

A clinical view of a practical doctor on disputable issues concerning pathogenesis and treatment of uterine myoma

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In the article results of scientific studies of uterine myoma's pathogenesis, classification – role of genetic factors, steroid hormones and their receptors are summarized. Causes of development of endometrial hyperplasia, apoptosis and development of an associated pathology of endo – and myometrium are represented.

A comparative analysis of various treatment methods, including uterine artery embolization aimed at choosing modern adequate volume of therapy especially in patients of reproductive age is performed.

Key words: *uterine myome, pathogenesis, treatment.*

A lot of works – investigations are devoted to the study of aetiology and pathogenesis of uterine myoma. Frequency rate of uterine myoma especially after 35 years reaches 35–50%. Uterine myoma (leiomyoma, fibroid and others) is a non-cancerous well-bordered incapsuled growth the source of which is smooth muscular cells of uterine neck. According to the performed investigations, Kohanevich E.V. and co-authors (1998, 1999) also consider uterine myoma to be a non-malignant hormonally-controlled hyperplasia of muscular elements of mesenchymal origin. During many years there has been a theory according to which the main causes of uterine myoma are hyperestrogenia, local insufficiency of luteal phase of menstrual cycle and, consequently, progesterone insufficiency, chronic unovulation and increased production of gonadotrophic hormones. Meanwhile, alongside with this theory there were published the results that in 70–77% patients with uterine myoma estrogens and progesterone content during a menstrual cycle is within reference values. A significant number of investigations on the pathogenesis of tumor growth are devoted to this problem which shows that not only estrogens but also progesterone, progestins and activators of progesterone receptors stimulate proliferation of myoma. The confirmation of it is testified by experimental studies of a number of authors who have shown that myoma growth is mainly conditioned by increase of progesterone stimulation. In spite of some contradiction in the works dedicated to the study of hormonal genesis of uterine myoma their common conclusion is about change in the content and ratio between hormones on various levels of endocrine system. Most authors claim that disturbances of hormonal balance in steroid hormones is a cause of expressed hemostesiological shifts in patients with uterine myoma [1–3].

According to the opinion of a number of authors uterine myoma possesses many features of a true growth [4, 5]. Sidorova I. and co-authors [6] report that alike any tumor a myoma is developed from one cell or a clone of cells of muscular tissue; marked by autonomous growth, caused by impact of growth factors; has vessels which are different from normal ones by their structure as they lack muscular membrane with a low-resistant character of blood flow; is characterized by presence of biochemical changes characteristic for tumors, particularly, high speed of aerobic and anaerobic glycolysis. Besides, uterine myoma in the growth process may reach huge sizes which is impossible for furnace hyperplasia.

We can distinguish three stages of fibroids' existence [86]:

- stage of development (maturation) of the node;
- stage of growth; – stage of regression.

The features of the process were managed to be clarified and, thus, allocate 4 phases: [86]

1. The first phase is characterized by the formation of classical growth zone around small vessel in the place of its degermatization; as a rule, in denatured section of the myometrium.

2. The second phase is manifested by transformation of the growth zone in nodosal proliferate, which begins the process of differentiation of proliferative myogenic elements.

3. The third phase of site fibroids maturation is characterized by the formation of chaotically located bundles of smooth muscle cells, making a new layer of heterogeneous myometrium.

4. The fourth phase is characterized by the appearance of tying tissue of a cardiovascular capsule on the surface of this layer, which begins the process of proliferation of myogenic elements of vascular origin.

Tihomirov A. [7] claims that in favor of the opinion that a myoma is a monoclonal hormonosensitive proliferate which consists of phenotypically changed smooth-muscular cells of myometrium of low mitotic myoma activity, a characteristic structure of a myomatous node with a chaotic location of smooth-muscular knots and different content of fibrosis tissue and in a series of cases with presence of hyalinoses as well as absence of a capsule. Again, this definition of uterine myoma remains to be a disputable issue of pathogenesis which is likely to be connected with insufficient study of this pathology's aetiology and pathogenesis.

Risk factors of uterine myoma development include: menstrual function disturbance, late beginning of the first menstruation, dysfunctional uterine bleedings, inflammatory processes of internal genitals, endocrinal sterility, celibacy (continence), genital infantilism. In the literature there is a report that excessive weight in association with low physical activity and high stress frequency refers to the factors which provoke development of this disease. It is also known that a myoma can rather often be associated with illnesses of cardio-vascular system, obesity, disturbances of the stomach – bowels – liver complex.

Uterine myoma is often observed in patients with pathology of mammal and thyroid glands. In women with uterine myoma children infectious diseases are often present in the anamnesis. In many of them there is presence of secondary immuno-deficient state.

While evaluating risk of uterine myoma development it is noticed a genetic predisposition (autosomic-recessive type of inheritance is supposed) to this disease's development, as in a series of scientific works presence of uterine myoma in proband relatives is shown [69]. In a cytogenetic investigation an abnormal karyotype is revealed in myoma cells 3 times more often.

Mutations of genes HMCI (C) и HMCI (V) are revealed, which in norm code proteins regulating DNA transcription [8]. A number of researchers [9, 10, 11] report a significant progress which is obtained in molecular genetics and molecular biochemistry which allows to put a question concerning identification of genetic factors and primary

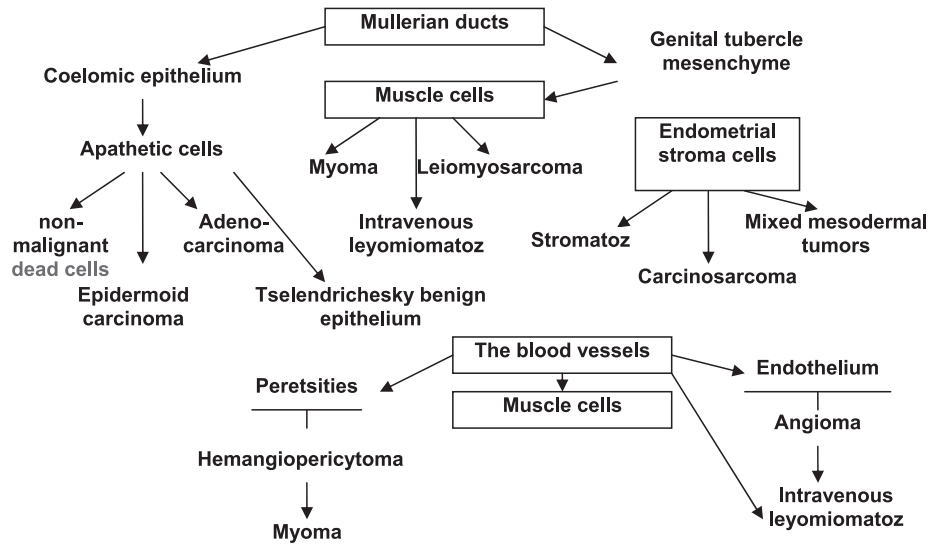


Figure 1. The scheme of embryonic origin of mesenchymal uterine tumors [85]

molecular defects which lead to development and evolution of myomatous changes in uterus. Results of multicentered studies of twins as well as analysis of diseases in patients with multiple hereditary uterine – skin leiomyomas confirm the role of genetic factors in these growths' pathogenesis, especially disorders in functioning of the genetic apparatus of somatic cells in smooth musculature.

Gene HMGIC is evolutionary – conservative and codes polypeptide which refers to the family of DNA – connecting histogenic proteins [12]. After mapping the gene of estrogenic receptor-beta (ESR_2) on the chromosome 14q23-24 this gene has become an interesting potential partner of HMGIC in a typical for uterine myoma cytogenetic translocation (12; 14) [13, 14].

An important value of estrogens for biology of uterine leiomyoma is confirmed by a series of well-known factors: myoma is seldom observed in a prepubertative age; its size can expressively increase during pregnancy; with a menopause advancement uterine myoma often regresses in its development. The performed analysis of differences in the structure and regression of the gene ESR_2 among growths with translocation (12; 14) and without it has shown absence of significant deviations in the level of ESR_2 -mPHK in carriers of the translocation (12; 14), and also absence of breaks of the gene ESR_2 in the process of t transformation (12; 14) [15].

In the analysis of the chromosomal area 7q22, which is often involved into transformations in cases of uterine myoma a gene-suppressor of tumor growth CUTLI is revealed: for this very gene in 15% samples of uterine myoma tissues loss of heterozygosity was revealed and in more than half of the samples reduction of its expression took place [16]. Consequently, the reduced fragments of the investigation convincingly testify the role of the genetic component in the aetiology of uterine myoma [17, 25].

A cytogenetic study of multiple myomas which were developing in a single uterus allowed to reveal different chromosomal aberrations in different nodes (they gave a molecular «profile» of every node), which gives the basis to suppose autonomous development of separate growths. Hashimoto K. et al. (1995) [18] assumes that an independent clonal character of a multiple uterine myoma development is proved by the results of a series of experimental investigations performed using various methodical approaches.

Lanchinskyi V.I., Ischenko L.V. (2003) [19], Morozova E.B. and co-authors (2005) [20] in their publications report that the discovery of chromosomal changes heterogeneity in case of multiple myomas quite corresponds to a well-known «multi-staged» hypothesis of growths' development according to which the function of a series of genes in multiple locuses leads to a tumor growth. Genetic

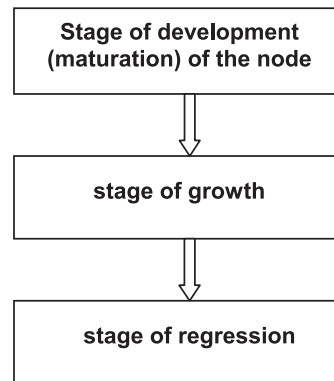


Figure 2. Stages of myoma's existence

(chromosomal) heterogeneity of tumors explains the clinical-pathological differences which are observed in cases of myomas including variations of myomatous nodes' sizes and differences in the reaction on hormonal therapy.

According to the results of Radzinskyi V. and co-authors [21], carriage of the allele PL-AII of the gene GP IIIa excludes the probability of uterine myoma development. However, Redecha M. [22] together with the above-mentioned researchers also claim that the origin of uterine myoma may be associated with mutations of specific causal genes which initiate the development of myomatous nodes. But in spite of the above – stated confirming genetic factors the main role in myoms's pathogenesis is traditionally given to sex hormones. That's why one of the central places in the problem of uterine myoma's pathogenesis is taken by the issue about peculiarities of hormonal status and functional state of reproductive system with the advancement of the disease.

Savitskiy G., Savitskiy A. [5] have determined that in case of uterine myoma there is local hyperestrogenemia which supports the growth of a myomatous node, its progression and hypertrophy of myometrium. Dobrohotova J., Ibragimova D. [17] assume that one of the causes of local hyperhormonemia may be multiple increase in aromatase activity in leiomyoma, as it is exactly aromatase which determines the process of conversion limit in the speed of androstenedione and testosterone into estrone. Also, in myoma it is revealed increase in activity of steroidsulfatase which promotes the transformation of estrone into estronesulfate. Because of the fact that in myomatium and myomatous nodes active estrogens synthesize

from androgens and sulfatized estrogens, increase in the quantity of synthesized in situ estrogens promotes further increased formation of their metabolism's products – catecholestrogeneothenones. There is an opinion of some authors that the result of the reaction of these metabolites with DNA may be initiation of hormone-dependent tumor growth when the DNA damages which happen in the result of the case affect oncogenes or genes-suppressors [4].

Following the results of a series of investigations V. Zhao and co-authors assume that in myomatous nodes the content of estrogenic receptors (ER) β and ν is increased which are transcriptional activators stimulating expression of estrogene-dependent genes among which are growth factors and their receptors, collagen of I и III types, progesterone receptor (PR) and many other proteins [4, 24]. Nevertheless, profound study of receptor apparatus in myomatous nodes allows to make a conclusion that myoma's growth is significantly caused by increased progesterone stimulation: increased expression of PR of effectorial type (type B) is revealed in myoma which has more in common with progesterone.

Malartic C. and co-authors in their investigations in which with the purpose to treat uterine myoma they used an anti-progesterone preparation «Мифепристон» also testify the leading role of progesterone and its receptors in the pathogenesis of this disease [7, 26]. But at the same time it still remains unclear why a positive effect is observed in case of a cyclic or continuous usage of gestagenous preparations in women with uterine myoma [17].

Augusciak-Duma A., Sieron A. [27] claim that mediators of sex steroids are cytokines and growth factors acting like humoral regulators in peak- and nanomolar concentrations which in normal and pathological conditions modulate functional activity of cells and tissues, directly influence the interrelations between the cells and also regulate the processes which take place in extracellular matrix. It is certain that stimulation of growth in cells of uterine myoma is performed with the assistance of various growth factors among which the most important role is played by insulin-like growth factor of the first type (IGF-1), epidermal (EGF) and transforming (TGF- ν) growth factors, and besides, vessel endothelium growth factor (VEGF).

Studies of Burroughs K. and co-authors [28] have shown that the local expression level of IGF-1 in myoma's cells is 7, 5 times more than in normal tissue of myometrium, meanwhile for all investigated tissue samples reverse correlation between the quantity of μ PHK IGF-1 and μ PHK of its receptor is revealed. The same results are obtained by Yu L. and co-authors [29]. However, Martin E. Chaves and co-authors [30] have not revealed statistically significant differences in the levels of the expression of the receptor IGF-1 in the nodes of leiomyoma and non-changed endometrium.

Kogan E. And co-authors [31] assume that one of the most important chains in the mechanism of myomatous nodes' growth is EGF expression which induces myotocyl activity of cells. According to the results of other works [29] μ PHK EGF expression is significantly increased in myoma in comparison with normal myometrium, meanwhile its highest level is revealed in luteal phase of the menstrual cycle which proves inducing influence of progesterone.

Augusciak-Duma A. and co-authors have also gained analogical results concerning TGF- ν expression (key regulator of growth and differentiation of smooth-muscular cells) in myomatous nodes [27]. And it is pointed out by Ibragimova D. and Dobrohotova J. According to the results of their investigations the level of TGF- ν 1 expression (homologous protein TGF) in myoma is 5–8 times increased in comparison with its level in non-changed myometrium. Alongside with the stimulation of proliferation proteins of TGF family take an active part in activation of neoangiogenesis and fibroid changes characteristic for myomas [17].

Poncelet C. and co-authors inform that an important component of proliferative processes is neoangiogenesis the realization of which is performed with an active participation of VEGF and its

receptors. High level of VEGF expression is revealed in myomatous nodes [32]. Zayratyants O. and co-authors [33] reckon that the process of neoangiogenesis in myomas is inseparably linked to morphogenesis of these tumors and to a great degree determines the peculiarities of the origin, growth character and clinical-morphological variants of a tumor (simple or proliferative uterine myoma). If there is absence of increased accumulation of VEGF in the tissue of simple myoma, it points at an extremely low level of angiogenesis in the tissue, whereas in proliferative myoma increased content of VEGF testifies the intensification of the angiogenesis process.

A leading role in supporting tissue homeostasis belongs to balanced interaction between proliferation processes and apoptosis [17]. According to the opinion of Kayisli U. [34], growth of myomatous nodes occurs as a result of proliferation with sex steroids via growth factors following the autocrinal-paracrinal mechanism with relatively low readiness of myoma cells to apoptosis. Keeping to the results of the investigations [6], nuclear marker expression of Ki-67 proliferation in tissue of simple myoma was 3 times and in the proliferative one – 70 times higher than in normal myometrium which pointed out high proliferative potential of growing myomatous nodes in spite of the revealed low myotocyl activity of tumor myocytes. Meanwhile, levels of apoptosis bcl-2 inhibitor expression twice exceeded the levels in unchanged myometrium.

Thus, despite the morphological likeness of myoma cells and intact myometrium there are big differences in molecular – biological characteristics and metabolism of the given tissues, particularly: in expression of sex steroids and their receptors, cytokines, factors of proliferation and apoptosis [35].

In the literature 2 types of leiomyoma are being discussed: genuine caused by proliferation of smooth muscular cells and false associated with increased fibrilliforming function of smooth muscular cells and degenerative changes in tumor node [36]. In a series of works [37, 38] an opinion is tracked that increase of uterus' size in case of leiomyoma in women of reproductive age in 2/3 of cases occurs at the expense of the so-called false growth and imitates fast tumor growth.

The authors claim that increase in the sizes of uterus in suchlike situations is associated with the tumor growth of an active inflammatory process. It is not seldom that revealing active forms of opportunistic infections in this very contingent of patients as well as changes of cellular and humoral immunities gave reasons to suppose participation of an infection in the development of alike secondary changes in a tumor. The role of an infectious factor in morphogenesis of uterine leiomyoma nodes is also noted by Tihomirov L.A. (2006) [39] who considers tumor's nodes to be reactive proliferatives around the centers of stimuli's persistence.

The immune system is a mechanism which controls the processes of regeneration, differentiation and tissue growth (particularly, myometrium). It is agreed to claim that the most important index of a hormonal function of an immune system is the ratio $CД4/CД8$ (the so-called immuno-regulative index), which normally is equal to $2\pm 0,2$. Reduction of this index in patients with uterine myoma in young age testifies misbalance of two most important subpopulations of T- lymphocytes: T-helpers and T-suppressors. After an operation in women with uterine myoma in young age gradual normalization of the percentage of $CД4$ lymphocytes' content takes place. Besides, study of the T- и B-lymphocytic systems state in patients with uterine myoma has shown that the biggest changes of indices are noticed in women with an associated pathology which develops on the background of unovular menstrual cycle and relative hyperestrogenia. Particularly, reduction of absolute quantity of common T-lymphocytes and their activated fractions is marked as well as T-helpers, whereas the quantity of T-suppressors remained unchanged, thus, disturbance of the immune balance towards the increase of T-suppressors' content was observed which testified oppression of cellular immunity in the investigated patients and weakening of control over the process of cells' proliferation [36].

Adamyany L.V. and co-authors (1997) [40] in their work show that the biggest changes in the system of local and general immunities take place in case of prolonged and burdened advancement of uterine myoma. In the study of peritoneal liquid in patients with uterine myoma a significant disturbance in the system of local immunity was revealed. With the purpose to define potential dependence of disturbances' expression in the immune system of organism on clinical peculiarities of a disease an attempt to reveal a connection between state of local immunity and duration of an illness, volume and localization of a tumor, morphological features of tumor tissue has been made. On the basis of the received data intensification of disorders of general and local immunity is revealed depending on the duration of the illness of more than 7 years, and of local immunity – already in the first 2–3 years of the illness. The most significant changes of local immunity were observed in women with subserous location of myomatous nodes and also presence of a big number of nodes – more than 5. Buyanova S.N. and co-authors (2008) [36] have made a conclusion that changes of immune status seem to be secondary and can be considered as mobilization of defensive forces of the organism aimed at the fight with the illness. That is why the mostly expressed changes of local immunity are a local defensive reaction. Changes of general immunity reveal themselves only in case of a prolonged advancement of the disease or in case of an extensive tissue lesion.

The results of Kovalenko T. and O. Sarkisyan's investigation are of some interest [41] – concerning peculiarities of antioxidant fermentative status of erythrocytes in various clinical forms of uterine myoma. According to the authors' opinion in patients with myoma there are expressed differences in the activity of the ferments of antioxidant organism defense the consequence of which is in the disturbance of the process of active oxygen forms neutralization which leads to formation of a genetically modified clone of smooth muscular cells and is considered to be one of the aspects of uterine myoma pathogenesis.

Investigations of Unanyan A. [42] concerning premorbidal background in women with different combinations of hyperplastic diseases of reproductive organs show that a combined pathology of endo- and myometrium represents a single pathological state of reproductive system which is revealed in hyperplastic changes of hormonal-dependent organs. More often non-malignant processes in endometrium are more often diagnosed in patients who suffer from uterine myoma.

Ibragimova D., Dobrohotova J. claim that high revelation frequency of hyperplastic processes in endometrium in patients with uterine myoma supposes alikeness of pathogenetical chains in formation of combined pathology and myometrium. In this connection some investigations have been performed, the results of which confirm commonness of main ways of proliferative uterine diseases' pathogenesis.

The investigations performed by the authors H. Dai, O. Erdem and some others [43, 44] demonstrate that in endometrial hyperplasia pathogenesis an important role is also played by disturbances of the expression of such growth factors as IGF-1, EGF, TGF, VEGF and their receptors. In the literature [45] there are investigations which show that degree of growth factors production and accumulation in endometrium with the presence of leiomyoma depends on the proliferative activity of the hyperplastic process. Significant increase in VEGF production and accumulation in case of active ferrous and ferrous-cystic endometrial hyperplasia in patients with clinical-morphological variant of proliferative uterine myoma characterizes high activeness of angiogenesis. Alternatively to it in case of superincumbent and weak active form of hyperplasia reduction of angiogenesis level in the presence of sclerotic changes in walls of vessels is revealed as well as high levels of TGF- β and fibronectine expression. Increase in the level of VEGF expression and accumulation in hyperplastic endometrium in women with uterine myoma are also revealed in other studies [46].

S. Bircan and co-authors [47], N. Kapucuoglu [48] report that alongside with growth factors a key role in uterine hyperplastic diseases pathogenesis belongs to the factors of proliferative activity which are necessary for replication of genome DNA among which the mostly studied ones are PCNA, c-myc, c-jun and also antigen Ki-67 which is considered to be an ideal marker of proliferative activity as it is revealed only during a mitotic cycle of the cell.

A series of authors [45, 49, 50] inform about the presence of high proliferative activity of hyperplasia but at the same time other scientists report about the reduction of proliferative activity in hyperplastic endometrium. Litvinova N. [46] reports that in the study of molecular-biological aspects of endometrial hyperplasia pathogenesis in women with uterine myoma it is revealed that the level of proliferation in endometrial cells Ki-67 in case of typical hyperplasia is reliably lower than in endometrium with normal proliferation [10].

According to the results of some authors' studies [46, 49] disturbance of tissue homeostasis in case of hyperplasia is a consequence of both changes of proliferative activity and reduction of apoptosis level in endometrial cells which leads to formation of hyperplastic changes in uterine mucous membrane.

In the literature some studies are represented in which it is claimed that besides growth factors and cytokines not a less contribution into the stimulation of proliferative potential in cells is made by disbalance in ferment cellular systems, change of telomerase activity, and also disturbance of metabolism of steroid hormones and their receptors' expression. The results of the published studies testify preferred content of estrogenic receptors of β type in uterus; most of the modern studies of ER in endometrium in case of hyperplasia are devoted to the study of this very type of receptors.

In the literature there are contradictive data of different studies of K. Hu and co-authors [51] which point out that ER β expression in hyperplastic endometrium is increased, meanwhile, according to the results of O. Nunobiki and co-authors' [50] and S. Bircan and co-authors' studies [47] – reduced. It is necessary to mention that in an immuno-histological study of ER β index in endometrium in case of hyperplasia without atypia statistically reliable differences in comparison with this index in normal proliferative endometrium are not revealed [51].

The performed studies of the ratio of PR isoforms' expression in pathologically changed endometrium show that in cases of hyperplasia and cancer an expression of one or another isoform prevails whereas cells of normal endometrium in 75% cases express equivalent quantity of PR-A и PR-B. At that expression of homodimer PR-B is revealed solely in tumor cells. However, as it is noted by R. Arnett-Mansfield [52], there are no statistically reliable differences between expression levels of PR-A and PR-B revealed in normal and hyperplastic endometrium, whereas in tumor cells of mucous uterine membrane the level of the both PR isoforms expression is reliably reduced.

Thus, nowadays the most interest in scientists is caused by molecular – biological aspects of endometrial hyperplasia pathogenesis because with the advance of new technologies exactly these aspects may become background to create pharmaceutical preparations able to make target influence on pathologically changed cells [17].

Pathogenesis of sterility in case of uterine myoma is considered to be associated with increase and deformation of uterine cavity, disturbance of myometrium retractive activity, increase in uterine tubes' tone, their anatomic impassability caused by intestinal and submucous nodes' growth, and also by rise of an non-ovulating follicle's phenomenon and development of luteal insufficiency with external remained parameters of an ovulatory menstrual cycle [5].

Taking into account all of the above-mentioned data and considering uterine myoma to be a hormonally-dependent growth it is perspective to treat uterine myoma with the preparations which block the gonadotrophic function of hypophysis. To this very group of preparations gonadotrophin – releasing hormone (HnRh) belongs

which is a peptide consisting of 10 amino acids. Two of them (in position 2 and 3) are responsible for biological activity and the other three (in positions 1, 6 and 10) – for tying hypophysis cells' receptors. Amino acids in position 6, 7 and 9, 10 split into aminopeptides [60].

Change of the molecular HnRh in position 6 и 10 allowed to create its agonists HnRh. The first agonist HnRh (6-HnRh) – leprolide-acetate was synthesized in 1974 [58]. Synthetical analogs of HnRh have increased likeness with its receptors, expressed resistance to the ruining effect of ferments, and also lowered metabolism which leads to the increase of their half – decay period. Constant prolonged usage of 6-HnRh at first leads to tying the most part of hypophysis cells' receptors and transitorial increase of LH, FCH and estradiol levels in blood serum, and further, during the process of inserting 6-HnRh, to disappearance of the receptors from the surface of the hypophysis' cells.

More than 2000 6-HnRh analogs have been synthesized so far which possess higher biological activity in comparison with an androgenic combination. One of them is the preparation Triptoreline (Dyffereline), Hozerelina – acetate, Naphareline and Buserelina.

Dyffereline (Triptoreline or Д-Трп6-LHRH) is an analogue of natural HnRh obtained by replacing glycine in position 6 into D – amino acid (D – triptophan). This replacement increases the period of half – eduction of the preparation up to 7,5 hours (the period of half – eduction of natural HnRh is 10 min.). Dyffereline is injected intramuscularly in the dose of 3,75 mg, Hozerelina – acetate – h/d, 3,6 mg. Both preparations are injected on the second – fourth day of the menstrual cycle, 1 injection – every 28 days during 4–6 months.

Naphareline and Buserelina are used as endonasal sprays in the dose of 900 mkg a day. The day dose of the drug is inserted with equal doses (a single dose of the preparation is 150 mkg) of a single injection to every nasal track 3 times a day with the interval of 6–8 hours on the first or second day of the menstrual cycle.

The mechanism of 6-HnRh effect which results in reducing the sizes of uterus and leiomyoma nodes has not been thoroughly studied so far. For the first time successful treatment of patients with uterine myoma with the help of 6-HnRh was reported by Filicori M. et al (1983) [54]. Friedman A.J. et al (1992) [55] claim that the most vivid effect of using 6-HnRh in patients with uterine myoma is noticed 3–4 months after the treatment with its further reduction 6 months later. Studies of Gesenhoe T. et al (1992) are of some interest, according to them it is possible to have an idea of possible effect of using 6-HnRh just after its first injection evaluating dynamics of reducing uterine size via ultrasound [56].

Attention should be paid to the report of Harding S. et al (1993) [57] about a patient aged 19 suffering from uterine leiomyoma. After the second injection of Hozerelina - acetate she experienced some pains in the abdomen. With the help of a computer tomography there were revealed ascites in significant quantity. With a diagnostic purpose laparoscopy with the removal of 5 litres of ascitic liquid and biopsy of the leiomyoma's node were performed. In the pathomorphological study there were revealed degenerative changes of the leiomyoma's node with absence of its malignization features. The patient was performed a myomectomy.

The above – given observation shows that usage of 6-HnRh does not lead to malignization of uterine leiomyoma, though it can be supposed clinically. Unfavourable influence of 6-HnRh is possible with the beginnings of the following symptoms in patients: surges, disposition to sweat, dryness in vagina, depression, nervousness, reduction of libido, appearance of peripheral edemas. Saveleva G.M. and co-authors (2000) [59] assume that one of the serious negative effects of 6-HnRh using is reduction of bone tissue thickness which is defined with the help of densitometry.

According to the data in the literature cessation of hormonal therapy leads to restoration of menstrual cycle 2–3 months after the preparation's abolition and fast recurring growth of uterus and leiomyoma up to the primary sizes [60].

Nowadays a modern antigestagene Gynestryl is widely used. This preparation Miphepristone (Gynestryl) is prescribed in cases of uterine myoma sized up to 11 weeks inclusive – 50 mg in 1 tablet once a day. The treatment course is 3 months.

We have performed treatment of 27 women with uterine myoma of rather small sizes using the method of lazeroreflexotherapy (LRT). The age of the patients varied from 27 to 42 years [61]. The essence of LRT is in the impact on biologically active skin points (BAP) in neuro – receptive zones. In case of the mentioned way of impact on the active points and hypodermic structure there appears a stream of impulses to the corresponding parts of the central nervous system (brain tube, reticular formation, subcortical centers, cerebral cortex) stimulating the development of a common reaction [61–63].

All the patients were performed traditional clinical hormonal investigations and ultrasound which was performed (transabdominally and transvaginally) periodically in the first and second phases of the menstrual cycle for comparison before and after LRT and half a year after its completion. Colour Doppler mapping was performed in the area of uterine vascular knots from the both sides and the state of myometrium was also studied. The sizes of the myomatous nodes were from 1, 5 to 5–6 cm; in 7 women – multiple nodes were located intramurally – subserously.

LRT was done according to the following methodics: during one session (which lasted 21–30 min) the impact was on not more than 6–8 BAPs including the so-called points of the common effect. The treatment course for a single patient consisted of 22 sessions which were performed daily 4 times a week starting from the seventh day of the menstrual cycle and ceasing 3 days prior to the following menstruation.

As a result of the treatment in 23 patients a normal menstrual cycle was settled. The treatment with LRT method in 85,2% cases provided normalization of FCH, LH, estradiol, progesterone excretion. It is necessary to note that in 7 out of 11 women in whom hyperexcretion had been observed content of 17-OKS and 17-KS with fractions in daily urine normalized. Confirmation of LRT effectiveness in 6–8 BAPs were in ultrasound results – in 5 patients myomatous nodes were not revealed, decrease of nodes' sizes was noted in 12 patients, stabilization of nodes' sizes – in 6 women. With the further follow – up during 6 months growth of the nodes in these patients was not observed.

Thus, target and qualified treatment with LRT in BAP ensures regulation of hypotalamo – hypophysal – ovarian system and is likely to make inhibitory impact on secretion of gonadotrophic – releasing hormones and gonadotropines which leads to suppression of proliferative uterine processes.

To perform surgical rehabilitation it is necessary to define indications in favour of an operative method of treatment which may be conservative (myomectomy) as well as radical (hysterectomy, extirpation of uterus).

According to the recommendations of American Association of Obstetricians – Gynaecologists indications in favour of conservative myomectomy are in patients who suffer from sterility or habitual miscarriage. Most authors consider myomectomy to be a more merciful operation as it provides preservation of uterus. Lately surgical treatment of patients with uterine myoma has more often been performed using laparoscopic access. Myomectomy performed by laparoscopic method reduces risk of adhesion process development in small pelvis.

Kulakova V.I. and co-authors (2002) claim that treating patients with uterine myoma it is necessary to use 6-HnRh of Dyffereline for prior operational preparation which enables to significantly optimize laparoscopic myomectomy in patients with disturbances of reproductive function and achieve advancement of pregnancy in almost each case. Meanwhile, it is necessary to mention that adequate therapy especially justifies itself in case of enucleation of interstitial myomatous nodes up to 10 cm, especially in case of their localization nearby vascular knots tube corners of uterus.

As it is known uterine myoma may be a cause of sterility, abortive pregnancy, development of feto – placental insufficiency, complications in delivery and post – delivery period that is why it is necessary to solve an issue concerning the choice of surgical rehabilitation method before the advancement of pregnancy. Conservative myomectomy belongs to the group of conservatively – plastic operations which preserve both menstrual and reproductive function.

Based on data in the literature it is worth mentioning that timely support of women with uterine myoma (who have myomatous nodes up to 10 cm) firstly provides for endoscopic myomectomy not only as a means of reproductive function rehabilitation but also as a way to reduce dramatically risk of reproductive losses and various complications during pregnancy and delivery. Reduction of operative risk is significantly encouraged by adjuvant pre – operative therapy [64]. Thus, implementation of high technologies and development of endoscopy during the recent 10–12 years have contributed new methods to the treatment of submucous uterine myoma. In practice of doctors – gynaecologists instrumental organ – preserving methods have started being used: transcervical myomectomy (by a mechanical method and with the help of hysteroscroscope), laser hysteroscopic myolysis.

It is noted that in 87,3–98,7% observations these manipulations give a good result and lead to complete recovery [50, 65]. It is necessary to point out main advantages of laparoscopic method – absence of cutting front abdomen wall, less volume of blood losses and a shorter period of recovery [19, 39]. It is clear that all these merits are undisputable. But at the same time a «boom» of operative endoscopy has led to the situation when with the help of this method there was a removal of those myomatous nodes which in the «classical» idea were not indicated to a surgical method of treatment. It could not have avoided severe consequences [50, 65]. The latter ones were uterine breaks during pregnancy as a result of inadequate «laparoscopic» hem [65]. According to the works of a series of authors [19, 39] laparoscopy does not allow to put on uterus the stitches which are able to ensure formation of an adequate hem. Putting stitches on the node stock in case of laparoscopic access is a rather complicated manipulation. Laparotomic access is not such a negative method which disturbs reproductive function as it is considered to be. According to the opinion of Tihomirov A. L. and co-authors (2006) [39] it happens rather often that expression of adhesive process is minimal after laparotomy. And in principle we claim that to perform myomectomy not depending on the access (laparotomy or laparoscopy), development of adhesive process and its expression depends on the so-called adhesive readiness of organism and, undoubtedly, qualification of a surgeon and his/her «hands».

According to the studied literature after conservative myomectomy a possibility to restore natural fertility during a following year is higher in patients with a single tumor node. A comparative analysis of 3 groups of patients with sterility in one of which there was a removal of myomas, in the second – surgical treatment was not performed and in the third group there were patients with sterility of unclear etiology has convincingly shown that after myomectomy advancement of pregnancy occurs more often than after medicinal treatment. The same fact is testified by the studies of the authors Eldar-Cova T. et al (1998) [67] according to which about 2/3 of patients with uterine myoma and other causes of sterility got pregnant after they had been performed myomectomy.

According to the opinion of Khalaf V. et al (2006) [68], Somigliana E. et al (2007) [69] excessive conservatism (wait – and – see tactics) in follow – up uterine myoma in young women leads to danger of the organ's loss in the next 3–10 years after uterine myoma has been revealed with a minimal chance of child – bearing function realization. Consequently, according to the modern conception early surgical treatment is pathogenetically grounded as growth removal prevents progressive development of myogenic hyperplasia and local hyperestrogenia, thus, hindering the progression of the disease.

Nowadays looking through the results of surgical rehabilitation based on the data of report documentation of practical health care institutions it is known that 55–85% of all operative interventions are radical operations – abovevaginal amputation and uterine extirpation. Hysterectomy is considered to be a relatively simpler in its performance radical operation in case of uterine myoma which excludes a chance of the disease's recurrence.

In the works which are dedicated to the study of neurovegetative – endocrine homeostasis state after hysterectomy there are data about reduction of ovarian functional activity, particularly, formation of hypoestrogenic state, after removal of uterus in reproductive age. Later, 6–8 months after hysterectomy improvement of anatomic – functional state of ovaries is observed which is expressed in restoration of blood flow, improvement of echographic indices (volume of ovaries is normalized, sound follicles appear) and data of Dopplerometria [70].

These changes are explained by development of collateral blood flow and restoration of normal ovarian blood flow and followed by restoration of estradiol level in blood, prevalence of ovulatory cycles including those with sound luteal phase. Faster and full restoration of ovarian function is observed after subtotal hysterectomy. Meanwhile, with further follow – up 1,5 years and more later the hysterectomy a series of authors assume progressive worsening of ovarian function, particularly, reduction of their volume in an ultrasound investigation at the expense of reduction of follicles' quantity and sizes – reduction of blood flow in the basin of internal arteria iliaca is especially observed in patients who have experienced total hysterectomy [70].

In distant terms especially after uterine extirpation progressive hypoestrogenia is observed. In patients aged 29–43 3–5 years after hysterectomy reduction of estradiol up to 34,3% is revealed as well as increase in the level of FCH in 25,3% cases [70]. In one – third of the patients of reproductive age 3–5 years after hysterectomy urological disorders are observed including day and night pollakiuria, enuresis with exertion, recurrent urinary infection [70].

In the studies of a series of authors [14] appearance of cardiovascular symptoms is observed and also metabolic signs of menopausal syndrome in patients after hysterectomy in young age correlating with reduction in estradiol level. Cooper K.G. et al (2003) [54] claims that in the genesis of cardiovascular disorders after hysterectomy a definite role is played by cessation of vasodilatation synthesis by endometrium, particularly, prostacycline (PqI-2) which is an inhibitor of trombocytes' aggregation and stimulates vasodilatation, besides, indirectly participates in increase of anticoagulation blood potential. Thus, a complex study of clinical – laboratory data and subjective indices of life quality is extremely important to evaluate expediency of performing myomectomy in women of reproductive age who already have children and do not plan to have more children in the future. The choice of the operative treatment volume in case of uterine myoma in young women still remains an actual problem.

To eliminate negative consequences of hysterectomy as well as to preserve a menstrual reproductive function in the latest decade there has appeared an alternative to a surgical method in treating women with large uterine myomas especially patients of reproductive age – embolization of uterine arteries (EUA). Since the beginning of the 90s EMA has been performed in patients with uterine myoma. Jacques Ravina used embolization of uterine arteries as a preparatory stage before an operation of uterine removal. All that he found out that in some patients after embolization the symptoms they had been suffering from disappeared and there was no necessity to have the operation itself. Later he suggested using EUA as a separate method [66].

According to the publication of Tatarchuk T.F. and co-authors (2009) [71] in Ukraine EUA in case of uterine myoma has been used since 1997, there have been more than 700 technically successful embolizations performed. High effectiveness of EUA was convinc-

ingly proved on the basis of the material which included combined experience of more than 100000 similar interventions. This minimally invasive endovascular operation in 93–97% leads to a drastic up to 40–60% reduction of myomatous nodes sizes during one year and immediate clinical symptoms elimination of the main disease not demanding removal of uterus itself [72].

According to the reports of the author [72] EUA allows to preserve or restore reproductive function in women with uterine myoma. Kapranov S.A. and co-authors (2003) [73] claim that the performed observation demonstrated an excellent EUA clinical result, as well as complete restoration of uterine structure at the expense of fast reduction of a myomatous node's size within 2 months after the procedure and its further transvaginal expulsion.

Some authors perceived expulsion as an unfavourable after-effect which may lead to infectious complications. However, the analysis of the received results has changed this point of view. According to the report of Worthington-Kirsch R. et al (2000) [74] who studied 4165 patients and found out that in 0,005% cases there is risk of secondary infection in the process of node's degradation or in case of expressed myomatous detritus which may demand hysterectomy. However, the author shows personal assurance that in overwhelming majority of cases timely antibacterial and detoxicative infusional therapy allows to suppress the infectious process.

Mechanism of EUA effect is in the following: necrosis of myomatous nodes appears; meanwhile constant myometrium suffers in the least degree. It is explained by the fact that the arteries which nourish myomatous nodes are terminal and myometrium has collateral blood circulation.

Thus, the main task of a practical doctor is correct selection of women with uterine myomas for EUA taking into account indications and contra – indications as well as a dynamic follow – up after the operation. Compulsory ultrasound investigation with Dopplerometry before the operation and in the post – embolization period allows to give adequate evaluation of topography and blood supply peculiarities in myomatous nodes, evaluate the effectiveness of EUA and define the tactics of the follow – up which is extremely important. Thus, EUA can be performed in patients of young and reproductive age and also in women with a somatic pathology as an alternative variant to hysterectomy and reconstructive – plastic operations [72].

So, N. Price and co-authors (2007) [76] report diagnosing a bladder – uterine fistula 12 months after EUA was performed. In the literature data on formation of uterine – peritoneal fistula are described in the patient after EUA and further laparoscopic myomectomy on the basis of which the authors make a conclusion that an endovascular intervention may be a cause of reparative processes' disorders in myometrium after myomectomy [77]. That is why the mentioned complications are able to introduce serious corrections into future reproductive plans of the patients.

The results of the authors' studies performed by us show that EUA's influence on reproductive women's function is so far the most disputable aspect of the problem which concerns safety of embolization process. In the literature among many scientists in spite of their sufficient experience of following-up pregnancy and delivery in most patients with uterine myomas who have experienced embolization there is no unified opinion regarding recommendations to this very method of treatment for the women who suffer from sterility. Such disagreements are particularly based on data about the influence of EUA on ovarian function as well as the endometrial one [17].

But at the same time as it is reported by M. Redecha and co-authors (2009) [22] that the developed tactics of follow – up for the patients with uterine myoma of this localization allows to avoid most of clinically important complications. Z. Hrgovic and co-authors (2008) [75] refer to common contraindications allergic reactions to injecting X-ray – contrastive substance which are used in case of embolization, to the gynaecological contraindications – inflammatory diseases of small pelvis organs in an aggregative stage, tumors and

tumor-like ovarian growths, suspicion of uterine sarcoma, atypical hyperplasia and endometrial cancer. That is why it is necessary to perform a clinical study before EUA.

Undoubtedly, besides traditional methods of investigation it is necessary to perform echography to reveal quantity, size and localization of myomatous nodes, presence of uterine cavity deformation, endometrial pathology, evaluation of ovarian sizes and structure, and also to define parameters of blood flow in nodes and endometrium. In an ultrasound investigation there is an opportunity to reveal criteria and angiographic features of myomasarcoma, as there is no chance to obtain material for morphological diagnostics of this pathology in case embolization is performed. Besides, effect of embolization operation depends on blood circulation in myomatous nodes, thus, Dopplerometry is a most important method in investigation of women in case EUA is planned.

We have mentioned above some complications which after the procedure of embolization do not exceed more than 5%. In some publications there are also indications on formation of intra-abdominal adhesions after EUA and fistulas.

Some researchers like W. Guo and co-authors report that in patients after EUA amenorrhea occurs which risk of development directly correlates with the age of a woman. According to the studies' results a cause of this complication's origin may be both disorder of ovarian function and atrophic endometrial changes after embolization [79].

In the literature there are represented some studies which report that EUA procedures as well as hysterectomy make an influence on ovarian reserve which is confirmed by increase in FCH level and decrease of antimuller hormone level after intervention [80]. M. Mara and co-authors (2007) [81] report that the results of hysteroscopy performed 3–9 months after EUA testify high frequency of intrauterine pathology development in patients of reproductive age. Normal results are diagnosed only in y 37% women of reproductive age; in the rest 63% cases the following hysteroscopic changes are revealed: deformation of uterine cavity, yellow – like colour of endometrium and intrauterine synechias. The authors also explain that as clinical significance, reversibility and influence on the next pregnancy of the revealed hysteroscopic results are not known, it is necessary to recommend this investigation to all women who plan pregnancy after EUA.

In the studies performed by K. Firouznia and co-authors (2009) [82] as well as by I. Honda and co-authors [83] in which influence of embolization on fertility was evaluated it is reported that advancement of a desirable pregnancy occurs in most women of reproductive age. But at the same time these very authors [82] point out that the procedure of embolization remains to be a relative contraindication for those women who suffer from sterility as there are data about high frequency of the following obstetric complications after embolization as: anomaly of placenta's fastening site, fetal hypotrophy, premature birth, after – delivery bleedings and some others.

Taking into consideration these complications M. Freed, J. Spies [78] claim that if a patient with uterine myoma plans a pregnancy it is more preferable to choose myomectomy as a treatment method. However, the opinion of other authors is contradictive, they assume that embolization is a highly – effective and safe procedure of treating uterine myoma in patients of reproductive age which allows to avoid risk of a laparotomic operation and ensure realization of reproductive function.

A proof of it can be found in the studies of Dobrohotov J. and co-authors (2013) [84] who report that complications during pregnancy, delivery and post – delivery period in patients who have been performed embolization due to uterine myoma do not reliably differ from those in women without uterine myoma. EUA is not considered to be a contraindication for pregnancy and delivery; also it is not a reason to interrupt a pregnancy. According to the authors' opinion using EUA to treat uterine myoma in patients of reproductive age

who plan a pregnancy represents a highly – effective alternative to surgical and medical methods of treatment.

It is reasonable to mention that most researchers support the given arguments in favor of embolization but at the same time they emphasize the importance of a thorough follow – up of the women during pregnancy aimed at timely prophylaxis of possible complications.

Thus, on the basis of the literature data and own investigations considering its high prevalence endometrial hyperplasia in patients with uterine myoma needs further studies of this pathology's pathogenesis and clarification of molecular mechanisms of its formation still remains an actual scientific problem.

Клинический взгляд на дискуссионные вопросы патогенеза миомы матки и ее лечения глазами практического врача

П.Н. Веропотвелян, Н.П. Веропотвелян, Т.Т. Нарытник, И.В. Гужевская

В статье обобщены результаты научных исследований патогенеза миомы матки, классификации, роли генетических факторов, стероидных гормонов и их рецепторов. Представлены причины развития гиперплазии эндометрия, апоптоза и развития сочетанной патологии эндо- и миометрия.

Проведенный сравнительный анализ различных методов лечения, включая эмболизацию маточных артерий, направлен для выбора современного адекватного объема терапии, особенно у пациенток репродуктивного возраста.

Ключевые слова: миома матки, патогенез, лечение.

Many publications testify that in the modern point of view embolization as a highly – technological insufficiently invasive organ – preserving method to treat uterine myoma may become an alternative to operative treatment and give a chance to women of reproductive age who plan a pregnancy. However, the issues concerning the choice of tactics to follow – up post – embolizational period in women of reproductive age with an associated non – malignant endometrial pathology so far remain actual.

Nevertheless, a comparative analysis of various methods to treat uterine myoma is necessary to be performed to choose modern adequate volume of the therapy, especially in patients of reproductive age aimed at restoration of reproductive menstrual function.

Клінічний погляд на дискусійні питання патогенезу міоми матки та її лікування очима практичного лікаря

П.М. Веропотвелян, М.П. Веропотвелян, Т.Т. Нарытник, І.В. Гужевська

У статті узагальнені результати наукових досліджень патогенезу міоми матки, класифікації, ролі генетичних чинників, стероїдних гормонів та їх рецепторів. Представлені причини розвитку гіперплазії ендометрію, апоптозу і розвитку поєданої патології ендо- і міометрію.

Проведений порівняльний аналіз різних методів лікування, включаючи емболізацію маткових артерій, спрямований для вибору сучасного адекватного об'єму терапії, особливо у пацієнток репродуктивного віку.

Ключові слова: міома матки, патогенез, лікування.

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