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Uterine Fibroids. What We Know and What We Need to Know

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Abstract- Uterine fibroids (UFs) are the most common tumours of the female reproductive system and represent a significant health issue worldwide. UFs develop during reproductive span and often shrink after menopause.UFs affect over 70% of women by the onset of menopause. Uterine fibroids arise from myometrial smooth muscle cells. UFs can be solitary or multiply and their size varies from microscopic to giant. Nowadays the exact cause of UFs remains unknown, but it is assumed that genetic abberations along with steroid hormones and growth factors play a pivotal role in thetumour development. In most cases UFs are asymptomaticand therefore it is difficult to estimate their actual prevalence. Symptomatic UFs present with abnormal menstrual bleeding, pelvic and low back pain, bulk symptoms, infertility and have a strong impact on health-related-quality-of-life (HRQL). Early diagnosisand treatment of UFs as well as preventive measures, especially for patients from high-risk groups, should be a priority.

This article presents current data about pathophysiology, diagnosisandmanagement of UFs.

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I. Introduction

Uterine fibroids (UFs), also known as leiomyoma or fibroids, are benign monoclonal tumours originating in smooth muscle cells of the cervix or uterine corpus. UFs are the most common pelvic benign tumour of the female reproductive system, occurring in 20-40% of reproductive-age women, >40% of women over the age of 40 years and >70% of women by age 50 [1,2]. The average age of detection of UFs is 32-34 years, and highest incidence is at the onset of menopause [3]. There is an increasing incidence of UFs in young women under 30 years of age who have not fulfilled their reproductive function.

II. Etiology and Pathogenesis of Uterine Fibroids

As is well known, the myometrium, the middle layer of the uterine wall, is the thickest tissue of the uterus and composed of longitudinal and circular layers. The myometrium is located between serous or peritoneal layer and mucosal layer called endometrium and consists not only smooth muscle fibres but also blood and lymph vessels and nerves.

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As previously stated, UFs have a clonal origin with proliferation of smooth muscle cells and fibroblasts [4]. Uterine fibroids develop from one primary mutant cell of smooth muscular tissue of myometrium, which acquires the ability to grow unregulated. Therefore “fibroid” is not accurate term for describing this tumour, because it does not arise from fibrous tissue, but it contains a large amount of extracellular matrix, including fibrillar component (collagen, elastin) and interfibrillar component (fibronectin, proteoglycans), and is surrounded by a thin pseudo-capsule. In UFs, ECM is composed mainly of collagen types I and III and mRNAs for *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, and *COL7A1*are up-regulated compared with normal myometrium. One of the mechanisms underlying the excessive accumulation of ECM in UFs is the down-regulation of miR-29b [5].

Visually, uterine fibroids present as round, hard, white or pale pink neoplasms composed of smooth muscle with varying amounts of fibrous connective tissue. If UFs are not microscopic and/or growing, they can significantly distort the surface of the uterus or its cavity.

The pathogenesis of UFs growth is highly complex. There are many factors that influence the development of uterine fibroids, but the changes in signalling pathways are crucial in cell proliferation. The most significant causes of UFs development are discussed below.

a) Genetic Changes

Genetic changes contribute to an increased proliferative or decreased apoptotic index and may be associated with UFs in approximately 90% of cases [6]. Genetic alterations in High Mobility Group AT-Hook 1 (*HMGA1*) and High Mobility Group AT-Hook 2 (*HMGA2*) genes and somatic mutations in Mediator Complex Subunit 12 *(MED12)* gene, particularly in exon-2 region, are the most significant in UFsdevelopment [7, 8, 9, 10]. *MED12* and *HMGA2* mutations are independent genetic events in UFs [11]. It has been shown that mutations in *MED12* and overexpression of *HMGA2* mRNA can be detected simultaneously in UFs [12]. Another genetic mutations *FH*, *COL4A5*/*A6* and the unknown ones may be responsible for UFs without changes in *HMGA2* and *MED12* [11].

i. *HMGA Family Member*

HMGA1 (6p21) and *HMGA2* (12q14–15) are a protein coding genes, influencing cell cycle kinetics [13]. These genes are involved in many cellular processesand participate in alteration of chromatin structure and activation of transcription. *HMGA1* encodes non-histone chromatin-associated proteins HMGA1a, HMGA1b andHMGA1c and*HMGA2* encodes non-histone chromosomal protein HMGA2.

The main role of proteins encoded by *HMGA1*are regulation of gene transcription, DNA repair, heterochromatin organization, cell (including stem cell) differentiation and proliferation [14]. *HMGA2* overexpression is the second most common genetic change in UFs, identified in 7.5–10% of cases. It also acts as a transcriptional regulator. HMGA proteins are often expressed at very high levels in benign tumors (lipomas, uterine leiomyomas, breast fibroadenomas, salivary gland adenomas, pituitary adenomas), where in most cases, chromosome rearrangements involving the *HMGA2* gene, but also *HMGA1* gene [15]. HMGA proteins are expressed at high levels during embryogenesis. Overexpression of HMGA lead to inducing neoplastic transformation and promote of metastatic progression therefore it can be considered that HMGA proteins influence cell growth [16].

HMGA2 probably influence activity of fibroblast growth factor pathway and lead to UFs growth. According to a study by Helmke BM and et al, UFs with rearrangements of the *HMGA2* were found to express significantly higher levels of *FGF2* than those with an apparently normal karyotype. In addition, there was a linear relationship between the expression of *FGF2* and the level of *HMGA2* overexpression and the size of UFs. [17]. The overexpression of *HMGA1* and *HMGA2* mRNA may lead to upregulation of angiogenesis [18].

ii. *MED12*

Transcription initiation is known to be partially controlled by the preinitiation complex (PIC). It includes a transcriptional coactivator complex called Mediator. Together with general transcription factors, Mediator stimulates PIC formation and activates RNA polymerase II (Pol II) transcription. The product of the *MED12* gene, MED12 protein, is part of the CDK8 subcomplex along with MED13, CDK8 and cyclin C and is required for activation of CDK8 kinase. The CDK8 subcomplex binds to the mediator and modulates the interaction of Mediator with Pol II.

Somatic mutations in *MED12*, especially in exon 2, are proposed to be one of the underlying cause of UFs. *MED12* gene is mutated in 70-75% of tumours [11, 19]. *MED12* plays an important role in regulating genes such as *WNT*, *CCND1*, *AXIN2*, and *MYC*, which pertinent to cell cycling and cell proliferation MED12 somatic mutation has the potentials for myometrial cell transformation by dysregulating oncogenic Wnt4/β-catenin signaling. In the study of El Andaloussi A and co-authors have been showed that cells with common *MED12* somatic mutation has increased levels of protein expression of Wnt4 and β-catenin, mTOR protein and oncogenic cyclin D1 which might lead to inhibition of autophagy, increase of cell proliferation and UFs development [20].

b) Steroids

There are estrogen receptors (ER) and progesterone receptors (PR) in myometrium. It is known that UFs contain ER and PR in higher concentrations. The relative expression levels of ER and PR are upregulated in UFs compared to the surrounding myometrium. Estrogens and progesterone (P4) act as stimulators of UFs growth, the effects of these steroid hormones in the development of UFs are complementary.

UFs cells are known to have increased levels of aromatase and 17-hydroxysteroid dehydrogenase, enzymes that contribute to estradiol production. Increased exposure to circulating oestrogen may contribute to tumour growth by increasing extracellular matrix production.

i. *Estogens*

Estrogens are one of the main hormones produced by the ovaries and responsible for the development and regulation of the female reproductive system. Their action is mediated by ER. There are two best studied isoforms of ER – ERα and ERß. Estradiol (E2), the most potent form of estrogen steroid hormone, enters the cell and binds to ER. Formed hormone-receptor complex translocates to the nucleus and binds to a specific DNA site, leading to activation of gene expression, synthesis of specific proteins and promotion of hormonal effects.

E2 acts mainly through the ERa. It induces the transcription of genes involved in proliferation, but its one of the main functions leading to growth of UFs is to increase myometrium tissue sensitivity to progesterone via induction of PR expression.

Conventionally, estrogens has been considered the major factor for UFs development. Estrogens are involved in activation of fibroblasts, which may play key role in proliferation of UFs cell. The expression levels of ER is known to be higher in cells of UFs than in surrounder miometrium. According to Luo N. and et al, fibroblasts are activated in UFs, and estrogen may stimulate fibroblast activation, increase their proliferative activity, and increase the expression of fibroblast activation protein (FAP), growth factors such as transforming growth factor-β (TGFβ), insulin-like growth factor-1 (IGF-1) and ECM components. Silencing of FAP expression can inhibit the effect of estrogen on tumour-associated fibroblasts (TAF), thus FAP plays an important role in oestrogen-mediated fibroblast

activation. To sum up, estrogen may promote UFs cell proliferation through fibroblast activation [21].

ii. *Progesterone*

It is now believed that, progesterone is the main hormone that stimulates the growth of UFs. UFs growth significantly in postmenopausal women who receive hormone replacement therapy with combined estrogen and progesterone, and not with estrogen replacement therapy. In Ishikawa H and et al study an animal xenograft model was used to elucidate the functions of ovarian steroids. It was found that treatment with estradiol alone did not increase or maintain the size of UFs [22].

The responses of progesterone are mediated by non-genomic pathway and genomic pathway [23]. The majority of the effects of progesterone in the human organism are mediated by PR. PR is a member of the steroid-receptor superfamily of nuclear receptors. There are two isoforms of PR, PR-A and PR-B, which produced from a single gene by translation initiation at two distinct start codons [24]. PR-A is a truncated form of PR-B. PR-A and PR-B vary in their transcriptional activity. PR-B acts as a potent activator of transcription of target genes and PR-A acts as a repressor of transcription of PR-B [25]. When progesterone binds to PR, a ligand-receptor complex is formed. This complex translocates to the nucleus, binds to DNA and activates the expression of specific target genes.

The ratio of PR-A to PR-B in specific tissues defines the responses to progesterone. There is increased expression of both PR-A and PR-B in UFs. Estradiol (E2) is an important inducer of RP expression supported progesterone action. According to Ishikawa H et al., progesterone is essential for maintenance and growth of uterine leiomyoma. E2 enhances the synthesis of ER, PR and androgen receptors. Progesterone, on the contrary, inhibits the synthesis of ER and PR.

During the secretory phase, when levels of progesterone are at their highest, proliferation markers and the count of mitoses are also highest in UFs tissues. Progesterone activates the AKT pathway and its effectors, glycogen synthase kinase-3b (GSK3b) and Forkhead box O-1 (FOXO1), leading to UFs cells proliferation and promotion their survival [26]. P4 also stimulates EGF, Bcl-2 expression and inhibites TNF-α expression in the cells, which lead to growth and survival of UFs cells [27].

One of the causes of UFs is the inhibition of mechanisms of apoptosis. There are influence of progesterone on the regulation of apoptosis in the myometrium. In Omar M and et al studies demonstrated that five progesterone-regulated genes (PRGs), playing crucial roles in cell proliferation, apoptosis, tumorigenesis, reorganization and renovation of tissues, such as *Bcl2*, *FOXO1A*, *SCGB2A2*, *CYP26a1* and *MMP11* exhibited significant progesterone-hyper-responsiveness in UFs cells compared to normal myometrial cells. Seven PRGs such as *CIDEC*, *CANP6*, *ADHL5*, *ALDHA1*, *MT1E*, *KIK6*, *HHI* showed increase repression in the case of progesterone treatment [28].

It is assumed that progesterone-dependent UFs growth requires a population of stem/progenitor cells. It has a reduced expression of ERα and PR, and depends on high levels of ERα and PR in the surrounding mature myometrium. Progesterone sends paracrine signals via activation of the WNT/β-catenin pathway from mature cells to stem cells [29].

c) Others

There are *tissue-specific stem cells* (SSC) in the myometrium. They allows uterus to regenerate and remodelate, which is particularly important during pregnancy [30]. Due to the presence of stem cells within the UFs, the tumour is able to reconstitute itself [31].

The growth factors such as epidermal growth factor (EGF), insulin-like growth factor (IGF), transforming growth factor-b (TGF-b), platelet-derived growth factor (PDGF) have a stimulating effect on UFs cell proliferation. Vascular endothelial growth factor (VEGF), tumour necrosis factor α (TNF-α), haematopoietic growth factors (HGFs) may be also involved in pathogenesis [18,32]. Growth factors act as the ultimate effectors of steroid hormones. Estradiol and progesterone regulate the expression levels of various growth factors in the myometrium. E2 stimulates EGF receptor (EGF-R) expression and P4 stimulates EGF expression in UFs cells [33].

Myostatin (MSTN) and activin A are the members of the TGF beta protein family. Myostatin and activin act as inhibitor of muscle cell growth. Their signalling is regulated by membrane and extracellular factors, including activin-binding proteins such as follistatin and follistatin-related gene (FLRG). Follistatin may inhibit the activity of MSTN and activin [34]. According to Lee SJ and et al, the higher expression of follistatin, FLRG and Cripto in UFs produce reduced sensitivity to the anti-proliferative effects of myostatin and activin on myometrial cells and therefore lead to UFs development [35].

The phosphatidylinositol 3-kinase (PI3K)/AKT/ mammalian target of rapamycin (mTOR) pathway is an intracellular signaling pathway involved in regulation of cellular functions such as metabolism, proliferation. The PI3K/AKT/mTOR signalling pathway is involved in the initiation and regulation of autophagy, but also play a key role in carcinogenesis. UFs growth is also associated with activation of the PI3K/AKT–mTORpathway. The PI3K/AKT/mTOR pathway contribute to tumor growth by stimulation of proliferation, invasion, metastasis and survival of tumour cells. Another signaling pathway playing a significant role in pathogenesis of UFs is Ras/Raf/MEK/ERK pathway [36].

Chronic inflammation characterised by the formation of new blood vessels, increased vascular permeability, proliferation of fibroblasts and other events may cause the development of UFs. Cytokines such as tumor necrosis factor-α, erythropoietin, interleukin-1, interleukin-6 as well as several chemokines and their receptors may implicated in development of UFs. Inflammatory cells which may contribute to excessive production of ECM as well as tissue remodeling have been found in UFs [37].

Epigenetic changes and microRNAs (miRNAs) may be involved in pathophysiology of UFs**.** It became known that the expression profile of miRNAs in UFs cells differed from that in normal myometrial cells. The relative expression level of miR-15b was upregulated, and the relative expression levels of miR-29a, -29b, -29c, -197, and -200c were downregulated in UFs. Moreover, the miRNA expression profile in UFs cells differed according to their ability to lead to UFs with endometrial cavity distortion. The expression profile of miRNAs in UFs may effect on occurrence or absence of endometrial cavity distortion [38].

According to the study of, vasculogenesis and angiogenesis may play significant role in UFs formation, which in turn may be part of a vascular disease process [18].

III. Types of Uterine Fibroids

The size and location of the tumour may influence the onset of symptoms, the need for treatment and the method of treatment. There are three main types and other rare types of fibroids depending on its location in the uterus. The universally accepted International Federation of Gynaecology and Obstetrics (FIGO) classification system (PALM-COEIN) for causes of abnormal uterine bleeding includes leiomyoma subclassification system. This system includes the submucosal, intramural, subserosal, transmural and other lesions (Fig. 1).

- Subserosal fibroidsgrow out toward the serosal surface of the uterus covered by peritoneum. They may be sessile, pedunculated (attached to the surface by a stalk) or intraligamentary (between the two peritoneal layers of the broad ligament).
- Intramural fibroids are the most common type and located within the myometrium separated from the surrounding tissues by pseudo-capsule. They may lead to distortion of the uterine cavity and its surface.
- Submucosal fibroids grow toward the endometrium, protruding into the uterine cavity.
- Cervical fibroids are located in the cervix. They are a rare type.

Submucosal	0	Pedunculated intracavity
	1	≤ 50% intramural
	2	> 50% intramural
Other	3	100% Intramural but contains endometrium
	4	100% Intramural
	5	Subserosal, ≥ 50% intramural
	6	Subserosal, < 50% intramural
	7	Subserosal pedunculated
	8	Other (cervical, parasitic)
Hybrid *(impact both endometrium and serosa)*	2-5	Submucosal and subserosal

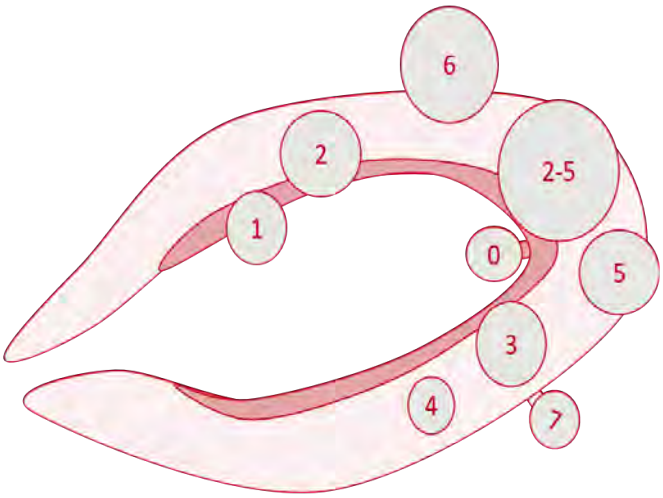

Figure 2: FIGO Classification of Uterine Fibroids According to Munro et al. (2011).

The FIGO classification of fibroids has clinical limitation. In the paper and co-authors showed that the FIGO classification of fibroids was not consistent between two gynaecologists and two radiologists specializing in UFs. Variations were clinically relevant (influencing surgical planning) for 36% of the fibroids [39]. Therefore, additional validation of the FIGO classification system for fibroids is required.

IV. Risk Factors

There are many risk factors associated with the development of uterine fibroids [3, 40]:

- Age – women aged 41-50 or 51-60 years are 10 times more likely to have myoma than those aged 21-30 years.

- Positive family history – in patients with positive family history, the risk for developing UFs approximately three-four times higher than in the general population.
- African American race – black women were found to have a two–threefold greater risk of developing UFs than white women. African-American women have more severe symptoms.
- Compared to white women.
- Early menarche (less than 11 years) – patients with an early age at menarche have a greater lifetime exposure of the myometrium to oestrogens.
- Absence of childbirth (nulliparity) vs high parity ($\geq$3) – parity is associated with a reduced risk of developing UFs.
- Time since last birth – the risk of developing UFs is increased in women who last gave birth 5 or more years ago compared with those who gave birth more recently.
- Obesity – an increased risk of UFs is associated with higher oestrogen levels in obese women because adipose tissue is a source of oestrogen.
- Premenopausal state – three to five times higher risk than in postmenopausal women.
- High blood pressure (hypertension).

The role of smoking as one of the protective factors of UFs is discussed. In one study, smoking was found to reduce UFs risk, but only in the case of patients with a low BMI ($\leq$22.2 kg/m^2). The use of food additive increases the risk of UFs. The intake of soybean products (eg milk) has been identified as risk factor for their endocrine-disrupting chemical (EDC) contain such as genistein. According to some studies, the use of oral contraceptives, injectable contraceptive (depot-medroxyprogesterone acetate) as well as reproductive characteristics such as later age at menarche, longer menstrual cycles and breastfeeding were found to reduce the risk of developing UFs and may be reproductive protective factors [41, 42].

Another potential risk factors may include intake of caffeine and alcohol, several reproductive characteristics (shorter menstrual cycles, late reproductive age), cervical neoplasia, pelvic inflammatory disease, chlamydial infection, use of perineal talc, diabetes mellitus, polycystic ovary syndrome, metabolic syndrome [43,44]. UFs may be associated with cardiometabolic risk factors and atherosclerosis [45].

V. Symptoms and Signs of Uterine Fibroids

According to various sources, symptoms are found in about 35–50% of patients. Important to understand that quality of life (QoL) depends directly on the severity of UF-associated symptoms.

Signs and symptoms of UFs include: heavy menstrual bleeding leading to anaemia; painful periods; pelvic non-cyclic pain; pelvic pressure; lower back pain; dyspareunia; bowel or bladder dysfunction [46].

UFs can be accompanied by sub fertility, pregnancy complications, spontaneous abortion, ectopic pregnancy or such obstetric outcomesas obstructed labour, cesarean delivery, fetal malpresentation, placenta previa due to interference with implantation of the ovum in the upper uterine segment, placental abruption, premature rupture of membranes, premature or threatening premature delivery, postpartum haemorrhage and aseptic necrobiosis of a uterine fibroid during pregnancy [47, 48].

VI. Diagnosis of Uterine Fibroids

The diagnosis of uterine fibroids is made on the basis of signs and symptoms, physical and instrumental examinations and laboratory tests.

a) Physical Examination

This stage of diagnosis may help to identify uterine fibroids as well as their localization. Uterine size is described in weeks (as that of a pregnant uterus). UFs may discovered by pelvic examination as a firm mass of an irregular shape on the uterus or as enlarged and irregular uterus. In the case of cervical UFs localization the cervix is smooth, asymmetrically positioned, displaced to the opposite pelvic wall.

b) Instrumental Examinations

The next step is doing one or more of different types of imaging techniques to confirm the diagnosis and identify the location, shape, size, number of fibroids and their types.

Pelvic ultrasound with using transabdominal and transvaginal transducer is non-invasive technique which recommended as the main screening and primary diagnosis of uterine myoma. Ultrasound allows to exam the uterus and the surrounding structures. This imaging technique provides an opportunity for topical diagnosis of UFs, their structure, hemodynamics, the severity of proliferative processes and detection of secondary changes in the nodes as a result of impaired blood circulation. It is also useful for differential diagnosis. On pelvic ultrasoundUFs are identified as a hypoechoic, well-circumscribed and round mass. Transvaginal ultrasonography is about 90% to 99% sensitive for detecting uterine fibroids.

The other types of imaging technology are: saline infusion sonography (sonohysterography), magnetic resonance imaging (MRI), hysteroscopy. Saline infusion sonography improves sensitivity for detecting fibroids. If ultrasound and sonohysterography are inconclusive, MRI is the most accurate imaging technology. MRI allows to detect the number and size of

fibroids, the degree of vascularisation, the location, boundaries with normal myometrium and relationship with the endometrial cavity and serosal surface, and, based on this, the type of UFs. UFs are well-defined masses and typically T2-hypointense compared to the normal myometrium and of intermediate signal intensity on T1-weighted images [49]. MRI is recommended for differential diagnosis with adenomyosis and for choosing the volume and access of reconstructive operation for patients with co-morbidities, large uterine fibroids sizes and also for patients planning to realize reproductive function and who have compression of adjacent organs.

Hysteroscopy is recommended in the case of suspicion of submucous localization of UFs, in order to exclude intrauterine pathology and for choosing the access to operative treatment.

c) Laboratory Tests

Examinations of the complete blood count, biochemical blood test, haemostasiogram are helpful in detecting complications (anaemia, impaired blood circulation in the node, etc.), in pre-operative examinations and in determining the treatment strategy.

VII. Management of Uterine Fibroids

In the case of patients with asymptomatic UFs, there's no treatment needed. Patients should see a gynecologist and undergo routine pelvic ultrasound once every 6 to 12 months.

In the case of symptomatic UFs, the most appropriate treatment strategy, depending on anamnesis, patient's age and future fertility desires, is recommended.

a) Medical Therapy

Medical therapy must be effective, safe, accessible and well tolerated. It should be evaluated every 3 months and if it is not effective, other treatment should be prescribed. Based on the pathogenesis, the main target of the current medical therapy is focused on control of estradiol and progesterone production or their action. The main aim of medical treatment is to alleviate or eliminate the symptoms associated with UFs, and to reduce the size of fibroids [50].

Nowadays, there are at least two options for medical therapy, which effectively reduce both fibroid size and bleeding and it is Gonadotropin-releasing hormone (GnRH) analogues (agonists) and selective progesterone receptor modulators (SPRMs).

i. *GnRH Agonists*

GnRH agonists turn off synthesis of estrogen and progesterone and thus suppress ovulation.GnRH agonists lead to hypogonadotropic hypogonadal state, hypoestrogenism and temporary menopause (pseudomenopause). These effects develop after 1-3 weeks of drug administration [51]. GnRH agonists include leuprolide, triptorelin and goserelin. Benefits of GnRH agonists use include decrease in fibroid size, reduction of endometrial thickness and vascularization, reductions in uterine volume and resolution of anemia by restore hemoglobin levels.

GnRH agonists may use as presurgical adjuncts to make surgery easier or improve operative technique. In addition to the effects described above, GnRH agonists reduce intraoperative estimated blood loss, fluid absorption, rate of vertical incisions and decrease operative time [52,53,54]. The duration of pre-operative GnRH agonists therapy is 3 months. The duration of medical therapy with GnRH agonists is limited to 6 months due to side effects, which mayinclude menopause-like symptoms such as hot flashes, fatigue, decreased concentration, insomnia, emotional lability, vaginal drynessand decreased bone mineral density [55]. GnRH antagonists cannot fully contribute to relief from tumor, and after stopping treatment UFs may grow back along with return of symptoms.

Add-back therapy with GnRH agonists may include estriol, tibolone, raloxifene and ipriflavone which help to preserve bone density. Also intake of medroxyprogesterone acetate (MPA) and tibolone may reduce vasomotor symptoms [56,57].

ii. *SPRMs for Uterine Fibroids*

With the knowledge of the significant role of progesterone in the pathogenesis of UFs, selective progesterone receptor modulators (SPRMs) have been developed. SPRMs are a new class of drugs, which target PR and exert an agonistic and antagonistic effects [58]. Tissue and cell type influence SPRM activity and the effect of SPRM is more influenced by the ratio of co-activators to corepressors [59]. SPRMs include mifepristone, ulipristalacetate (UPA), telapristone acetate, onapristone, asoprisnil.

SPRMs have been shown efficacy and safetyin reducing the size of UFs, inducing amenorrhea and improving main symptoms and quality of life. The most widely discussed SPRMs is ulipristal acetate (UPA) [51]. UPAis tissue-selective synthetic steroid which reduce the proliferation of UFs cells and induces apoptosis [60]. It has been demonstrated that administration UPA reduces fibroid size, controls uterine bleeding and improves QOL [61,62,63]. In contract to GnRH agonists, UPA has a sustained effect (up to 6 months) on UFs size. According to several studies, UPA is well tolerated treatment option with less than 5% of cases with discontinuing treatment due to side effects [64,65].

In the end, SPRMs may be effective treatment for women with symptomatic (moderate and severe symptoms) fibroids, for preoperative use and for intermittent long-term treatment, but there are needs to well-designed RCTs comparing efficacy, cost-

effectiveness and safety of SPRMs and other treatment options in UFs therapy.

b) Preoperative Adjuvant Therapy: SPRMs vs GnRH Agonists Leuprolide

Women receiving UPA have significantly less faced with hot flashes and achieved amenorrhoea 2 weeks earlier than women receiving leuprolide [63,66]. UPA is more effective and well-tolerated option for the preoperative therapy.

Another medical options may include aromatase inhibitors and selective estrogen receptor modulators (SERMs). The first one modulate estrogen signaling pathway and the second one act differently in various tissues by blocking or stimulate estrogen-like action. Unfortunately their effectiveness is controversial [67,68].

c) Surgical Treatment

The evidences for surgical treatment of UFs are menstrual abnormalities leading to iron deficiency anemia; bulk symptoms (pressure symptoms); large tumour size (over 12 weeks gestation); rapid tumour growth (more than 4 weeks within 1 year); tumour growth in postmenopause; submucosal, interligamentary or cervical location of nodes; reproductive disorders (pregnancy failure, infertility in the absence of other causes); signs of circulatory disturbances in UFs [69,70].

Surgical treatment of UFs is performed during the 1st phase of the menstrual cycle (day 5-14) in a planned manner. When choosing the best surgical technique, the size and number of fibroids, their location, surgical history, age of the patient and the patient's preferences (e.g. preserve the uterus and fertility or not) should be considered. Other surgical approaches include hysteroscopic myomectomy, laparoscopic myomectomy or laparoscopic hysterectomy.

Myomectomy is the standard of care for women with symptomatic fibroids who wish to preserve fertility, but can be detrimental on pregnancy outcome [71].

i. *Hysteroscopic Myomectomy*

Hysteroscopic myomectomy is the standard minimally invasive surgical procedure in the treatment of submucosal UFs (especially, Figo type 1-2). Most commonly, hysteroscopic myomectomy is performed in two steps: under hysteroscopic control, the protruding part of fibroid is resected or ablated; the remaining intramural component rapidly migrates into the uterine cavity, allowing complete and safe excision of the myoma during the second step.

ii. *Laparoscopic Myomectomy*

Laparoscopic myomectomy (LM) is the gold standard in the treatment of women of reproductive age. However, it is worth noting that there is a significant risk of uterine rupture during pregnancy or delivery, and this is primarily due to the inability to adequately match the wound margins during LM (especially type 3-5 and type 2 with an intramural component of more than 20%) and the use of electrosurgical devices (tissue burn and disruption of its regeneration). Also note that it is recommended to use morcellator in a special container (endobag) to avoid dissemination. Currently, the ideal condition for LM is UFs type 7.

a. *Minilaparotomy as Analogue of LM*

Minilaparotomy implies an extra special incision in the abdominal wall with an extension of the umbilical puncture to 3-5 cm. Minilaparotomy myomectomy is a minimally invasive surgical intervention that allows the surgeon to maintain tactile contact with the uterus and close the myometrial defect after fibroids enucleation easily. Minilaparotomy myomectomy becomes a good solution in the case of limited laparoscopic suturing skills and may provide better uterine reconstruction in the case of large fibroids [72]. Another advantages of minilaparotomy is a faster removal of UFs from the cavity and reduction in the time of myomectomy [73].

b. *Benefits of LM*

LM was associated with longer operative time but fewer general complications, lower blood loss, lower decline in haemoglobin concentrations and less postoperative pain (on avisual analogue scale) and a faster recovery after surgery compared with abdominal (open) myomectomy [74,75,76].

iii. *Hysterectomy*

Hysterectomy is performed in patients with symptomatic UFs who not planning pregnancy or in the case of post-menopausal women. Access (laparoscopy, laparotomy, transvaginal) and the extent of surgical intervention (subtotal without or with uterine adnexa, total hysterectomy or panhysterectomy) depend on the patient's age, the size of the uterus and UFs, the presence of concomitant pathologies of the cervix or uterine adnexa, the surgeon's qualifications and the patient's preference.

Other ways to perform myomectomy include robotic assisted laparoscopic myomectomy, laparoscopic-assisted minilaparotomy (LA-MLT), single-port laparoscopically assisted-transumbilical ultraminilaparotomic myomectomy (SPLA-TUM), single port laparoscopic myomectomy (SP-LM) [77-81].

d) Alternative Treatment

i. *Uterine Artery Embolization*

Uterine artery embolization (UAE) was originally introduced in 1995 [82]. Nowadays, UAE is a well-established safe and minimally invasive treatment for UFs which provides good symptom relief. UAE should be considered as one of the treatment options as well as the conventional surgical treatments. It may apply in the case of patients at high surgical riskor for patient with increased risks of complications of general

anesthesia, as an alternative to surgical treatment; for those patients, who categorically reject surgical or hormonal treatment. It should be noted that UAE use remains controversial for women who wish to procreate, because the procedure can affect fertility and the course of pregnancy.

Before the UAE, accurate pre-treatment diagnosis with MRI is recommended. UAE is performed by interventional radiologist with specialised experience in embolization. Through a small incision in the groin, the radiologist set a catheter into femoral artery, after the catheter is threaded into uterine artery, the blood vessel that supply the uterus. Under X-ray control small spherical particles of medical material are delivered through the catheter to form a blockade to the blood. UAE induces ischemic necrosis of UFs, while normal myometrial tissue revascularizes, that is to say, UAE leads to devascularization of UFs without affecting healthy uterus tissue. The majority of UFs have a limited supply by the uterine arteries, thus after UAE they are impacted simultaneously. Deprived of nutrition, UFs become smaller for the three to six months following UAE.

The early and medium-term results of UAE are promising. Particularly it is effective for abnormal menstrual bleeding. The randomised controlled trials (RCTs) of UAE versus any surgical therapy for symptomatic uterine fibroids included in review by Gupta and et al. compared UAE with surgery. OAE, as well as surgery, was shown to improve quality of life, but with reduced the length of the procedure, decreased the likelihood of needing a blood transfusion, length of hospital stay and time to resumption of routine activities, however UAE was associated with higher rates of minor complications (e.g. puncture site bruising and self-limiting vaginal discharge in 20-30% of patients). No significant difference was found between UAE and surgery in terms of patient satisfaction [83].

Although UAE is highly effective in treating symptomatic UFs, there is risk of surgical reintervention within two to five years of the initial procedure. As reported by Gupta and et al., 7% of women will require further surgery within two years of hysterectomy or myomectomy, between 15% and 32% will require further surgery within two years of UAE [84].

UAE may apply as preparation for surgery. It decrease both uterine and UFs volume, reduces intraoperative bleeding and increases the possibility of uterus preservation [85].

There are differing opinions about the effectiveness of this technique. It is important to identify what determines the success of UAE. UAE has been reported to provide a good success rate in women with a single symptomatic intramural myoma and can be considered as an effective alternative procedure for UFs treatment [86]. Patient selection and counselling is of paramount importance due to the high risk of the need for further surgery.

There are a number of contraindications to UAE. For example, it is contraindicated if there is evidence of a current or recent infection and if there is significant doubt about the diagnosis of a benign pathology.

Patient selection and counselling is of paramount importance due to the high risk of the need for further surgical intervention, and especially in the case of patients of childbearing age who wish to become pregnant. The authors are divided on the use of UAE in women of reproductive age [87]. This is largely due to the fact that the exact effects of UAE on fertility are unclear. The increased risk of caesarean section and the possibility of increased pregnancy complications such as abnormalities of placental implantation, spontaneous abortion, premature delivery after UAE should be stipulated as well asholding pre-treatment fertility assessment [87]. Obviously, well-designed RCTs are needed to assess the impact of UAE on fertility and to subsequently compare the results of UAE with myomectomy. Recent research in the field has questioned the appropriateness of UAE as the main treatment for women wishing to give birth. UAE may be alternative in the case of patients of childbearing age not eligible for myomectomy According to Serres-Cousine O and et al, restoration of uterine anatomy and protection of the ovaries may be the main predictive factors for obstetric success, reducing the risk of miscarriage, and the main predictive factor for clinical success of UAE [88].

e) Other Minimally Invasive Therapy

Vaginal occlusion of the uterine arteries and uterine artery occlusion by laparoscopy (UAOL) may become one of the treatment options for symptomatic UFs [89,90]. To assess the overall effects of vaginal occlusion of the uterine arteries and UAOL, there are need in RCTs with long-term follow up.

f) High-Frequency Magnetic Resonance-Guided Focused Ultrasound Surgery

High-frequency magnetic resonance-guided focused ultrasound surgery (MRgFUS) is a minimally invasive technique. It introduction in 2004 by the Food and Drug Administration (FDA) for the ExAblate 2000 for the treatment of UFs. MRgFUS is a thermoablative technique using MRI. MRI is used to identify target fibroid tissues, assess proximity to critical structures and monitor tissue temperature. During the procedure, ultrasound energy waves are directed at a focal spot within a UFs (target) to be destroyed. Ultrasound energy waves heat target tissues to > 55°C, thereby resulting in protein denaturation and thermocoagulation tissue necrosis of UFs with minimal damage to surrounding normal myometrium [91]. The current platforms used for MRgFUS are the ExAblate 2000, ExAblate 2100, Sonal-leve MR-HIFU.

MRgFUS is recommended as organ-preserving treatment of patients with UFs, if the conditions are right and there are no contraindications. Potential patients with UFs are examined with MRI to localize a target tissue in 3 dimensions and determine whether they meet the selection criteria for treatment [91]. Good visualisation of the fibroid and its location, the number and size of the nodules, and the proximity of critical structures are important. Exclusion criteria are large weight, serious health complications, contraindications to MRI, abdominal scarring, uterine size greater than 24 weeks, and presence of pedunculated, highly calcified fibroids. Potential complications after MRgFUS include skin burns, nerve damage and deep venous thrombosis.

MRI-guided focused ultrasound surgery may be a promising treatment for women wishing to future conceive [92-94].

The use of UFS-QOL questionnaire before and after treatment as an informative tool for assessing the severity of UFs symptoms and quality of life may be helpful in the case of patients who have undergone alternative treatment [95,96].

VIII. Conclusion

The clinical and social impact of UFs on population is increasing as well as the number of cases in younger women. At the same time the age of first pregnancy is increasing. Surgical treatments are still considered to be the most effective for women with symptomatic UFs, but medicine does not stop. We are convinced that the complex pathogenesis of uterine myoma suggests numerous molecular targets for open up new treatment options of these benign tumours and improving its management and that controlled research with involving specialists from different fields is needed to continue the study of UFs etiopathogenesis.

New data about pathogenesis of UFs and complete understanding the role of stem cells and their paracrine interactions, steroids, growth factors, genetic and epigenetic changes as well as their connection with each other will explore new options for prevention and help to new, effective, uterine-sparing therapeutic strategies for patients with UFs.

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