

PROGESTERONE: A LITTLE-KNOWN ROLE OF THE WELL-KNOWN HERO



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INTRODUCTION

According to modern views, the pathogenesis of endometrial polyps (EP) reminds a complicated organized structure consisting of multiple links. Today one thing is clear, it is a multifactorial disease, which involves a variety of complex mechanisms in order to occur. Popular today ideas on the formation of EP are based primarily on the individual pathophysiological mechanisms, with hormonal mechanism being dominant [1]. However, the steadily growing number of publications on the inflammatory genesis of endometrial hyperplasia, as well as the accumulation of a large amount of experimental data on the activation of stem cells overgrowth by local inflammatory microenvironment, proves undisputedly the alternative inflammatory mechanism for polyps occurrence.

EP and chronic endometritis (CE) are two most common causes of unexplained infertility in women of reproductive age. Given that CE is always identified with the existence of micropolyps (MP) [2], the idea that EP and MP are phases of the same disease is the subject of the most heated scientific debates to date.

The aim of our study was to conduct a comparative analysis of the hormonal homeostasis and the state of the receptor apparatus of the endometrium in women of reproductive age with EP and MP.

MATERIAL AND METHODS

In order to conduct our study the patients aged 18–35 years, who were admitted to the Endocrine Gynecology Department of the SI "Institute of Pediatrics, Obstetrics and Gynecology of the NAMS of Ukraine" for the purpose of pregnancy planning, were divided into 4 groups.

All patients wrote a single scheme, including studies of passport information, health complaints, medical history, and general clinical and gynecological examination, ultrasound examination of organs of lesser pelvis.

On the basis of these data 30 healthy women of childbearing age have been allocated. These women did not demonstrate any gynecological diseases, did not use intrauterine contraceptive devices, and never had spontaneous, induced abortions and intrauterine intervention history. This category of women was control **group III**.

Those patients diagnosed with a variety of reproductive disorders such as infertility, miscarriage, endometrial polyps had hysteroscopy.

After analyzing the results of hysteroscopic inspection and histopathological study women were divided into three groups.

The **II group** consisted of 30 women with the MP, whose polypoid bulge, 1–2 mm in size, was first detected at hysteroscopy and were not discovered at the previously held sonographic inspection. Given that the peculiarity of the detection of the MP with CE makes up 99%, the group was solely based on those women whose micropolyp positive hysteroscopy results combined with histologically confirmed CE. In fact the accuracy of morphological verification of CE was increased by mandatory detection of plasma cells using CD138 marker.

Women with EP were divided into two subgroups. The first one (**IA**) included 34 patients with EP only, the second one (**IB**) consisted of 36 women with EP and MP, and the presence of CE was confirmed by expression of CD138.

In order to eliminate the possibility of concealed presence of CE in patients from group III, the endometrial biopsy was performed using a suction curette Pipelle de Cornier on the 7th–10th day of the menstrual cycle with the subsequent morphological and immunohistochemical (CD138) study of the obtained data.

All patients gave written informed consent to participate in the study. Exclusion criteria were congenital malformations of the genital organs; any extragenital diseases in the acute or sub-acute stages; antiphospholipid syndrome; malignant tumors of any localization.

The following research program was carried out in cohorts of selected patients in accordance with the purpose of the study and its objectives: clinical and statistical analysis; ultrasound examination of organs of lesser pelvis; hysteroscopic inspection of the endometrial lining; the control group patients had a biopsy of the endometrium using suction curette Pipelle de Cornier on the 7th–10th days of the menstrual cycle; morphological study of the endometrium; assessment of hormonal status of blood for follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol and progesterone (PG); evaluation of the expression level of estrogen receptors (ER) and progesterone receptors (PR) based on color intensity and percentage ratio of receptor distribution in the stroma and glands.

Clinical assessment of the health of the women surveyed was carried out under the aegis of individual statistical cards developed by us.

Ultrasonography of organs of lesser pelvis was carried out on patients from all the groups through a series of longitudinal and cross sections on an ultrasonic device "Nemio XG" (Toshiba, Japan) using a multifrequency transvaginal probe with the frequency of 4.0–7.5 MHz, and if necessary using an abdominal probe with the frequency of 3.5 MHz. The study was conducted on the 5th–9th and 17th–21st days of the menstrual cycle.

Diagnostic hysteroscopy was performed on the 7th–10th day of the menstrual cycle with the help of "K.Storz" company equipment (Germany) via the standard method. Sterile irrigation solution turusol was used as the optical medium.

Hormonal range of gonadotropins (FSH, LH) and sex steroid hormones (estradiol, prolactin) were evaluated during the first phase of the menstrual cycle (day 3–5). PG level was determined on the 21st day of the menstrual cycle. Endocrinological studies were performed in "Dila" medical laboratory.

Morphological studies were conducted in the laboratory of the SI "Institute of Pediatrics, Obstetrics and Gynecology of the NAMS of Ukraine". Serial paraffin sections stained with hematoxylin and eosin were used for morphological studies. Immunohistochemical study was conducted by using a double antibody detection system Ultra Vision Quanto polymer peroxidase and DAB Plus chromogen. The following monoclonal antibodies were used as primary antibodies: Thermo Fisher Scientific Anatomical Pathology (UK): CD138 Ab-2 (Clone Mi 15) – plasma cells marker; Estrogen Receptor (Clone SP1) – estrogen receptors; Progesterone Receptor (Clone YR85) – progesterone receptors.

Statistical data processing was carried out by standard software package "Statistica for Windows" (V. 13.0, StatSoft Inc., USA).

RESULTS AND DISCUSSION

The results of our study have shown that the performance of the basal levels of gonadotropins and the basal level of estradiol in women of all surveyed groups were within the normal range (Table 1).

Since FSH is the most important hormone that influences maturation of an egg, its basal level and the ratio of FSH/LH had a predictive value for determining the level of fertility in the examined patients. A significant increase in FSH indicating decrease of follicular reserve has not been found in any of the groups. Thus, the FSH concentration in venous blood were 6.2

(5.3–7.3) U/l in group IA, 7.21 ± 3.01 U/L in group IB, 4.93 ± 1.3 U/l in group II, 5.73 ± 1.73 U/l in group III.

There were no significant differences between the content of LH in cohorts with EP, MP in healthy women were not found. The level of LH in the I phase of the menstrual cycle in patients IA group was 4.5 (4.3–7.7) U/l, IB – 6.43 ± 2.82 U/l, II – 4.44 ± 1.01 U/l, III – 6.12 ± 3.13 U/l.

However if the representatives of IB and II groups and healthy women had the ratio of FSH/LH was within the norm and nearing to 1, the women with EP, the group IA, this figure increased to 1.4, indicating the decrease of steroid production in ovaries.

Determination of prolactin level showed that the majority of women surveyed were in the range of normal values. The concentration of PRL in the EP group was 14.08 ± 4.59 ng/ml, in a group where EP combined with MP – 12.91 ± 8.13 ng/ml in women with MP – 18.64 ± 4.75 ng/ml and representatives of the control group – 15.43 ± 5.34 ng/ml. Statistically significant differences were not found between the indexes.

Analysis of sex steroid hormones revealed more significant changes in the system of hormonal homeostasis.

Average indexes of estradiol concentrations were highest in the group of women with the MP – 99.71 ± 17.41 pg/ml and the lowest in EP in combination with MP – 61.51 ± 25.81 pg/ml. IA and group III were characterized by intermediate values – 70.4 ± 36.45 pg/ml and 88.99 ± 17.63 pg/ml, respectively. However, during the statistical analysis revealed differences were not regarded as statistically significant.

Average serum value PG during the II phase of the menstrual cycle in the cohort with EP was 5.25 ± 2.99 ng/ml, which is 2.5 times lower than in the control group – 13.1 ± 2.11 ng/ml ($p < 0,001$) and 3 times higher than in the II group – 15.6 ± 2.44 ng/ml ($p < 0,001$). Patients included in the IB group also tended to demonstrate signs of hypoprogesterone, but statistically, the average values of 9.32 ± 5.65 ng/ml did not significantly differ from healthy women.

It is noteworthy that the ratio of estradiol/progesterone fluctuated significantly due to decreased progesterone only in group IA, equal to 13.4 and 2 times higher than the figure of the same name in groups IB (6.7), II (6.4) and III (6.8).

Considering the fact that the effect of any hormone is realized through receptors, in the present study we examined the peculiarities of hormonal hemostasis in combination with receptor apparatus of endometrium.

Table 1. Hormone level in examinees

Indicators	IA group (n = 34)	IB group (n = 36)	II group (n = 30)	III group (n = 30)	p value
FSH, U/l	6.2 (5.3–7.3)	7.21 ± 3.01	4.93 ± 1.3	5.73 ± 1.73	0.221 ^{a,b}
LH, U/l	4.5 (4.3–7.7)	6.43 ± 2.82	4.44 ± 1.01	6.12 ± 3.13	0.789 ^{a,b}
Estradiol, pg/ml	70.4 ± 36.45	61.51 ± 25.81	99.71 ± 17.41	88.99 ± 17.63	0.076 ^{a,b}
PRL, ng/ml	14.08 ± 4.59	12.91 ± 8.13	18.64 ± 4.75	15.43 ± 5.34	0.291 ^{a,b}
PG, ng/ml	5.25 ± 2.99 ^{1,3}	9.32 ± 5.65	15.6 ± 2.44 ²	13.1 ± 2.11 ²	< 0.001 ^c

Depending on the distribution of the indicator, data are presented as:

M ± SD (Shapiro-Wilk test, $p > 0.05$) or Me (IQR) (Shapiro-Wilk test, $p < 0.05$)

a – parametric ANOVA variation (ANOVA);

b – there is no difference in the groups, carrying out the analysis in pairs is impractical;

c – Kruskal-Wallis rank analysis of variance;

1 – reliable difference with respect to group III;

2 – reliable difference with respect to the group IA;

3 – reliable difference with respect to group II

Expression of steroid receptors in the endometrium of patients from study groups is presented in table 2.

Despite numerous data in scientific literature on dysfunctional violations of tissue reception during CE, that are often revealed in the increased expression of steroid receptors in the glands and stroma, our study did not reveal similar patterns.

Expression of steroid receptors of estrogen and progesterone in the nuclei of glandular epithelial cells in the presence of the MP in the IB group was $100.0 \pm 1.58\%$ and $99.33 \pm 1.58\%$, in the II group $99.43 \pm 1.72\%$ and $97.43 \pm 4.79\%$ and was comparable to the control group ($99.29 \pm 1.8\%$ and $97.0 \pm 4.16\%$). The stromal cells observed a similar trend. The expression level of ER in the IB group ($89.44 \pm 4.61\%$) and in group II ($89 (85-91)\%$), as well as the expression level of PR ($88.22 \pm 6.3\%$ and $84.57 \pm 14.42\%$, respectively) did not differ significantly from that of healthy women. The average content of ER and PR in the endometrium of women with EP (group IA) did not differ from that of other groups with the same indexes. ER reached $99.67 \pm 2.0\%$ in the epithelium of glands, PR – $96.78 \pm 4.55\%$, in the stroma ER – $88.11 \pm 5.51\%$, PR – $87.44 \pm 6.19\%$.

It is known that hormonal regulation is determined by the balance of tissue reception. Therefore, the most correct analysis is not revealed in the absolute values of the content of ER and PR in endometrium but in their relationship. Factor ER/PR in the epithelium of the control group was equal to 1.02, in groups IA, IB and II – 1.03, 1 and 1.02 respectively. The ratio ER/PR in stromal cells with EP was 1.01, in the group of the MP – 1.05, in the control group – 1.03. Thus, in case of EP as well as MP physiological ratio of steroid receptors remained.

Universal consensus on the imbalance between estrogen and progesterone receptors, as a determinant in the development of EP, is not reached today. Numerous immunohistochemical studies that examined the connection between hormone receptors and polyps in women with

preserved menstrual function, showed opposite results. Most researchers agree that the polyps in women of reproductive age are characterized by increased expression of ER and PR in the epithelium of the glands and a low level of PR in the stroma.

Research of the spectrum of distribution in the ER and PR in EP showed that IB and IA groups and their expression were comparable to the performance of epithelial glands and stroma for each type of receptor in the surrounding endometrium (Table 3).

The representatives of the group IA the EP tissue concentration of ER and PR in the glands ($99.33 \pm 2.35\%$ and $97.44 \pm 4.48\%$, respectively) and in the stroma ($90 (89-92)\%$ and 89.11 ± 5 and 67% , respectively) did not differ from that in group IB. The existence of EP in the background of CE in this cohort of patients did not result in significant changes in the receptor apparatus of any glandular or stromal component of the polyp.

Traditionally, it is considered that there are two key moments in the development of EP. First one is realized when an imbalance in the system of progesterone and estrogen receptors is shifted towards the overexpression of the latter. Second – when the absolute or relative hyperestrogenia in the absence of counterbalancing anti-proliferative effect of progesterone leads to stimulation of the basal cell layer, the formation of focal hyperplasia and lately in the development of EP.

As our study revealed women with EP progesterone shortage existing at absolutely unchanged receptor system, as well analysis of numerous modern literature, made it possible to identify individual, initiated PG, non-hormonal pathophysiological mechanisms. They prove that in the occurrence of EP involves diverse and highly complex mechanisms of cellular regulation, at the forefront of which is progesterone (Picture).

Table 2. Expression of steroid receptors in the endometrium

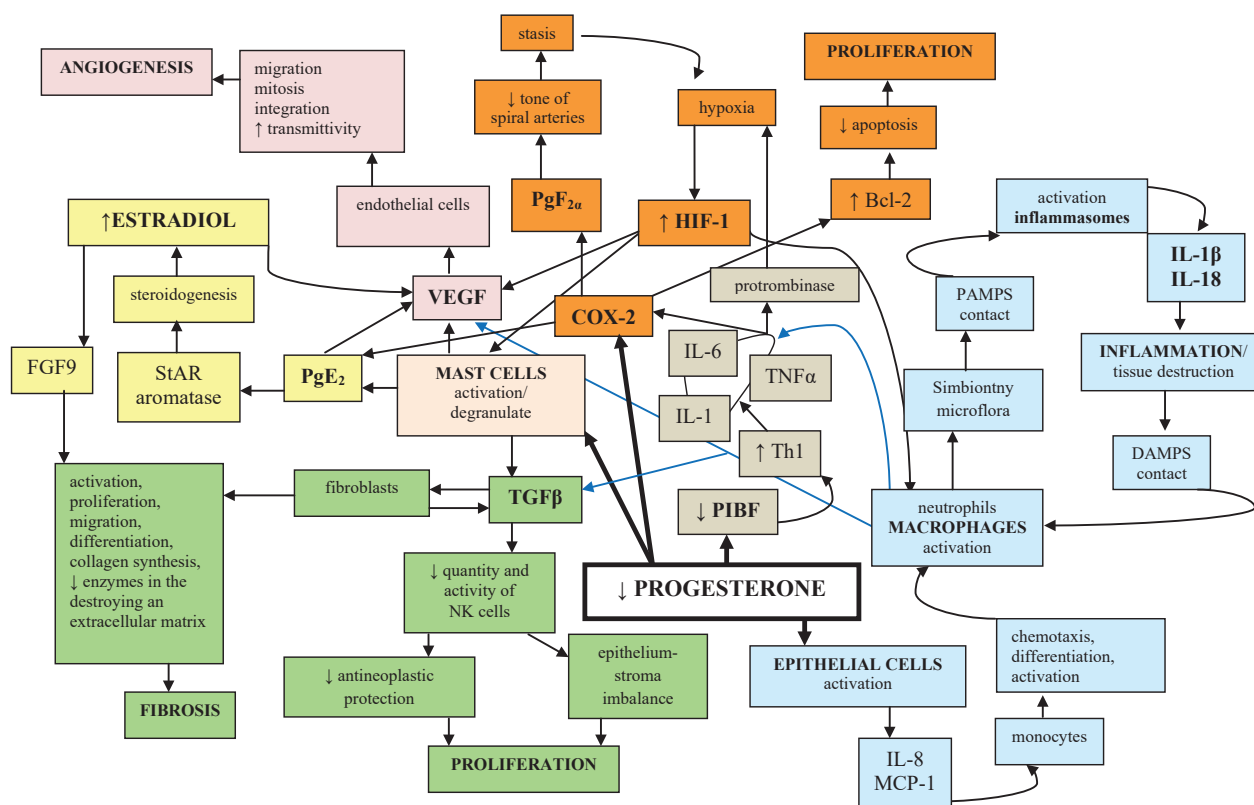
Indicators (%)	IA group (n = 34)	IB group (n = 36)	II group (n = 30)	III group (n = 30)	p value
ERα glands	99.67 ± 2.0	100.0 ± 1.58	99.43 ± 1.72	99.29 ± 1.8	0.863 ^{a,b}
ERα stroma	88.11 ± 5.51	89.44 ± 4.61	89 (85–91)	88.29 ± 4.35	0.902 ^{c,b}
PR glands	96.78 ± 4.55	99.33 ± 1.58	97.43 ± 4.79	97.0 ± 4.16	0.717 ^{c,b}
PR stroma	87.44 ± 6.19	88.22 ± 6.3	84.57 ± 14.42	85.43 ± 14.42	0.821 ^{a,b}

Depending on the distribution of the indicator, data are presented as:
M ± SD (Shapiro-Wilk test, p > 0.05) or Me (IQR) (Shapiro-Wilk test, p < 0.05)
a – parametric ANOVA variation (ANOVA);
b – there is no difference in the groups, carrying out the analysis in pairs is impractical;
c – Kruskal-Wallis rank analysis of variance.

Table 3. Expression of steroid receptors in endometrial polyps

Indicators (%)	IA group (n = 34)	IB group (n = 36)	p value
ERα glands, Endometrial polyp	99.33 ± 2.35	99.56 ± 2.96	0.862 ^a
ERα stroma, Endometrial polyp	90 (89–92)	90 (89–91)	0.825 ^b
PR glands, Endometrial polyp	97.44 ± 4.48	99.33 ± 2.5	0.285 ^a
PR stroma, Endometrial polyp	89.11 ± 5.67	89.89 ± 5.49	0.770 ^a

Depending on the distribution of the indicator, data are presented as:
M ± SD (Shapiro-Wilk test, p > 0.05) or Me (IQR) (Shapiro-Wilk test, p < 0.05)
a – Student t-test for independent samples;
b – Mann-Whitney criterion



Picture. Pathogenesis of endometrial polyps (explanation in the text)

Progesterone, mast cells and fibrosis

One of the most important functions of PG in the secretory phase of the menstrual cycle is to run “reaction of decidualization”.

Decidualization process is a morphological and functional remodeling of the endometrial stroma, characterized by massive involvement “uterine natural killer cells” into the endometrium, differentiation of endometrial stromal cells in decidual and angiogenesis. In a narrower sense, decidualization is a process in which endometrial stroma cells differentiate into morphologically distinct decidual cells with a unique biosynthetic and secretory phenotype.

This mechanism is implemented only in the presence of PG. Approximately 10 days after postovulatory increase of PG levels in fibroblasts, surrounding spiral arterioles, transformation process starts. Turning into epithelioid like, secretory cells they finally form the basis of the mother cell-component in mother-fetus relationship [3].

And what happens in terms of PG deficit? Nature doesn't accept vacuum so it is not logical to assume that estrogen produced and awaiting decidualization process of fibroblasts do not become active participants in other processes.

According to current views, an inflammatory reaction occurs in response to a decrease in PG levels. Of the total abundance of white blood cells that arise in this period in the endometrium, highly active and large in number become mast cells. It is the interaction between mast cells and fibroblasts is a critical event for the phenomenon of fibrosis. This interaction is realized in two ways.

The first way is the way of paracrine influence. Activation of mast cells leads on the one hand, to the formation and release of large amounts of profibrotic mediators: histamine, proteases, tryptases, transforming growth factor β (TGF-β), PGE2, which cause the proliferation, migration, concentration, differentiation of fibroblasts and stimulate the synthesis of collagen. On the other hand, it leads to an excessive amount of vascular endothelial growth factor (VEGF), initiating angiogenesis response, allowing endothelial cells to proliferate, migrate, and assemble into tubes to form a network to survive and enhance its permeability.

The second way is the way of direct interaction, mast cells have a unique ability to form gap junctions with fibroblasts. This direct intercellular communication leads to delivery of profibrotic mediators to fibroblasts “lossless” and more large-scale implementation of all parts of fibrosis [4].

Fibroblasts, undoubtedly, are number one priority targets for mast cells, however, far from the only ones. Acting on endothelial cells they trigger angiogenesis; when interacting with epithelial cells their growth is initiated; stimulating the growth of tumor cells, they nevertheless have an immunosuppressive effect on the immune system cells, inhibiting their ability to detect tumor cells.

These versatile abilities of mast cells are extremely interesting for oncologists, especially since there was already a number of a report about the discovery of a large amount of mast cells in the tissue surrounding the tumor. To date it is a fact that mast cells are involved in the carcinogenesis by tissue remodeling, angiogenesis and inflammation promotion [5].

Biology of polyps is very similar to tumor growth. The studies confirming the presence of mast cells in the structure of nasal polyps, intestinal polyps and polyps of the endometrium prove their catalytic role in formation of these neoplasms [6].

The mast cells are present in endometrium throughout the menstrual cycle and amount to 3–5% of the total cell population, although they become highly active only in response to a decrease in the level of progesterone. Mast cell degranulation following activation processes triggers angiogenesis and fibrosis, which ultimately leads to the formation of the major histological features of EP such as thick fibrous stroma and blood vessels.

Progesterone and aseptic inflammation

Among all the mucous membranes, the uterus is unique in the way that sex steroid hormones modulate both efferent and afferent immune responses. Affecting the permanent and temporary population of immune cells in the subepithelial layers of the endometrium, they ensure completeness of implementing of all biological functions in each phase of the menstrual cycle.

For example, immediately prior to menstruation, resulting in reduction of PG endometrial epithelial cells begin to actively produce IL-8 and MCP-1 (monocyte chemoattractant protein 1), which results in chemotaxis and activation of monocytes and neutrophils. These cells have two tasks: start the process of release and activation of matrix metalloproteinases (MMPs), which trigger menstruation, and to carry out immune surveillance by protecting of vulnerable in this phase endometrium from pathogens [3]. During menstruation the damaged portion of the epithelial layer is filled with cytokines and chemokines. Providing an immediate impact on the movement and activation of immune cells they form an epithelial barrier. Part of neutrophils fills the spaces of tissue degradation, the other part crosses epithelium and penetrates into the cavity, where together with the macrophages and dendritic cells, also drawn to the endometrium, remove microorganisms more actively from the epithelial surface.

Interestingly, the recovery of the uterus lining begins when the degradation process is incomplete. At this time, large numbers of neutrophils are still present in the endometrium. Despite the short life into the circulation, their existence is extended by cytokines in the tissue environment. Set in the endometrium, they begin to realize one more a function – regeneration. Talking about factors that induce migration of fibroblasts and promote angiogenesis, it ought to be mentioned that neutrophils provide endometrial proliferation in a new menstrual cycle.

It is easy to imagine that the above-described normal physiology of the endometrium, clearly bounded by time intervals and hormonal balance, when the duration of the processes taking place changes against the background of low PG values, easily turns into pathological.

The abundance of cytokines inevitably leads to an abundance of immune cells. Building up on the surface of the endometrium, they come into contact with symbiotic microorganisms of the uterus. In response to contact of immunocyte with microbes, inflammasome is assembled and activated [7].

Inflammasome is a specific cytoplasmic supramolecular structure, assembly of which takes place in cells of the immune system (neutrophils, macrophages) and precedes any inflammatory reaction. There are currently four types of inflammasome that have been studied (NLRPI, NLRC4, NLRP3, AIM2), although it is assumed that there are likely to be much more.

The basis of an inflammasome consists of NLR proteins (nucleotide oligomerization domain receptor). They form a kind of protein platform on the basis of which, when microbial agent enters into the cell (PAMPs – pathogen associated molecular patterns) and the immune system regards it as a pathogen, an accumulation of pro-caspase-1 takes place. Accumulating to a critical level, procaspase-1 is converted into a caspase-1, triggers the transformation of prointerleukins (pro-IL-1 β and pro-IL-18) into interleukins (IL-1 β and IL-18). These compounds, belonging to the group of cytokines and triggering a proinflammatory response, have been known for a long time, but no one knew before the discovery of inflammasomes how and where they are produced. Once outside the cells, cytokines stimulate the involvement of other immune cells and cause a full-blown inflammatory reaction [7].

This process lasts a short time, and after the inflammatory response collected inflammasomes are quickly deconstructed. Typically, the process of eliminating the inflammasomes is complete within 18–24 hours. Often, however, the balance in a pair of “assembly-deconstruction of the inflammasomes” breaks, undeconstructed complexes of inflammasomes continue to operate, constantly generate inflammatory reaction and damage nearby tissues. DAMPs (damage-associated molecular patterns – molecular structures associated with injury, ATP, fragments of DNA and RNA) penetrate into the extracellular space from the disrupted cells of damaged tissue. By activating Toll-like receptors of macrophages, they like RAMPs initiate assembly of the inflammasomes, closing the vicious cycle of chronic inflammation and turning it into autoimmune situation [8].

It is possible that the lack of PG production, and as a consequence the inflammatory destruction of the endometrial tissue, together with symbiotic microflora of the uterine cavity are quite irritating stimuli for too active and too long operation of inflammasomes in immune cells. Abnormal “longevity” of which, through an intensive production of proinflammatory cytokines forms pathological cascade of reactions leading to the formation of excessive proliferation and EP.

Progesterone and prostaglandins: a direct link

Insufficient concentration of PG in the second phase of the cycle leads to the abnormal increase of prostaglandins in the endometrium. Even in 1980 it was found that the synthesis of prostaglandins in the uterine mucosa is hormonally dependent process. Two enzymes play a key role in it – cyclooxygenase-2 (COX-2) and COX. Estrogens stimulate their activity, PG suppresses. At physiological decrease of progesterone shortly before menstruation the activity of enzyme of 15-PGDH is reduced. This leads to a sharp increase in activity of COX and COX-2. The concentration of prostaglandins F2 α and E2 is growing explosively in the endometrium and triggers a

pronounced inflammatory response [3]. Prostaglandins E2 cause vasodilation and increase the permeability of the spiral arteries. prostaglandins F2 α increases the tone of the blood vessels of the endometrium, initiates stasis and causes hypoxia of the functional layer of the endometrium, destroying its cell by necrosis. Menstruation occurs. Interestingly, COX-2 is also in charge of the regeneration of the endometrium after menstruation. Due to its ability to increase the expression of Bcl-2 this enzyme inhibits apoptosis and recovering tissue homeostasis brings endometrium into a new cycle.

Progesterone deficit inevitably entails overexpression of COX-2 and increased concentration of prostaglandins E2, F2 α . COX-2 leads to inhibition of apoptosis and activation of neoangiogenesis and increase of adhesion of proliferating cells to the extracellular matrix. Prostaglandins E2, regulating steroid regulatory protein (StAR) and aromatase, increases the synthesis of estrogen. Stimulating the synthesis of VEGF, prostaglandins E2, affects leukocytes and enhances angiogenesis. It also inhibits apoptosis and activates the fibroblast growth factor-9 (FGF-9), which in turn promotes the proliferation of endometrial cells [9, 10]. Such mechanisms provide an impetus to the formation of abnormal autonomous hearth of proliferation in the endometrium with its local regulation of hormonal and immune structure, which is, in fact, cornerstone of the pathogenesis of PE.

Local effects of hyperprostaglandinemia are most studied in endometriosis and endometrial carcinoma. It is believed that the high level expression of COX-2 is correlated with the degree of malignancy and tumor invasion depth [11]. A COX-2 inhibition is effective in reducing the proliferation of epithelial cells in endometriotic lesions [12]. Today it is a matter of fact that the COX-2 initiates the development of colorectal and gastric polyps. Despite the fact that this enzyme almost doesn't show in the normal intestinal mucosa, in colorectal polyps and carcinomas its content goes up to 50% and 80%, respectively [11].

In our research we studied the expression of COX-2 and prostaglandins in EP. However, a comprehensive analysis of modern literature data suggests that increase in COX-2 makes an important contribution into the development of EP. And the role of the trigger factor in this process is played by progesterone.

Progesterone and immune system mistakes

PG functions are certainly varied, but one of the most important is large-scale immunomodulation in order to preserve and prolong pregnancy. It stimulates the production of PIBF (progesterone-induced blocking factor), the main agent of immune control by Pg lymphocytes and decidual endometrial cells.

It is PIBF that provides the necessary for pregnancy immunotolerance. The protective mechanism of this protein is that under its influence the balance Th1/Th2 is biased in favor of the latter, which is necessary to avoid overly aggressive immune system response to the growing embryo.

The absolute or relative deficiency of PG reduction and natural PIBF decrease is accompanied by a predominance of Th1-type reactions with the release of pro-inflammatory cytokines in the blood (IL-1, IL-6, INF- γ , TNF- α).

In addition to direct cytotoxic effects, proinflammatory cytokines include several mechanisms. First, they rapidly transfer NK-cells into the status of lymphokine-activated, contributing to their rapid degranulation and the release of perforin. And second, they activate the enzyme that increases blood coagulability, prothrombinase. The resulting microthrombuses violate local microcirculation and cause hypoxia. This process not only prevents the successful invasion of the trophoblast, but also leads to increased formation of VEGF, which plays a key role in the proliferation of the endometrium and the formation of EP. Effect of hypoxia is primarily performed by induction of transcription factor HIF (hypoxia inducible factor), which targets genes that provide control and regulation of angiogenesis, apoptosis and cell cycle. In addition, HIF induces differentiation of monocytes into macrophages, neutrophils and dendrocytes, reprograms them so that they form an inflammatory microenvironment that protects pathological tumor growth.

CONCLUSIONS

Thus, in case of progesterone deficit perverse mechanisms literally overlap in an attempt to start the process of tumor. Inflammation is an important component of the physiological menstrual cycle, during prolonged hypoprogesteronemia it becomes pathological. It is directly involved in the formation of such a microenvironment for endometrium in which the mechanisms of fibrosis fully realize their potential, cell proliferation and angiogenesis, creating a strong foundation for the subsequent formation and growth of EP. To date, it is proved that an imbalance in estrogen-progesterone system actually increases the risk of developing EP, but not always through steroid receptors. The variety of vicious connections launched by the PG, on the one hand, encourages the active therapeutic strategies and, on the other hand, requires a thorough understanding and analysis of the appropriateness of prescribed medicines.

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PROGESTERONE: A LITTLE-KNOWN ROLE OF THE WELL-KNOWN HERO

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Endometrial polyps and chronic endometritis are two most common causes of unexplained infertility in women of reproductive age.

The aim of our study was to conduct a comparative analysis of the hormonal homeostasis and the state of the receptor apparatus of the endometrium in women of reproductive age with endometrial polyps and micropolyps.

For a research 4 groups of women were chosen: 34 women with endometrial polyps (IA group), 36 patients with endometrial polyps and micropolyps (IB group), 30 women with micropolyps (II group) and 30 healthy women (III group). In all groups of women the content in blood serum for 3–5 day of a menstrual cycle of gonadotropic hormones (follicle-stimulating hormone, luteinizing hormone) and sex steroid hormones (estradiol, prolactin) was studied, for 21 days of a cycle estimated the content of progesterone. Level of an expression of receptors of progesterone and estrogen estimated in endometrium and at endometrial polyps, also in I a cycle phase.

The conducted research revealed reliable decrease in level of progesterone at women with endometrial polyps against the background of lack of significant changes in the receptor device. At patients with micropolyps the tendency to a hypoprogesteronemia was also observed, but changes in an expression of steroid receptors it was not also revealed.

The authors conclusion is the low concentration of progesterone initiate non-hormonal pathophysiological mechanisms of development of endometrial polyps which should be considered at purpose of antirecurrent therapy.

Thus, in case of progesterone deficit perverse mechanisms literally overlap in an attempt to start the process of tumor. Inflammation is an important component of the physiological menstrual cycle, during prolonged hypoprogesteronemia it becomes pathological. It is directly involved in the formation of such a microenvironment for endometrium in which the mechanisms of fibrosis fully realize their potential, cell proliferation and angiogenesis, creating a strong foundation for the subsequent formation and growth of endometrial polyps. To date, it is proved that an imbalance in estrogen-progesterone system actually increases the risk of developing endometrial polyps, but not always through steroid receptors.

Keywords: endometrial polyp, micropolyps, chronic endometritis, infertility, progesterone.

ПРОГЕСТЕРОН: МАЛОВІДОМІ РОЛІ ВІДОМОГО ГЕРОЯ

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Поліпи ендометрія і хронічний ендометрит – дві найпоширеніші причини нез'ясованого безпліддя в жінок репродуктивного віку.

Метою дослідження стало визначення концентрацій гонадотропних і статевих стероїдних гормонів, а також оцінка стану рецепторного апарату ендометрія в жінок репродуктивного віку з поліпами ендометрія та мікрополіпами.

Для дослідження було обрано 4 групи жінок: 34 жінки з поліпами ендометрія (ІА група), 36 пацієнок із поліпами ендометрія і мікрополіпами (ІВ група), 30 жінок із мікрополіпами (ІІ група) та 30 здорових жінок (ІІІ група). В усіх групах жінок було вивчено вміст в сироватці крові на 3–5 день менструального циклу гонадотропних гормонів (фолікулостимулюючого та лютеїнізуючого) та статевих стероїдних гормонів (естрадіол, пролактин), на 21 день циклу оцінювали вміст прогестерону. Рівень експресії рецепторів прогестерону та естрогену оцінювали в ендометрії та в поліпах ендометрія також у І фазу циклу.

Проведене дослідження виявило достовірне зниження рівня прогестерону в жінок із поліпами ендометрія на тлі відсутності значущих змін у рецепторному апараті. І пацієнок із мікрополіпами спостерігалася аналогічна тенденція до гіпопрогестеронемії, але змін в експресії стероїдних рецепторів також виявлено не було.

Автори дослідження дійшли висновку, що низькі концентрації прогестерону ініціюють негормональні патофізіологічні механізми розвитку поліпів ендометрія, які обов'язково потрібно враховувати при призначенні протирецидивної терапії.

Таким чином, запалення є важливим компонентом фізіологічного менструального циклу, який за тривалої гіпопрогестеронемії стає патологічним. Прогестерон бере безпосередню участь у формуванні такого мікросередовища для ендометрія, в якому механізми фіброзу повною мірою реалізують свій потенціал, клітинну проліферацію і ангіогенез, створюючи міцний фундамент для подальшого формування та росту поліпів ендометрія. На сьогоднішній день доведено, що дисбаланс в системі естроген-прогестерон фактично збільшує ризик розвитку поліпів ендометрія, але не завжди через стероїдні рецептори.

Ключові слова: поліп ендометрія, мікрополіпи, хронічний ендометрит, безпліддя, прогестерон.

ПРОГЕСТЕРОН: МАЛОИЗВЕСТНЫЕ РОЛИ ИЗВЕСТНОГО ГЕРОЯ

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Полипы эндометрия и хронический эндометрит – две самые распространенные причины необъяснимого бесплодия у женщин репродуктивного возраста.

Целью исследования стало определение концентраций гонадотропных и половых стероидных гормонов, а также оценка состояния рецепторного аппарата эндометрия у женщин репродуктивного возраста с полипами эндометрия и микрополипами.

Для исследования было выбрано 4 группы женщин: 34 женщины с полипами эндометрия (IA группа), 36 пациенток с полипами эндометрия и микрополипами (IB группа), 30 женщин с микрополипами (II группа) и 30 здоровых женщин (III группа). Во всех группах женщин было изучено содержание в сыворотке крови на 3–5 день менструального цикла гонадотропных гормонов (фолликулостимулирующего и лютеинизирующего) и половых стероидных гормонов (эстрадиол, пролактин), на 21 день цикла оценивали содержание прогестерона. Уровень экспрессии рецепторов прогестерона и эстрогена оценивали в эндометрии и в полипах эндометрия также в I фазу цикла.

Проведенное исследование выявило достоверное снижение уровня прогестерона у женщин с полипами эндометрия на фоне отсутствия значимых изменений в рецепторном аппарате. У пациенток с микрополипами наблюдалась тенденция к гипопрогестеронемии, но изменений в экспрессии стероидных рецепторов также выявлено не было.

Авторы исследования пришли к выводу, что низкие концентрации прогестерона инициируют негормональные патофизиологические механизмы развития полипов эндометрия, которые обязательно нужно учитывать при назначении противорецидивной терапии.

Таким образом, воспаление является важным компонентом физиологического менструального цикла, который при длительной гипопрогестеронемии становится патологическим. Прогестерон принимает непосредственное участие в формировании такой микросреды для эндометрия, в которой механизмы фиброза в полной мере реализуют свой потенциал, клеточную пролиферацию и ангиогенез, создавая прочный фундамент для последующего формирования и роста полипов эндометрия. На сегодняшний день доказано, что дисбаланс в системе эстроген-прогестерон фактически увеличивает риск развития полипов эндометрия, но не всегда через стероидные рецепторы.

Ключевые слова: полип эндометрия, микрополипы, хронический эндометрит, бесплодие, прогестерон.