POKORA, Karolina, POKORA, Szymon, PODSIEDLIK, Adam, STEFANOWICZ, Agata, POLOCZEK, Alicja, SZCZERBA, Jakub, JELEŃ, Katarzyna, SOJKA, Paweł, POKŁADNIK, Dominika and ŻYMŁA, Tatiana. Uterine fibroids - a literature review. Journal of Education, Health and Sport. 2024;59:145-157. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2024.59.009
https://apcz.umk.pl/JEHS/article/view/48131
https://zenodo.org/records/10656249

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 16.01.2023. Revised: 08.02.2024. Accepted: 14.02.2024. Published: 14.02.2024.

UTERINE FIBROIDS - A LITERATURE REVIEW

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ABSTRACT

Uterine fibroids are the most common benign neoplastic lesions occurring in women. They are formed as a result of proliferation of smooth muscle tissue cells. Their appearance and proliferation are influenced by both genetic and environmental factors. 70% of them remain asymptomatic, so they are often detected only during a routine gynecological examination or pelvic imaging studies. Uterine myomas can generate pelvic and lower abdominal discomfort and pain, abnormal, prolonged, heavy bleeding, anemia, dyspareunia, frequent urination, bloating, constipation, abdominal cramps, low back pain and obstetric complications. Available therapeutic strategies include conservative, pharmacological and surgical treatment. The choice of a particular method is considered on an individual basis and depends on the presence of clinical symptoms, the size, location of the myomas, or the age and procreative plans of the patient.

MATERIALS AND METHODS

The above article was written on the basis of a review of current scientific knowledge available within the literature present in PubMed, Google Scholar databases, as well as based on the latest gynecological guidelines. The following keywords were used to search for relevant scientific content: uterine fibroids, clinical symptoms, diagnosis and treatment of

uterine fibroids. Selected articles included gynecological guidelines, descriptive articles, cases and clinical studies. This paper describes the epidemiology, pathophysiology, clinical manifestations, diagnosis, and treatment of the disease.

KEYWORDS: Uterine fibroids, clinical manifestations, risk factors, diagnosis and treatment of uterine fibroids

ENTRY

Uterine fibroids are one of the most common benign tumors occurring in nearly 70% of women of reproductive age [1]. They arise as a result of the growth of smooth muscle tissue cells [2a] They differ in size, shape and location. Taking into account the location of these changes, uterine fibroids are classified according to the FIGO (International Federation of Gynecology and Obstetrics) system into 8 subtypes (from 0 to 7) [1]. They tend to grow, although they may not change their size for many years. Due to the generation of clinical symptoms and their accidental detection in imaging tests, they are an indication for resection. The scope of the procedure may include simple myomectomy, but also hysterectomy with abnormal nodular structures. For women with reproductive plans, this is unacceptable, therefore different clinical procedures should be taken into account. Depending on the patient's age, her maternity plans, the size and location of the tumor(s), and the presence of symptoms, we distinguish different therapeutic strategies. They include conservative and pharmacological methods as well as surgical procedures [3]. More than 50% of

premenopausal women have asymptomatic uterine fibroids, which are detected accidentally during a gynecological ultrasound examination [4].

CLINICAL SYMPTOMS

Uterine fibroids may remain asymptomatic, but as they grow and increase in number, the size of the uterus increases, which leads to clinical symptoms. These include: discomfort and pain in the pelvis and lower abdomen, abnormal uterine bleeding (intermenstrual and postmenopausal) and prolonged, heavy menstrual bleeding, anemia, dyspareumnia, frequent urination, flatulence, constipation, abdominal cramps, pain in the lumbar spine [5, 2]. The above symptoms are reported by 25-30% of patients with fibroids [1]. In women of reproductive age, they may lead to difficulties in the implantation of the embryo in the uterine cavity, which is the cause of infertility, and also contribute to early pregnancy loss, incorrect implantation of the placenta, or lead to an increase in the risk of premature birth [1]. The presence of fibroids increases the likelihood of termination of pregnancy by cesarean section, and also generates complications in the form of postpartum hemorrhage due to the significant vascularization of these lesions. The above obstetric pathologies are a consequence of the distortion of the structure of the uterine cavity by growing myomatous lesions.

RISK FACTORS AND PROTECTIVE FACTORS

The appearance of uterine fibroids depends on many conditions. The risk factors for uterine fibroids include: positive family history, age, African-American origin, nulliparity, late age at menopause, and early age at menarche [6, 7]. Uterine fibroids develop in women of reproductive age, and the risk of their occurrence increases with age, especially in the group ≥ 40 years of age. In the group ≥50 years of age 70% of white women and approximately 80% of black women have these benign tumors in the reproductive tract [8]. Modifiable aspects related to lifestyle that influence the development of these changes include: obesity accompanied by insulin resistance and type II diabetes, hormone replacement therapy [9], arterial hypertension, especially diastolic hypertension, vitamin D deficiency [10], overconsumption of dairy products, soy and milk soybean, abnormalities in the microbiome of the reproductive tract, environmental and food pollution by chemicals that disrupt the hormonal balance, excess vitamin E [11], chronic stress [12, 7]. The above factors contribute to the generation of inflammation, lead to structural damage (mutations) and instability of the genetic material, resulting in abnormal cell proliferation and the accumulation of intercellular matrix [12, 6]. The cells that make up uterine fibroids are sensitive to female sex hormones:

estrogens and progesterone, therefore an endogenous increase in their synthesis and concentration, or exogenous use, promotes an increase in the size of these changes [2].

Factors that have a protective effect on the development of these changes in the uterus are: late age of menarche, early age of menopause, multiparity, oral contraception [13] and in the form of depot injections (medroxyprogesterone) [7], but after puberty [12], vitamin D3 supplementation [10], eating a diet rich in green vegetables, citrus fruits, fish [12], calcium, smoking in women with low body weight who gave birth [7]. Recent scientific studies emphasize the protective role of epigallocatehin gallate, present in green tea, as well as curcumin and resveratrol [12, 3].

GENETICS

A positive family history of uterine fibroids indicates the involvement of genetic and epigenetic factors contributing to the formation of these benign uterine lesions. The most common abnormality found in the cells of this tumor is a somatic mutation in the Xq13 gene, encoding a subunit of the RNA polymerase II (Pol II) mediator complex, i.e. MED12 [12]. This mutation occurs in more than half of cases (45-90%), regardless of the ethnic origin of the patients [12]. The MED12 mutation promotes the formation of numerous small-sized fibroids with typical histological structure, in the form of leiomyomas, usually located under the serosa [14, 15]. The pathology of the tumor mainly involves smooth muscle cells, which harbor the MED12 mutation, as well as tumor-associated fibroblasts (TAF), which synthesize collagen and intercellular matrix. In addition, a small component of vascular smooth muscle cells, endothelium and immune cells is also present. Therefore, the tumor is heterogeneous in terms of its structure [16]. Hormonal stimulation is important for the growth and development of uterine fibroids. Progesterone stimulates the division of smooth muscle cells, while estradiol promotes the growth of fibroblasts [17]. The above aspects are important in the selection of pharmacological therapy. The patients' parity was a protective factor for the occurrence of tumors with this genetic abnormality. Moreover, the MED12 mutation negatively correlated with a positive history of pelvic inflammatory disease [15]. Studies have also shown that this mutation is not associated with such risk factors for uterine fibroids as: BMI, hypertension, diabetes, thyroid disease, smoking, use of oral contraceptives, or a positive family history of these tumors [15]. Less frequently, it can also be seen in leiomyosarcomas and muscle tumors of undetermined malignant potential (STUMP) [18]. Other genetic disorders predisposing to the development of uterine fibroids include overexpression of the high electrophoretic mobility protein A2 (HMGA2) gene or deletions of

the α5 and α6 chain genes of type IV collagen (COL4A5, COL4A6), which occur in 2%, as well as rare mutations within fumarin hydratase (FH) gene [12]. In the case of uterine fibroids with abnormalities in the HMGA2 gene, lesions with a predominant structure of smooth muscle tissue occur. This component constitutes over 90% of the histological structure of the tumor and is also sensitive to progesterone stimulation [17]. In turn, the FH mutation is present in 1.6% of uterine fibroids with atypical structure and is associated with the co-occurrence of hereditary leiomyomatosis syndrome and renal cell carcinoma (HLRCC) [19].

The genetic factor is also considered in the case of the occurrence of these changes at a young age, although it takes into account a different molecular basis. Uterine fibroids are rare among teenagers. They constitute less than 1% of cases [20]. The presence of these changes in young women is facilitated by genetic changes in the form of translocations within chromosomes 12 and 14 [12].

CLASSIFICATION

Based on the FIGO classification, we distinguish 8 subtypes (0-7) of uterine fibroids depending on their location in relation to the endometrium, myometrium or serosal membrane [21].

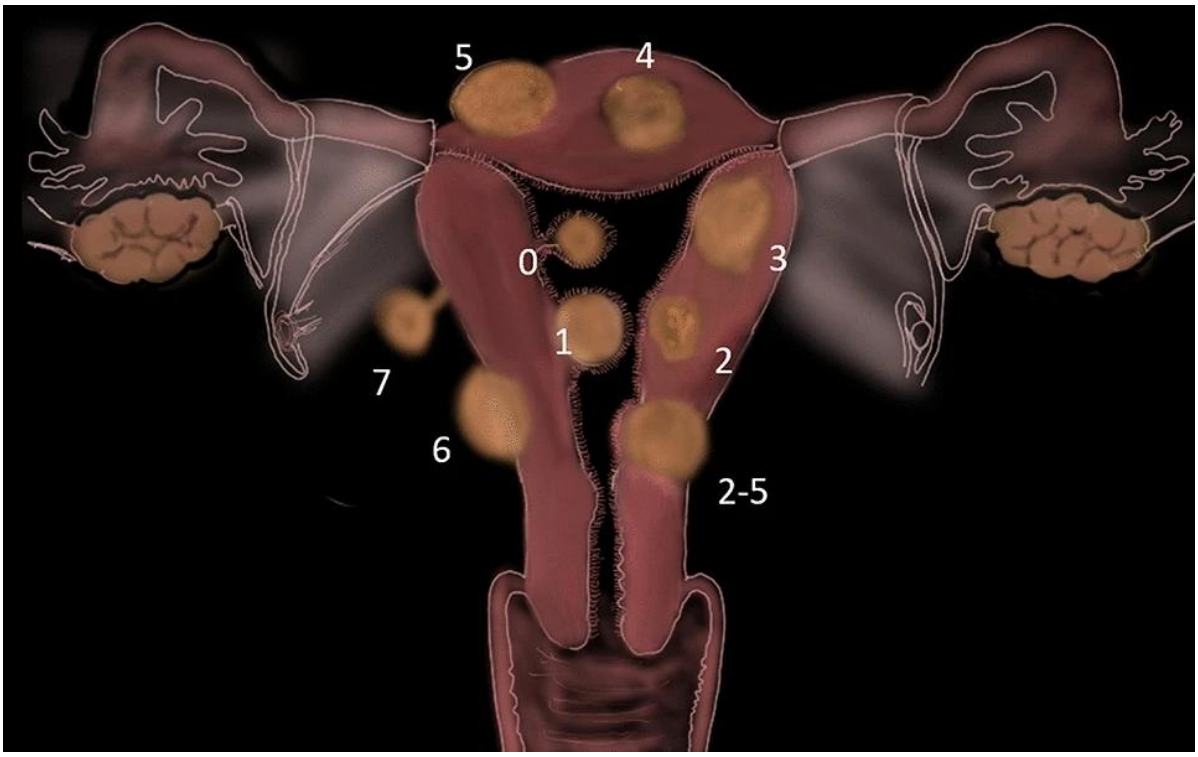

Figure 1: Classification of uterine leiomyomas according to FIGO (International Federation of Gynecology and Obstetrics). Source: [21]

DIAGNOSTIC METHODS

There are several diagnostic methods for detecting and differentiating uterine fibroids. The most common and easily accessible tool is transvaginal ultrasound (TVS). It can be used to visualize the following features of changes in the uterine area, which are highly likely to suggest uterine myomatous changes. These include: regular tumor boundaries, peripheral and intralesional vascularization, usually non-homogeneous echogenicity, and visible endometrium. These features are helpful in differentiating them from other pathological structures, including malignant tumors such as sarcomas. The above characteristics should always be compared with the patient's age [22]. Other imaging methods are rarely used, including magnetic resonance imaging (MRI), which is characterized by high accuracy, or computed tomography (CT). These tests can be used to assess the growth dynamics of uterine fibroids [2]. Another diagnostic method, which is also a therapeutic option, is hysteroscopy. It can be used to visualize the inside of the uterine cavity along with changes in its area, using an optical device inserted through the vagina and the dilated cervix. Symptomatic submucosal fibroids may be removed or enucleated during examination [2]. Two classifications are helpful in qualifying the patient for this procedure. The three-level Wamsteker scale (0-2), which determines the depth of penetration of the fibroid in relation to the uterine wall, and Lasmar, which additionally assesses the size of the tumor, its location in relation to the inside of the uterus, as well as the distance of the fibroid from the serosal membrane. Based on the sum of points obtained for the above parameters, a decision is made to perform or abandon the procedure or to carry it out in two stages [23]. Other methods of visualizing uterine fibroids include hysterosalpingography using X-rays and sonohysterography, during which the reproductive organ is filled with fluid and assessed under ultrasound control [2]. Laparoscopy is useful for the invasive evaluation of fibroids located outside the uterine cavity, which can also be used to remove these lesions from the pelvis [2].

TREATMENT

There are several indications for therapeutic procedures in the presence of uterine fibroids. 30% of women with these tumors experience clinical symptoms such as heavy, painful menstruation, anemia, intermenstrual bleeding, or pelvic pain. The above symptoms are an indication for fibroid resection [3]. Moreover, the rapid increase in the size of the lesion or the uncertainty as to the malignant nature of the tumor, as well as fertility disorders, are other

important aspects in terms of qualifying the patient for treatment [2, 12]. Available methods include expectant management, pharmacological (non-hormonal and hormonal), and surgical procedures, including endovascular procedures [3]. The above strategies are aimed at: limiting abnormal and excessive bleeding from the uterine cavity, reducing pain, stopping the development of fibroids, and reducing their size. The use of pharmacological agents is the primary line of treatment. It includes the use of such groups of drugs as: non-steroidal anti-inflammatory drugs (NSAIDs) - mainly ibuprofen and naproxen, GnRH (gonadotropin-releasing hormone) analogues and antagonists, progestogens, estrogens, estrogen-progesterone contraceptives, selective progesterone receptor modulators (SPRM), antiprogestogens, blockers GnRH receptor, aromatase inhibitors, [24, 3]. The use of GnRH analogues and antagonists is associated with side effects such as bone loss, hot flashes, and negative effects on the cardiovascular system, which is why therapy with their use has time limits, usually up to 6 months [24]. This procedure is particularly important for premenopausal women who have reproductive plans. Additionally, pharmacological treatment is aimed at reducing bleeding or compensating for the loss of iron and hemoglobin caused by these tumors. In this regard, the following applications apply: combined hormonal contraceptives, intrauterine devices (IUDs) releasing progestogens, tranexamic acid, NSAIDs, and iron supplementation [2, 3]. In addition to the above drugs, we can offer substances and supplements that influence the signaling pathways related to the pathogenesis of fibroids. These include: vitamin D, epigallocatechin gallate (EGCG), curcumin, resveratrol, trans-retinoic acid, simvastatin, methyl jasmonate, cabergoline, somatostatin analogues, gestrinone [12, 3]. Despite a wide range of pharmacological preparations, not all of them are available and approved for use in all countries. Ulipristal acetate, which is a SPRM with high effectiveness in reducing the size of fibroids and limiting excessive bleeding, is not used in some countries due to possible hepatotoxicity. It is also the only preparation used in the 3-month adjuvant treatment preceding surgery [25].

Preparations that are GnRH receptor agonists are also successfully used. These drugs, after a temporary "flare-up" phenomenon, reduce the synthesis of gonadotropins and sex hormones, which in turn leads to a reduction in the size of these tumors by 35-65% within 3 months and reduces the risk of bleeding. These are very beneficial effects in terms of subsequent treatment procedures [26, 2]. Due to side effects related to the deficiency of ovarian hormones, including menopausal symptoms and bone loss, it is advisable to use low-dose hormone replacement therapy (HRT) at the same time [26]. If they are used for less than 6 months, they

can be administered without HRT, but if the therapy covers a period of up to 12 months, it is advisable to take HRT simultaneously [2].

In turn, surgical procedures include myomectomy, which can be performed in three ways: through classic laparotomy, laparoscopy, or hysteroscopy. This surgery aims to remove the myomatous lesions while leaving the uterus in the pelvis. It is recommended for patients who have maternity plans and want to keep their uterus [3]. In addition, the choice of treatment depends on the size, number and location of the fibroids. Laparoscopic myomectomy should be the therapy of choice for intramural and subserosal fibroids due to numerous benefits in the form of: reduced blood loss, reduced pain and shortened hospitalization period compared to laparotomy [27]. Hysteroscopy, however, is justified in the case of smaller type 0 or type 1 submucosal fibroids [28]. In the case of numerous and large fibroids, especially in women who have completed childbearing, hysterectomy may be performed. Most often, it is performed using minimally invasive procedures using a transvaginal or laparoscopic approach, but classic laparotomy is also used. [27]. The advantages of this method are: final elimination of fibroids, a small number of complications at the level of 0.4%, and reoperations [27]. Other, rarely performed procedures include laparoscopic radiofrequency thermal volumetric ablation (RFVTA) under ultrasound guidance and endometrial ablation, which is expected to reduce bleeding [3]. Less available, but applicable options are interventional radiology procedures such as uterine artery embolization [29] and fibroid ablation with high-frequency ultrasound (FUS or HIFU) under magnetic resonance imaging (MRgFUS).

SUMMARY

Uterine fibroids are benign gynecological tumors, which in 70% of cases remain asymptomatic and may be accidentally detected during routine gynecological ultrasound diagnostics. When they generate symptoms such as pain, abnormal bleeding, anemia, micturition and defecation disorders, they constitute an indication for the implementation of therapeutic procedures. The presence of fibroids in the reproductive organs in women during the reproductive period contributes to infertility and obstetric complications, such as early pregnancy loss or recurrent miscarriages. Available treatment options include conservative, pharmacological and surgical treatments. The use of a specific method depends on many parameters, including the patient's age, her reproductive plans and the size, number and location of fibroids.

CONFLICT OF INTEREST

Author Contributions

All authors contributed to the conceptualization, formal analysis, research, methodology, writ-ing and editing of the original draft and read and agreed to the published version of the manu-script.

Funding

This research did not receive any external funding.

Statement of institutional review board

Not applicable.

Statement of informed consent

Not applicable.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or fi-nancial relationships that could be construed as a potential conflict of interest

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