19,2%, weak expression of ER was 6,1%. Attention was drawn to a strong receptor dependence on PR, amounting to 49,3%. A negative reaction (lack of expression) of PR in we observed in 24,5%.

Receptor dependence	Estrogen expression (%)	Progesterone expression (%)
Missing (0 - 2)	14,4	24,5
Weak (3 - 4)	6,1	1,3
Moderate (5 - 6)	19,2	24,9
Strong (7 - 8)	60,3	49,3

**Table 2:** Indicators of receptor dependence of steroid hormones in the endometrioid foci of the uterus.

Based on an analysis of the data, it was found that in the group of patients with uterine fibroids, epithelial cells with pinopodia were registered about the same as in the control group, on average, from 50 to 75%, but they were not abundant. The main share accounted for ripening pinopodia (up to 80%), the level of mature ones was much lower, sometimes withering forms (5,5%) were found. In the endometrial biopsy specimens of patients of this group, there was an unreliable increase in the level of ER expression in the surface epithelium and glandular epithelial cells, a tendency to increase the level of ER expression in the stroma, however, these indicators were significantly lower than in patients of the first and third groups. As for PR, the average level of its expression was slightly lower than the level of the control indicator, and this was mainly due to a decrease in the intensity of expression of the PR label by endometrial stroma cells. The PR/ER ratio for superficial glandular epithelial cells and glandulocytes was  $1,7 \pm 0,04$ , for stromal cells -  $1,3 \pm 0,01$ .

It is well known that uterine fibroids is a multifactorial pathology with dominant aspects of steroidogenesis, while discussions about sanogenesis and pathogenesis continue in the literature. Infertility in patients with large uterine myoma, which deforms the uterine cavity, is justified by a change in the anatomical and topographic ratios, while the question of reproductive dysfunction in patients with small forms of subserous and intramural uterine fibroids remains open. According to some authors, in patients with submucous and intramural forms of leiomyomas, the state of the myometrium and endometrium, regardless of the deformation of the uterine cavity, is characterized by a chronic inflammatory process and, as a result, unsatisfactory indicators of fertility [9,11,13,15].

It is proved that uterine fibroids are closely associated with hyperestrogenemia, which, in turn, causes hyperplastic processes and local endometriotic foci. It should be noted that one of the key mechanisms of synchronized expression of receptivity factors is the interaction of sex steroid hormones - estrogen and progesterone - with endometrial receptors. Estrogens and their receptors play an important role

in the development of uterine fibroids of various localization and its combination with endometriosis, which, as a rule, can be accompanied by other pathological processes in the pelvic organs. According to some authors, the structural feature of the endometrium with a combination of uterine fibroids and endometriosis is the mosaic structure of the uterine mucosa with alternating foci of fibrosis, atrophy and polyposis, which is due to pronounced expression of ER and a decrease or absence of expression to PR [8,12,16,17].

Therefore, a study of receptor hormonal status showed that in the tissues of normal myometrium and endometrium, submucous fibroids and adenomyosis, there were differences in the expression of estrogen and progesterone receptors. It must be assumed that the heterogeneity of the morphological hormonal status during combined dishormonal processes in the endometrium and myometrium may be one of the reasons for the lack of a therapeutic effect in the conservative treatment of this pathology.

### Conclusion

Thus, we found that in women with uterine fibroids, combined with adenomyosis, there is a pronounced endometrial dysfunction, manifested by a violation of secretory transformations, an increase in fibroblastic changes in stromal cells and its progressive fibrosis, damage to the surface epithelium of the endometrium, a decrease in the level of expression of progesterone receptors and an increase in intensities of expression of estrogen receptors both in the nuclei of superficial epithelial cells and gland glandulocytes, and in stromal cells. In this regard, we believe that endometrial dysfunction may be one of the main causes of reproductive health disorders in women with uterine fibroids and adenomyosis. Therefore, this group of women requires specially designed treatment and rehabilitation measures that are simultaneously effective in relation to clinical manifestations and allow to maintain reproductive function.

When choosing treatment measures, it is necessary to evaluate two conditions: node morphotype and the presence of adenomyosis, due to the prevailing expression of estrogen receptors over progesterone receptors, which may be associated with proliferation and endometrial hyperplasia and its ectopy in the myometrium, treatment measures should include the appointment of progestins or antiestrogen medicines.

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**Volume 9 Issue 7 July 2020**

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