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Etyopathogenetic diagnostic aspects and treatment of hyperplastic endometritis processes

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In the overview article the modern results of the literature which concern different aspects of the are summarized hyperplastic processes of endometrium. It is identified that in the study of HE it is necessary not only to specify some clinical aspects, but also to find a systemic pathogenetic approach to the problem which is vital in order to work out a differentiative approach to the treatment in every single case of the given pathology.

Key words*: endometrial hyperplasia, etiology, pathogenesis, treatment.*

In the modern gynaecology endometrial hyperplasia is considered to be the most widely – spread pathology of tunica mucosa uteri followed by its structural changes.

The study of issues concerning etyopathologenesis, diagnostics and treatment of hyperplastic processes in endometrium represents a huge scientific, medical and social interest.

Among the women in the structure of gynaecological pathology HE is revealed with the frequency equal to 15–40%.

According to the frequency of negotiability the frequency of HE varies depending on its forms and the age of patients. In woman younger than 35 years old with different disturbances of the reproductive function ferrous hyperplasia occurs in 6,6% cases, whereas in patients with polycystic ovary syndrome the risk of HE development may be equal up to 75–91%. V. Zaporozhan [1] and the coauthor E. Vihlyaeva [46] reckon that HE is more often revealed at the age of 45–55 years.

According to the opinion of Amezcua and the coauthor [2], HE is diagnosed in 50% patients in their late reproductive and perimenopausal period. O. Chepik [3] thinks, that the issue of the development of HE's malignant transformation remains open.

M. Davidov and others [7] point out that the degree of the malignasation risk of different variants of HE is determined by the morphological condition of endometrium and primarily depends on cellular atypia and less depends on age, condition of ovaries, associated endocrine diseases and other factors.

Endometrium is a target organ for reproductive hormones due to the presence of specific receptors. Well – balanced hormonal infiuence via specific cytoplasmatic and nuclear receptors provides with a periodic cyclic transformation of tunica mucosa uteri. A disorder of a woman's hormonal status may lead to the changes in growth and differenciationof cellular elements in endometrium and involve the development of hyperplastic processes.

It is primarily important that the pathology refers to the number of proliferative processes and in case of its prolonged advancement without any treatment may become a background for the development of endometrial cancer.

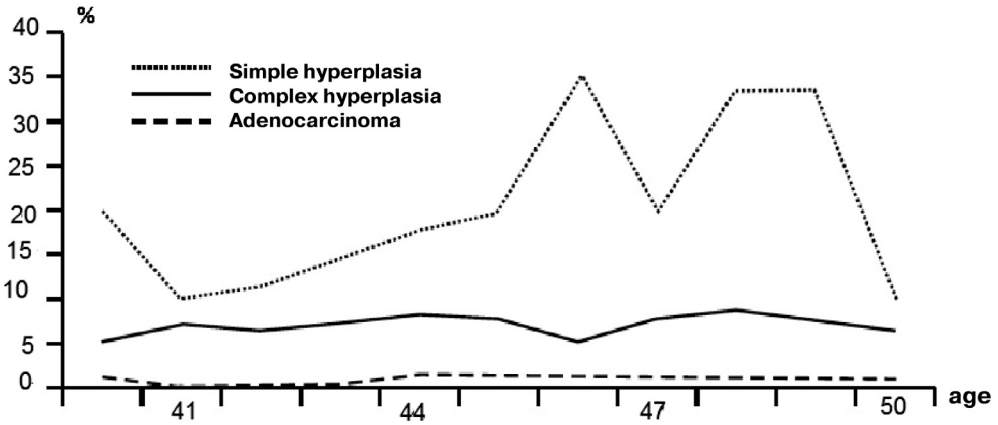
The absence of a tendency to the decrease in the number of HE cases may be conditioned by the increase of hormonal – dependent morbidity in the reproductive as well as in perimenopausal periods. High frequency of HE recurrence dictates the necessity of the improvement in tactics of patient's treatment and optimization of hormonotherapy wage.

Meanwhile, family doctors and obstetrician – gynaecologists should remember that HE can be a prognostic factor of endometrial adenocarcinoma's development or co – occur (co – associate) with atypia hyperplasia and adenocarcinoma.

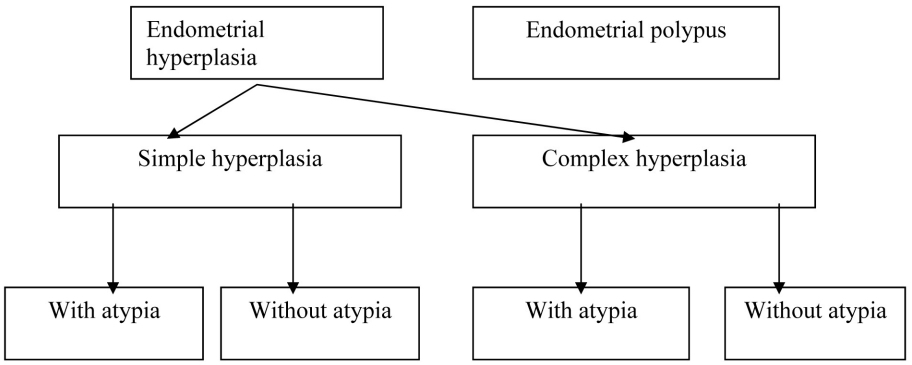
The results of publications testify that in the first decade of the 21th century a progressive increase of endometrial cancer prevalence occurs. Annually about 150 000 new patients with an uterus body cancer are revealed in the world and 42 000 patients die of this pathology.

V. Zaporozhan, T. Tatarchuk and others report that according to the data of foreign scientists half of the cases of endometrial cancer development in peri – postmenopause is the result of hyperplastic processes' malignazation, moreover, the frequency and terms of this malignazation vary in high rates (0,25–0,50%) and significantly depend on the degree of expression of hyperproliferation in endometrium.

The authorsemphasire that exactly its timely diagnostics and adequate therapy of HE are the keys to successful prophylaxis of endometrial cancer [1].



Pic. 1. Prevalence of hyperplastic processes in endometrium depending on the women's age [66]



Pic. 2. Classification of HE, WHO, suggested in 1994

Unfortunately, in Ukraine about 5000 new cases of cervical cancer are registered annually, besides, every forth – fifth ill woman is in the reglected 3–4 stage and 2000 patients die of this disease.

Many morphologists, oncologists and gynaecologists consider endometrial cancer in close association with HE.

R. Seullyu and coauthors identify the following morphological forms of HE according to the classification of the WHO (World Health Organization) (1994): simple non-a typical hyperplasia of endometrium; complex non – atypical hyperplasia of endometrium; simple atypical hyperplasia of endometrium; complex atypical hyperplasia of endometrium; adenocarcinoma [4]. The same author [4], later V. Chissova and A. Trachtenberg [5] report that for simple hyperplasia glands of various sizes and forms are character's tic, and a part of them have a cystic dilation.

Different classifications of HE are based on the morphological principle. Nowadays the classification which was suggested by the WHO in 1994 is more commonly used. According to this classification simple and complex hyperplasia are differentiated depending on the degree of the tunica mucosa uterine body structural changes, moreover, taking into consideration presence or absence of cellular atypia. Endometrial polipi exceed the limits of this classification and are considered to be tumor – like formations of tunica mucosa uterine body which don't have any features of a genuine proliferative process. Only an adenomatosis polypus is an exception which represents a central form of a complex hyperplasia with / without atypia.

Pavement of glands corresponds to the proliferative phase of the cycle,though figures of mitosis are extremely rare. Stroma is rich in cells. Such changes seldom transform into cancer and more often end in cystic atrophy in which epiteliumand stroma become atropnical. In cases of complex hyperplasia of endometrium (CHE) the quantity and sizes of the glands are increased. The differential features of complex hyperplasia are crimpiness and close location of the glands. Their pavement is multilined – multilayered, more expressed (more marked) than in case of simple hyperplasia, but even outlines of the glands' gaps are remained.

There is no cellular atypia. Meanwhile, malignazation occurs in more than 4% of cases.

In case of atypical hyperplasia along with the above – described changes irregular internal outlines of the glands' pavement are revealed. Stratification is very well – developed which is accompanied by the precipitation of scalloped silhouette of the pavement.

Expressed (marked) atypia of epitheliocytesisadded by the loss of polar cellular location, hyperchromatosis of some nuclears. In practical investigations very big epitheliocytes are come across, as well as mitosis' figures [3].

I. Sidorova, T. Ovsyannikova [6] claim that in endometrial scrapes it is difficult to differentiate atypical hyperplasia and highly – differential adenocarcinoma. Investigations of a number of authors [7, 8] have shown that in about 23–32% patients with atypical hyperplasia endometrial cancer develops.

According to the results of F. Lin's studies [9], atypical hyperplasia is subjected to malignant transformation in almost 52% cases. As for the risk of typical hyperplasia's transformation into atypical, the author claims that its prevalence is equal to 10,5%, and into the cancer of endometrium – to 2% [9].

In case of recurrent endometrial hyperplasia occurrence of invasive cancer of uterine body is registered in 20–30% cases [10]. R. Scully and coauthors [4], G. Mutter [11] unify simple and complex hyperplasias without atypias into a single category "hiperplasia", and use the notion "endometrial neoplasia" for atypical hyperplasia and adenocarcinoma.

N. Sheshukova and coauthors [12] under the notion "hyperplasia" mean an increase in the number of cells, instracellular structures and intercellular formation due to the intensive function of the organ or as a result of a pathological tissue neoplasm. HE is overproliferation of epithelium and, less, of stroma, thus, regarded to be a common pathology which requires intent attention as it may occur as background for the development of adenocarcinoma. Evolution of hyperplasia into an adenocarcinomal process isn't compulsory, but possibly in case of corresponding risk factors [13]. C. Ferquhar and coauthors (1999) [14], E. Ricci and others (2002) [15] refer the following to the factors of HE's development: early menarche, late menopause, absence of delivery, obesity, hyperlipidemia, insulin – dependent diabitis, disorder of menstrual cycle conditioned by anovulation, endocrinal sterility, polycystic ovary syndrome, substitutive hormonotherapy in postmenopause. In pathogenesis of HE the leading role is long since given to estrogenes.

V. Barker and coauthors (1996) [16] point out that usage of preparations which contain only estrogenes increases the risk of HE's development including atypical hyperplasia up to 4–14 times.

As V. Smetnik writes [13] these data have forever aroused fear of estrogenes in souls of both doctors and patients. As there has been no significant increase in estrogene's level revealed in case of hyperplasia, it has been supposed that an important role is played by relative hyperestrogenia (on background of progesterone) as well as the duration of estrogenes' effect / influence but not the degree of their concentration in blood. In patients with hormonal – dependent neoplasms the mostly – marked disorders occur in 3 homeostatic systems: reproductive, energetic and adaptational [6]. If a body mass / weight exceeds the norm for not more than 23 kg. The risk of uterine body cancer increases 3 times, if more than 23 kg – 10 times [28].

According to modern views, hormones themselves do not directly evoke a tumor – like transformation of the cell because they do not change the primary structure of DNA [6]. Nevertheless, they do create conditions in which probability of cancer precipitation is increased under the influence of a genuine cancerogenial factor. There are at least 3 conditions of this kind: increase of pool in proliferative cells, weakening of anti – tumoral immunity and decrease of ability to DNA reparation. From sources in literature it is clear that in a number of patients with HE this vary disease is not autonomous, and the morphological marker of hyperestrogenia is as a consequence of non – malignant growth or primary stage of ovary cancer. Precipitation of atypical hyperplasia and endometrial cancer in young age can be regarded as a late complication of untreated polycystic ovary syndrome [12]. Presence of receptive uterine apparatus active to estogenes may evolve endometrial hyperplasia in conditions of relatively low estrogenial level [29]. At the same time data of the study about possibility of HE's development on background of hormonal disorders absence testify in favour of other mechanisms of endometrial hyperplasia formation associated with local disorder of cellular proliferation regulation and local changes in tissue exchange [30].

High risk of atypical hyperplasia and adenocarcinoma is marked in the presence of centers of persistent hyperplasia which represent newly – nascent hyperplastic processes. From the studies of a number of authors G. Chernuha and coauthors [17, 19], H. Refn [18] it is clear that sensitivity to hormonal impacts in large depends on endometrial receptive phenotype. So far 2 types have been identified: ER – ER – a and ER – B; and two isoforms PR – PR – A and PR – B. ER and PR are revealed both in epithelial and stromal endometrial cells.

During a normal menstrual cycle their content changes and subjects to appropriate (regular) variations: the level of ER significantly increases in late proliferation phase, reaches the peak in the middle of the cycle and gradually decreases during the secretarial phase; the level of PR gets its maximum in the early phase of secretion. As the author claims [3], concentration of ER and PR varies not only depending on the phase of the menstrual cycle, but also on the beginning of the pathological process in tunica mucosa uteri. Nevertheless, data of literature on the content of receptors to sex steroid hormones in case of HE are extremely contradictory.

G. Chernuha, I. Gupta, P. Chien [17, 20] reckon that there is an interconnection between a receptorial phenotype and a HE form focusing on high ER content in case of simple HE (SHE), decrease in case of a complex one (CHE), particularly in case of atypical (AHE). V.Chen points out that such a regularity occurs referring to PR [21]. Meanwhile in a series of other studies pallalel to this one T. Maruo and coauthors [22] have not revealed any significant changes of the receptorial endometrial phenotype in HE as well as dependence of receptors expression on its form. Nowadays there is a point of view according to which various expressions of sex steroids receptors in hyperplasive endometrium is accosiated with a different reciprocal reaction on therapy with progestagenes which alike natural progesterone neutralize the influence of estrogenes via decrease in ER and PR content.

According to the opinion of E. Akesson and coauthors [23] high expressia of sex steroid hormones is regarded as a prognostic factor of an adequate reaction on the impact of exogenic hormones. Reduction of expressia is connected with a dysfunction of signal tracts which regulate the influence / work of sex steroids and is often associated with an increase of expressia of the growth factors. As A. Vereide and coauthors claim different kinds of progesterone and schemes of their prescription inhibit both PR and ER expression in glands and endometrial stroma to different degrees as well as proliferative activity [24].

Data in some publications show that one of the main causes of proliferative diseases of endo – and miometrium development seems to be a disbalance in processes of proliferation and apoptosis. However, in the literature results of the studies concerning the level of expression of proliferative markers Ki-67 and PCNA in ferrous and stromal components of endometrium in HE are different. Thus, in some investigations this controversy shows that increase of proliferative markers' expression in hyperplasive endometrium is revealed [25, 26], while some other studies have gained data concerning low expression of Ki-67 and in comparison with proliferative endometrium [27] and absence of significant differences in various forms.

Studies of M. Gomez and coauthors [31] show that mechanisms of therapeutic impact of KOK, progestagenes,aGnRGon autopic and ectopic endometrium is mediated by decrease of proliferative activity and activation of apoptosis. The same effect occurs in case of using intrauterine system with levonopgestrele (2NG) aimed at contraception, treatment of endometriosis and protection of endometrium while performing SHT.

According to the publications 2NG is successfully used to treat HE because it is effective due to its specific impact, possesses a reversible effect, minimizes systemic unfavorable (undesirable) influences and is charactenzed by profitability. However, as scientists G. Chernuha and coauthors claim [19], molecular mechanisms of an intrauterine contraceptive with LNG (LNG – IUC) effect are still being investigated, so issues of the influence of LNG – IUC on proliferative markers are still not thoroughly studies as well as its influence on expression's modulation in different forms of HE.

The authors have put a goal to define possible mechanisms of realization of LNG – IUC therapeutic effect in different forms of HE on the basis of study of receptors' expression to sex steroids and proliferative activity of endometrial cells. The results of the performed work have shown that intrauterine impact of LNG is followed by decrease in proliferative activity of ferrous and, particularly, stromal cells of endometrium as it is testified by the level of expression of proliferative markers Ki-67 and PCNA which in simple and complex HE approximately decreases up to 2 and a half times, in atypical – only up to one and a half times and by the end of the therapy course it is almost twice as high as the analogical parametres of patients with SHE and CHE ($p<0,05$). It gives the authors some rights to consider it as a scientifically – proven fact that LNG can be intranterinely used as a highly – effective means to SHE and CHE and as an alternative one to treat AHE in patients of the reproductive age who are interested in pregnancy.

Apart from estrogenes activators of proliferative endometrial activity are growth factors and markers of proliferation which are necessary for a genomic DNA replication. One of the main genetic disorders needed to develop a growth / tumor is inactivation of genes – suppressors.

As it is pointed out by M. Shalkova [32], genes – suppressors and genes of reparation in tumors can be inactivated as a result of their structural inquiry (deletion or/and mutation) orfunctionalinjuiry (abnormal methilation). Methylation is reversible covalent DNA modification when a cytosine remnant in CG – dinucleotide is methylated in position #5 of the pyramidial ring. Methylation of cytosine remnants occurs with the help of DNA ferments – methyltransferas which transport metyl group S – adenozynmethyonine. The authorsclains that such a modification is the only admissible in physiological conditions of DNA chemical modification and is stably supported in a series of cellular divisions that is provided by a family of DNA –methyetransferas. Taking into consideration the fact that nucleotide sequence of DNA in methylation doesn't change this vary process is a reversible event under an ampact of demythylative agents or ferments alike genuine mutations of DNA.

E. Daura oller [33] claim that one of the earliest and most common mechanisms of genes – suppressors' inactivation is methylation of CpG – islands in promotive and regulative areas of these genes.

Abnormal methylation of CpG – islands leads to suppression of genes' functioning as suppressors, meanwhile the sequence of genes does not change, but it stops functioning. [32, 34, 35]. Many authors have shown in their studies that in recurrent endometrial hyperplasia and atypical hyperplasia it is identified the increase in the frequency of genes hmLHI, RASSF A methylation prevalence, high occurrence of p6, PTEN, RASSF, GSTPI methylation in adenocarcinoma [9, 33, 36, 37]. According to the opinion of G. Berek [38] HE can be genetically predefermined. The gene of glycoprotein GP-IIIa is represented by 2 allele forms – PL – AI and PL-All. Consequently, every person can be a carrier, of a single form of gene – homozygote (AIAI, AIIAII) or have in his / her genotype simultaneously 2 alleles (AIAII) – heterozygote. The frequency of AIAI genotype in the population equals 73,1%, AIAII – 24,8%, occurrence of homozygote AIIAII reaches 2,1%.

The author points out in the work that the polymorphism's frequency of glycoproteine gene GP – IIIa in HE presence, according to the number of investigators, is the following [38]: among patients with ferrous hyperplasia of endometrium homozygote on PL-AI allele of 90,6%, with typical hyperplasia – 90,9%.

It is obvious that AI allele of GP-IIIagene defines a genetic predisposition to active implantation, and all allele's carriage of GP-IIIa gene can be regarded as a genetic factor which prevents HE development.

Nestler J.E. and others [57], Toprak S. et. al [58] claim that with a normal body weight / mass estrogenes stimulate GCSS (globulin connecting sex steroids) output by liver in case of hyperinsulinemia, insulineresistancy, obesity, thus in presence of metabolic disorders, content of GCSS in blood decreases.

Scientific data, obtained in the latest decades, have proven the dependency of metabolic processes on the content of steroid hormones in the organism. Meanwhile, as it is mentioned above, steroid hormones themselves can metabolize in different tissues of organism. Interaction of insulin – dependent tissues of organism (fat, muscular, liver) and steroid hormones is of a huge scientific – practical interest.

Thus, decrease in GCSS level is a factor which on the one hand stimulates an increase in estradiol availability but, on the other hand, reflects the presence and severity of metabolic disorders. So, patients with ovary hyperandrogenia are characterized by a decrease in GCSS level and an increase in free steroids content.

It should again be noted that in case of hyperinsulinemia suppression of globulin connecting sexual hormones in liver synthesis is observed and, consequently increase of free estradiol in blood plasma. The level of free androgens also depends on the concentration of globulines which connect sexual steroids. Apart from it, hyperinsulinemia in woman with ovary hyperandrogenia may promote formation of HE directly ruflueneing the endometrium.

Guidice L. (1994) according to his reliable studies has proved a direct stimulating influence of insulin and insulin – like growth factor on endometrium [60], quantity and bioavailability of which in hyperinsulinemia are increased [61]. Watson H. and coauthors [62] report that hyperandrogenia strengthens the stimulating effect of epidermal growth factor on endometrial proliferation.

Konishi I. and coauthors [63] point out an increase in the quantity of LH receptors in hyperplasial endometrium which can also testify this hypophysis hormone's participation in HE development. So, in patients with hyperandrogenia and inflammatory diseases of internal genitals, particularly in the second group, content of pro- and autiinflammatory cytokines – interleikin – 1β (IL – 1β) and a – factor, tumor necrosis (TNF – 2 – tumoz necrosis factor) in blood plasma the less levels of proinflammatory cytokines are revealed, in which in hyperandrogenia in pathogenesis of severe hyperplasias increase of bioavailability E2 is one of the factors of complex impact on endometrial state.

Severity and duration of estrogenic impact on tunica mucosa uteri were evaluated by us according to potential duration of ovary function disorder (hyperpolymenorrhea, algodismenorrhea and unovulative cycles). Duration of ovary function disorders, particularly with hyperpolymenorrhea and unovulative cycles in woman is more than 2,5 years of CHE and atypia (9,1±1,5 years; $p<0,01$) in comparison with the other variants of endometrial structure [40].

Regardless of the type of menstrual function disorders, especially in ovary dysfunction (with hyperpolymenorrhea and unovulative type) the risk of HE development increases up to 2,5 times with the duration of the pathology equal to 5 and more years on background of inflammatory processes in internal genitals, particularly in patients older than 30 years.

In the performed clinical analysis of different HE schemes / pictures it was noted that the character of ovary dysfunction had its peculiarities depending on endometrial structure and is practically not associated with a disorder type of the menstrual function, like for instance, hyperpolymenorrhea, unovulation.

In woman with endometrium without any features of functional activity oligomenorrhea in association with secondary amenorrhea was recorded more often than other types of disorders ($p<0,01$). In patients with SHE oligomenorrhea alternating with dysfunctional uterine bleeding episods was reliably more often (in 9 out of 11 – 81,8%, $p<0,01$).

Out of 16 woman with CHE 3 patients with atypia in the second group had oligomenorrhea. Taking into consideration literature reports that oligomenorrhea is the mildest disorder of menstrual cycle, such woman don't consult doctors obstetricians – gynaecologists for a rather long time, thus, consequenlly, duration of ovary function disturbances increases and, undoubtedly, risk of severe kinds of hyperplasia development [47, 58].

The analysis of results in defining anti-inflammatory cytokines has revealed in patients of the first and third groups levels of anti-inflammatory cytokines IL-1β and TNF-a reliably decreased in comparison with the control group. And only in patients of the fourth group (which on the background of ovary disfunction with inflammatory diseases of internal genitals has no deviation of hormonal indices) these indices were within the low normal limits.

Thus, data from literature and results of own investigations have once more confirmed the role of hyperestrogenia in HE development. However, some differences in pathogenesis and clinical picture of SHE and CHE have been discovered. So, it is appropriate that for SHE development presence of hyperestrogenia becomes an essential and sufficient condition while for CHE development, including the one with atypia, hyperestrogenia is essential, but meanwhile an insufficient condition [47].

As Chen Y. and coauthors point out [67] – an additional factor for CHE development on the systemic level should be considered to be hyperinsulinemia which indirectly and directly stimulates proliferation and suppresses apoptosis. But not a less important role is played by local endometrial changes which lead to an unnatural reaction on tissue, on hormonal and paracrine impacts [47].

And, finally in patients with CHE who suffer from ovary dysfunction with inflammatory diseses of genitals content of proinflammatory cytokines IL-β and TNF-a in blood serum were low in comparison with midly – lowered indices in patients from other groups, particularly the fourth one (in which no deviations of hormonal indices were revealed) and in patients of the control group. But, besides hyperestrogenia, activators of endometrial proliferative activity are growth factors (IGF – 1, EGF, TGFα)

as well as the above – mentioned proliferative factors (PCNA, Ki-67), necessary for genomal DNA replication. In the literature there are data that in CHE with atypia and without atypia high production and accumulation of vascular – endothelial growth factor (VEGF) are reported which indicates active processes of angiogenesis and high risk of malignization [48].

In the analysis of molecular basis of HE development big attention is paid to the state of extracellular matrix, as well as ferments participating in its modification. In this connection I.Makarov, T.Ovsyannikova and others [49] have made a good of their study – to define the role of lysyl oxidase in HE genesis. Lysyl oxidase (LOX) is a copperbearingaminooxydase which belongs to the family that according to the latest data consist of 5 members: lox and lysyl oxidase – like proteins – LOXL, LOXL2, LOXL3, LOXL4. The mostly studies is LOX itself. Its main function is initiating the formation of intramolecular cross – linkages in collagene and elastine which leads to increase in strength and elasticity of fibres and also to the formation of integrated structure of these fibres. Consequently, LOX is necessary for a normal organism activity. It is proved that LOX takes part in control over intracellular activity. LOX expressia significantly increases in hypoxia, at that a connection between LOX expression and hypoxia of the inducing factor (HIF) is already found out.

The state of anoxaemia is a characteristic feature of cellular metabolism in centress of inflammation and traumatic injuiry. Thus, nuclear factor HIF – 1 and LOX can become one more connecting component between hyperplastic processes in endometrium and tumor – like formation. 66 patients were performed an investigation LOX expression was defined with the help of immunohistochemical investigation which was performed by a method of indirect immunofluorescence with the usage of specific polyclonal antibodies to LOX on paraffin sections.

After the performed study the authors [49] have come to the conclusion that immunohistochemical investigations haven't revealed any principal difference in production and accumulation of LOX in simple and complex morphological forms of HE without atypia. Reliably high level of LOX in patients with atypical HE testifies the presence of cellular hypoxia and disorder of intercellular and cellular – matrix interaction in endometrial tissue. Women with complex and simple hyperplasia with atypia refer to the high risk group of potential malignization.

If was noted down earlier that chronical inflammation is considered to be a predisposal factor for further development of hyperplastic and neoplastic diseases. Meanwhile, molecular mechanisms which promote disorder of tissue and cellular homeostasis with the rise of hyperplastic changes in long-prolonging lical inflammatory reaction in endometrium are not studied thoroughly enough. On the basic of publications data on immunobiochemical study T. Nieminen and coauthors, O. Bozdogan and coauthors have found out the change in expression of the genes which are in charge of apoptosis, proliferation, neoangiogenesis, remodeling of intercellular matrix in HE depending on its morphological variant as well as presence of associated hyperplastic diseases (myoma of uterus, adenomyosis) [50,51].

I. Stanoevich, V. Zemlyakova and coauthors [39] made an investigation the aim of which was to define the participation of abnormal methylation of genes-suppresors of tumor growth RASSFIA, CDH1, P21waf1 CD44 in HE development on the background of chronicalendometrit (CE).

The investigation was performed on 52 patients with morphologically verificatedHE: simple HE without atypia in 41 woman, coplex HE without atypia in 9 and complex HE with atypia in 2 patients. Average age of the patients was 37,9±3,8 years.

Depending on the presence of histological features of CE the woman are divided into 2 groups: the first group is formed of 27 patients with HE without signs of HE; the second – 25 patients who have a mixture of HE and CE. Genomal DNA was extracted from operational material (samples of endometrium) of the woman by the method of phenolchloroformal extraction. To define methylation of CpG-is lands of promotor areas of the target genes the method of methylsensitivity polymerase chain reaction (MSPCR) was used.

The authors have found out that possible mechanisms of HE development in CE are absence or pause (stop) of proliferative signal via hypermethylation of P2 gene and disturbance in endometrial cells connection with intercellular matrix of CD44 gene's methylation.

G.I. Suchih and coauthors [44] also claim that one of important chains of HE ethiopathogenesis is chronicalendometritis in which not only endometrial cells proliferation is increased, but also apoptosis besides the balance between these processes supports tissue homeostasis. In the mechanisms of apoptosis an important role is played by a tumor necrosis factor α (TNF-α) which transforms growth factor β (TGF-β) produced by macrophages. According to the authors' opinion development in case of chronicalendometritis of pathological endometrial proliferation or atrophy is possible if the balance between differently – directed processes of apoptosis proliferation (especially on the back – ground of a virus infection) is disturbed.

We have made an investigation of genetic polymorphism of estrogenes metabolism ferments CY 1A1, CYP1A2, CYP19 and SULT1A1 in 34 woman with hyperplasia in endometrium of a late reproductive age 37–45 years. The first group consisted of 22 patients with hyperplastic processes. The second group was formed of 12 woman without any endometrial pathology.

In the first group of the woman in comparison with the second one a mutant allele A of CYP1A gene was registered reliably more often, besides there was revealed an increase in the percentage of heterozygote genotype G/A of SULT1A1 gene. The results of the studies show potential involvement of CYP1A2 and SULT1A1 ferments into HE pathogenesis [40].

According to the opinion of N.Artimchuk and coauthors [42], any disorder in one of these systems caused by a change in ferments' activity leads to a change in estrogenes content which may be a reason of proliferative processes appearance. G. Chernuha and coauthors defined the clinical significance of μPNK genes expression participating in the processes of apoptosis and the gene – suppressor of tumor growth PTEN in different HE types and endometrial carcinoma.

A clinical – laboratory investigation was performed and excavation of endometrial tissue samples in 133 patients. The main group was formed of 64 woman with HE (31 – with simple, 18 – complex, 15 – atypical); the group of comparison included 22 patients with endometrioidal carcinoma; the controlgroup included 47 woman with morphologically unchanged endometrium in proliferative stage (n=26) or secretion stage (n=21). The study of μ PNK expression of apoptosis genes: inhibitors BCL2, BAG1, BIRC5 and inductors BAX, NDRG1 was performed by the method of polymerase chain reaction with a reverse transcription (in PCR).

Expression of PTEN gene was defined by 2 independent methods (in PCR and immunohistochemical). The authors came to the conclusion that the received data testify a potential role of a programmed death of cells in development of endometrial carcinoma. Reduction of μPNK gene NDRG1, PTEN, NDRG1/BIRC5 index expression can supposedly regarded as molecular – genetic predictors of cancer endometrial transformation risk [41].

O. Lisenko, S. Zan'ko [56] have studied content of cytokines and s Fas-liganda on local and systemic levels in hyperplastic

processes and polipe of endometrium in reproductive and premenopausal age periods. 131 patients have been investigated. The woman are divided into 6 groups depending on age and histological conclusion. In aspirate from uterine cavity and blood serum of the patients concentrations of interleikine – 2, interleikine – 4, tumor necrosis factor, s Fas – liganda are defined by the method of hardphasicimmunofermental analysis. The index $p<0,05$ is taken as reliable.

The investigations have shown that a cause of localimmunity and Fas-dependent apoptosis disfunction in endometrial pathology can be earlier inflammatory diseases, intrauterine interventions, interauterine contraception.

Definition of cytokines and sFas – liganda in aspirates from uterine cavity can become a useful diagnostic marker of hyperplasia and endometrial polipi.

Issues of hyperplastic processes therapy remain actual so far and are performed taking into consideration the age of a patient, endometrial structure clinical symptoms, contradictions to a treatment method, absence of allergy to therapeutic preparations, associated extragenital and gynaecological pathology, presence of metabolistic syndrome. Achieved successes in HE diagnostics define the main task of providing adequate treatment.

Ability of hormonal therapy (progestagenes) to arouse HE regression is highlighted in many studies. Let's focus on one of them – D. Marsden [55] who has visually shown in his work that progestagenes arouse regression of endometrium in many studies. Among possible causes of disorder in therapeutic effectiveness of progestagenes it should be noted the presence of persistent hyperplasia centers, apoptosis processes disorder, production decrease and accumulation of transformatinggronth factor 3. One of the progestagenes therapeutic effect components can be apoptosis activity induction which explains expressed reduction of ferrous apparatus in case of effective treatment. However, before a hormonal therapy is started, it is necessary to perform hysteroscopy and get the results of the obtained material of the histological study. From the point of view of the approach, the way of treatment the most significant are 2 effect of progestagenes: secretarial transformation of endometrium and ovulation suppression. Syntheticalprogestagenes are actively connected with estrogenes and progesterone receptors in tissue of an organ – targets, thus, makes a direct anti – rstrogenic and anti – progesterone effect. Highly – selective progestagene, specifically connected with progesterone receptors, is dydrogesterone. Investigators characterize this preparation by its one of the highest energies of connection with progestagenial receptors and lowest energies of connection (or complete lack of connection) with other kinds of steroid receptors. Thus, clinical usage of dydrogesterone is of not only therapentic significance but practically, thus, factually, doesn't lead to any side effects [12, 44].

Hormonal therapy with gestagenes is directed at endometrial suppression. To treat HE dydrogestagene is prescribed to be taken a day x10 mgr continuously during 6–12 months. Practical doctors should follow the order of Ministry of Health Protection (MHP) of Ukraine dated 31.12.04 #676, where it is pointed out that duration of therapy is 6 months with recurring histological investigation every 3 month (in case of simple HE it is possible to have a histology 6 month later if ultrasound criteria of hyperplasia are absent). In resence of hyperplasia after 3 months of therapy its correction is made, and in case of atypical hyperplasia a consultation of an oncologist – gynaecologist is prescribed.

In doctor's practice as a rule it is possible to identify pathological endometrial processes before clinical symptoms precipitation by an echographictransvaginal scanning in complex with coloured Doppler mapping.

There is a clear interconnection between endometrial thickness measured with the help of an ultrasound investigation and presence of endometrial pathology. Endometrium is evaluated based on results of one linear measurement on the 5^{th}–7^{th} day of the menstrual cycle – increase of anteroposterior size of M-echo to the whole extent or locally up to 7–9 mm is regarded as a pathology.

Threshold of normal endometrial thickuess in postmenopause equals to 5 mm [45].

Cytological investigation of aspirate from uterine eavity has a high diagnostic value but it is not enough to make a reliable diagnose [1, 14]. The performed studies prove that in case of aspirative biopsy incomplete diagnostics of cancer occurred in 45% cases whereas in case of separate diagnostic scraping – in 30%. In other words practically over a third of cases of endometrial cencerwas missed in a complete curettage of cervical duct and uterine cavity [1].

V. Zaporozhan, T. Tatarchuk and coauthors claim that in this contex special significance is given to methods of endometrium's visualization diagnostic value of which has significantly increased with development of modern optical systems.

Hysteroscopy allows to visualize pathological changes of endometrium and define peculiarities and location, control the quality of a histological scraping with a target deletion of possible remnants of hyperplastic endometrium or polipy with minimal traumatism of healthy tissue and perform intrauterine operations with the usage of electro – lazer surgery.

Thus, target biopsy is a fine diagnostic method to define endometrial pathology. It is necessary to point out that histology is a golden standard in those cases when diagnosties of endometrial proliferative processes is performed by a pathomorphologist of high qualifications. A number of publications claim that nowadays different approaches to HE treatment are used – deletion of pathologically changed endometrium, hormonal therapy and operative treatment.

According to the performed overview so far there is no common (unified) HE classification which prevents clear understanding of this very pathological process and can often lead to disagreement between clinicists and morphologists which is reflected on the choice of treating woman with HE.

Taking into consideration the fact that atypical types of HE a result of hyperestrogenia the key moment in treatment of the pathology is exactly the correction of estrogenes' prevalence, thus, hormonotherapy.

V. Prilepskaya [52] underlines that effectivity of hormonal therapy in case of HE without atypia is 42% according to the results of a number of studies. The data of E. Novikova and coauthors' investigations [53] are the following: recurrences of HE are diagnosted in only 26% patients who got hormonal treatment.

We have performed a study of 97 patients aged 21–42. In the process of the investigation the woman were divided into 4 groups depending on ovary disfunction character [40].

Literature data [53] show a large number of recurrent cases of EH-endometrial hyperplasia (0,25–64,7%) expecially in those who have ovary function disorders and inflamatiry diseases of uterine adnexa, the presence of which due to oncowatchfulness is mostly crucial in choice of hysterectomia in patients of reproductive age.

That's why in such woman more significant differences have been obtained via analysis of bioavailable E2, calculated according to its ratio to GCSS (index of free E2). The lowest indices were reported in patients without HE in comparison with all the rest ($6,5\pm1,1$; $p<0,05$), besides, there was no relationship discovered with endometrial structural changes. It can be observed in woman with hypoestrogenia who in most cases have no HE risk factors.

In case in woman with HE reliable differences were discovered concerning the level of free E2 according to the types of

hyperplasia, this index was the highest in patients with CHE with atypia (13,1±0,8), lower in case of CHE without atypia (9,7±0,7; p<0,05) and even lower in HE (7,9±0,5; p<0,01).

The results of the investigation testify that expression of estrogeniac impact is a significant factor of endometrial hyperplasia growth. It should be paid attention that an increase in the level of general E2 is of importance in HE formation and development of CHE occurs on the background of normal general E2 concentration but with increase of its bioavailability. In such cases increase of ratio between E2/GCSS of more than 8 leads to growth of relative HE risk up to 2,1 times, of more than 9–10 – the relative risk of CHE is 3,7 times more.

According to the literature data [47, 54] and own investigations the obtained results shouldn't be regarded from the point of view of pathogenesis of different hyperplasia's variants depending on the level of estrogenic impact. Misfit in the level of E2 bioavailability in SHE and CHE cannot be regarded as basis to take this very factor as the main one in hyperplasia expression formation because content of free estrogenes is difined not only by content of general E2 in blood plasma, but also by quantity of GCSS as level of GCSS is regulated by many factors.

In case of hyperplasia presence 3 months later the correction of the therapy is performed, and in case of atypical hyperplasia it is prescribed to have a consultation of an oncologist – gynaecologist according to the protocole approved by the MHP of Ukraine order dated 31.12.2004 #676.

It is reasonable to point out that an advantage of the preparation dydrogestagene (dufaston) is an opportunity of its prescription in HE presence in patients with disorders of endometrial receptoral activity.

Progestenes can be used in any forms of HE. The morphological index modified the choice of progestagene and regime of its usage. N.Sheshukova, I.Makarov, M.Fomenko point out that in case of endometrial atypical hyperplasia acetatmedroxiprogesterone (depoprovera) is prescribed, the dose and regime of its taking are chosen individually [12].

Gestrinone (antiprogestine) – its main effect is in the impact on hypothalamo – hypophysal system, thus, in suppression of gonadotropin dismissal and their synthesis in slight inhibition [1, 45, 53].

For HE monotherapy agonists of gonadotropin releasing – hormone (αHnRH) are successfully used. These preparations having an impact on the system hypophysis – ovaries – endometrium arouse amenorrhea ("pseudomenopause") which is of a temporary and reversible character. Besides, these preparations makes an autiproliferative effect on endometrial cells due to their connection with highlyaffine specific receptors to αHnRH [1, 44, 53].

The preparation of choice to treat HE in patients of reproductive age is combined oral contraceptives (COC) which are prescribed during 6–12 menstrual cycles according to a standard scheme (21 – days dose with 7 – days break). The therapeutic effect of COC is in their ability to stimulate regression and advanced transformation of endometrial glands, deciduo – like transformation of stroma to suppress the development of spiral arteriole.

The overview of publications and own investigations have shown that HE is a polyethiological disease in which development a significant role is played not only by dyshormonal disorders but also by an infectious and traumatic factor.

In this connection in the literature the issues concerning the treatment of chronicalendometritis are being widely discussed [44].

The first stage of a complex therapy of chronicalendometritis is directed at elimination of the inflammatory process pathogenic organism and reduction of the virus infection activity. With this purpose it is traditional to use antibacterial and antivirus preparations in connection with immunostimulators.

N. Sheshukova, I. Makarov, M. Fomin [12] includes "Aktovegin" into the second stage of the treatment. The authors have prescribed "Aktovegin" 5 ml intramuscularly during 7–10 days with a further change to a peroral form 1 tablet 3 times a day during 14–25 days.

We have used "Aktovegin" in the complex therapy according to the following methodies: 2 ml intramuscularly every other day, the cours is 22 injections.

"Aktovegin" is an antihypoxant which normalizes metabolic processes in endometrium on the account of processes normalization in tissue regeneration including restorement of a series of indices of endometrial receptiveness.

The performed complex therapy (gestagenes + "Aktovegin", vitamin of B group) stimulates valuable cyclic endometrial transformation which is the basic for prophylaxis of the disease's recurrences especially in treatment of simple endometrial hyperplasia. We have consulted 77 patients disturbed menstrual function suffering from HE who were prescribed vegetable non-hormonal preparation "Tazalok" which is corresponding to modern approaches to the therapy of proliferative diseases of mammal glands, uterus and ovaries. "TAZALOK" (PROPHARMA) was received by the woman in a non – stop regine during 180 days on the following scheme: 50 drops in 100 ml of boiled water of a room temperature 30 min. before meals 3 times a day. Side – effects were not observed by us in the studies woman.

13 patients with a polypus – like form of endometrial hyperplasia alongside with the preparation "Tazalok" the preparation "Dufaston" (dydrogesterone) was prescribed to be taken 10 mg once a day from the 16th to the 25th day of the menstrual cycle during 6 months according to a commouly – used (traditional) scheme. The analysis of the performed therapy effectiveness has shown that by the end of the 3rd week a positive dynamic of the treatment was abserved in 8 (44,4%) out of 18 woman, the pain syndrome weakened in 7 (36,8%) out of 19, in those suffering from oligomenorrhea menstruations became with milder blood of 50–60 ml during 3–4 days and, finally, in 5 (62,5%) out of 8 woman who had hyperpolimenorrheamenstruations became less plentiful the duration of which was equal to 5 days [65].

High effectiveness of the preparation "Tazalok" is in normalization of relationships in the system hypothalamus – hypophysis-ovaries – adrenals – organs – targets (endometrium) in 76,6% cases, as well as morphological recovery: normalization of menstrual function in 65 (84,4%) woman and effective reduction of estrogenes' level in blood plasma.

In case of absence of clinical or/and morphological effect of a conservative hormonal treatment during 3 months a surgical intervention is foressen. These are small invasive transcervical operations – thermal ablation and resection of endometrium. It is more proferrable to use lazer ablation of endometrium as a less traumatic and safer operation.

The final method of HE treatment in case all the above – mentioned methods of therapy are not efficient is nowadays hysterectomia. In practice this method of treatment is used in woman of perimenopausal age especially in association of HE with myoma, adenomiosis on the background of dysfunctional uterine bleeding. Other kinds of therapy are possibly only in strictly – selected groups of patients and are acceptable in young woman who want to preserve their reproductive function. Presence of persistent hyperplasia centers is regarded as a prognostic factor of endometrial cancer development and, consequently, active tactics – hysterectomia – is also necessary.

Thus, from the results of literature sources overview and performed own investigations it is clear that the choice of optimal method of HE treatment is determined by the age of a patient, degree of the pathological process' expression presence of associated gynaecological and extragenital pathology.

Этиопатогенетические, диагностические аспекты и лечение гиперпластических процессов эндометрия

П.Н. Веропотвелян,Т.Т.Нарытник, Н.П. Веропотвелян, И.В. Гужевская, Л.А. Жабицкая

В обзорной статье обобщены современные результаты обзора литературы, которые касаются различных аспектов проблемы гиперпластических процессов эндометрия. Отмечено, что при изучении ГЕ необходимо не только уточнять клинические аспекты, но и знать системный патогенетический подход к этой проблеме, что необходимо для выработки дифференцированного подхода к лечению в каждом конкретном случае при данной патологии.

Ключевые слова: *гиперплазия эндометрия, этиология, патогенез, лечение.*

Етіопатогенетичні, діагностичні аспекти і лікування гіперпластичних процесів ендометрія

П.М. Веропотвелян, Т.Т. Наритнік, М.П. Веропотвелян, І.В. Гужевська, А.А. Жабіцька

В оглядовій статті узагальнені сучасні результати літератури, що стосуються різних аспектів проблеми гіперпластичних процесів ендометрію. Вказано, що при вивченні ГЕ необхідно не тільки уточнювати клінічні аспекти, але й знайти системний патогенетичний підхід до цієї проблеми, що необхідно для вироблення диференційованого підходу до лікування в кожному конкретному випадку даної патології.

Ключові слова: *гіперплазія ендометрію, етіологія, патогенез, лікування.*

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