



A COMPREHENSIVE REVIEW OF UTERINE FIBROIDS: PATHOGENESIS, DIAGNOSIS, TREATMENT, AND FUTURE PERSPECTIVES

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Abstract

Fibroid, myoma, and leiomyoma are interchangeable terms used to describe the most common gynecological tumors, which are benign neoplasms originating in the smooth muscles of the uterus. These tumors are a leading cause of hysterectomies. The prevalence of fibroids varies between studies and countries, ranging from 4.5% to 68.6%, with their occurrence increasing with age, peaking in one's early 40s. Age and race are the primary risk factors for uterine fibroids, with African American women experiencing higher incidence rates compared to Caucasian women. A family history of uterine fibroids also increases the risk of developing them. Lifestyle factors such as obesity, dietary choices, sedentary living, and smoking have been linked to fibroid occurrence, possibly due to their influence on estrogen production. Stress may also be a contributing risk factor for fibroids, as it is associated with a higher body mass index. A diet rich in red meat has been connected to a 70% increased risk of fibroids. These tumors are often asymptomatic, but when symptoms do occur, they typically manifest as menorrhagia, pelvic pain, pressure symptoms, or infertility. Diagnosis relies on a combination of medical history, physical examination, and imaging studies, such as ultrasound and MRI. Medical treatment, including hormonal and non-hormonal options, can be employed to manage symptoms, especially heavy menstrual bleeding. Surgical interventions, such as hysterectomy,

myomectomy, and uterine artery embolization, are available based on the patient's specific needs and desire for fertility preservation. It's worth noting that large fibroids can impact the uterine cavity's configuration, potentially affecting embryo implantation and increasing the risk of miscarriage.

1. Introduction

The terms fibroid, myoma, and leiomyoma are interchangeable and refer to the most prevalent gynecological tumors (1). Uterine fibroids are common noncancerous growths in the uterine wall that affect many women, particularly around the age of 50. While most fibroids do not cause symptoms, they can lead to heavy menstrual bleeding, pelvic discomfort, pressure on the bladder or rectum, and abdominal pain, impacting a woman's quality of life. In some cases, they can also interfere with fertility and lead to complications in pregnancy (2, 3). The growth of fibroids is influenced by ovarian activity and hormone levels, with most shrinking or not developing after menopause. Despite their noncancerous nature, they are a leading cause of hysterectomies, which come with significant healthcare implications. Therefore, their clinical significance lies in their potential to impact a woman's health, well-being, and quality of life. (1, 4-8).

Uterine fibroids UFs or uterine leiomyomas ULs are benign neoplasms of smooth muscles of the uterus. They are rich in the extracellular matrix, originate in myometrium cells, and due to their hormonally responsive nature, only occur during the reproductive years of women and regress down after menopause (6). In numerous cases, myomas can lack symptoms and are identified coincidentally during clinical examinations or imaging procedures (4). They are clinically important because they are a major cause of abnormal uterine bleeding that leads to hysterectomy i.e. removal of the uterus or other interventions (9). The occurrence of fibroids differs across various studies and nations ranging from 4.5% to 68.6% due to the nature of the research, diagnostic approaches employed, and the ethnic and racial composition of the analyzed population (6).

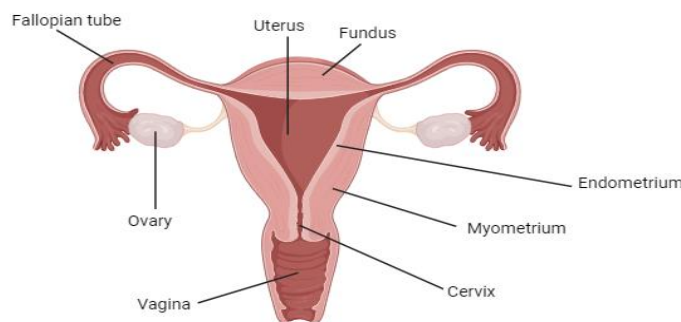


Figure 1. Labelled diagram of uterus.

The development of uterine fibroids, also referred to as uterine leiomyomas or myomas, remains a subject of incomplete comprehension, but it is influenced by several contributing factors. Genetic predisposition is believed to play a significant role in the formation of uterine fibroids. If you have a family history of fibroids, your risk may be elevated. Additionally, the growth of uterine fibroids is affected by the female sex hormones estrogen and progesterone (4). These hormones stimulate the muscle cells in the uterus, often leading to the growth of fibroids in response to these hormonal signals (10). Typically, fibroids exhibit growth during the reproductive years when hormone levels are elevated, and they may regress after menopause when hormonal levels decrease. Furthermore, various growth factors, including insulin-like growth factor, may also contribute to the development of fibroids by promoting cell division. Notably, uterine fibroids are more prevalent in particular racial and ethnic groups, especially among African American women (11) (12). The underlying causes of these disparities are not entirely clear but may involve a combination of genetic, hormonal, and environmental factors. While the precise role of environmental factors, such as dietary patterns and

exposure to environmental toxins, in the development of uterine fibroids is not fully understood, ongoing research explores their potential involvement in this process. Uterine fibroids can be classified based on their location within the uterus (13). Types of uterine fibroids includes Intramural, submucosal, Subserosal and Pedunculated Fibroids. The clinical manifestation of uterine fibroids can exhibit significant variation among individuals, and some women may not display any symptoms. Among the prevalent symptoms, heavy and extended menstrual periods, which have the potential to induce anemia, are noteworthy. Uterine fibroids can also introduce irregular or unpredictable menstrual cycles (5, 14). Furthermore, certain women may encounter a persistent, throbbing pelvic ache or discomfort, commonly concentrated in the lower abdomen or back. This condition can also lead to discomfort during sexual intercourse. In cases where fibroids are substantial in size, they might exert pressure on the bladder, resulting in heightened frequency of urination. Additionally, these fibroids may provoke an enlargement of the lower abdominal area, creating the illusion of pregnancy. Meanwhile, pressure on nerves within the back or pelvis can trigger backaches or leg pains. Moreover, uterine fibroids have the potential to disrupt fertility or contribute to recurrent miscarriages by affecting the embryo's ability to implant (15, 16).

Diagnosing uterine fibroids generally entails a comprehensive approach that encompasses reviewing your medical history, conducting a physical examination, and employing various imaging techniques. During the medical history assessment, you'll discuss any symptoms you've encountered, including heavy menstrual bleeding, pelvic discomfort, or alterations in your menstrual cycles. A pelvic examination is then performed to assess the size and shape of the uterus for any irregularities (17). To confirm the presence of uterine fibroids, healthcare providers often employ imaging tests, such as ultrasound, which provides detailed images of the uterus. In specific cases, additional diagnostic procedures like hysteroscopy, involving a thin, illuminated instrument to visualize the uterus directly, or a biopsy to obtain uterine tissue samples, may be conducted to gather more information or rule out other conditions (8). A comprehensive examination of the management choices for uterine fibroids encompasses a range of medications, which include Nonsteroidal Anti-Inflammatory Drugs, various hormone therapies, Gonadotropin-Releasing Hormone Agonists, tranexamic acid, and other options. These medications primarily focus on symptom management by alleviating pain and reducing excessive bleeding. There are also diverse minimally invasive procedures that can be contemplated for the treatment of uterine fibroids, such as Uterine Artery Embolization, myomectomy, Radiofrequency Ablation, and Laparoscopic Surgery, among others (6). In cases of severe fibroids or when other interventions prove ineffective, a hysterectomy, a surgical procedure involving the removal of the uterus, may be advised. Many women with fibroids have successful pregnancies without any issues, but uterine fibroids can have varying effects on fertility and pregnancy. Fibroids can sometimes lead to a higher risk of miscarriage, preterm birth, fetal growth restriction, etc (18).

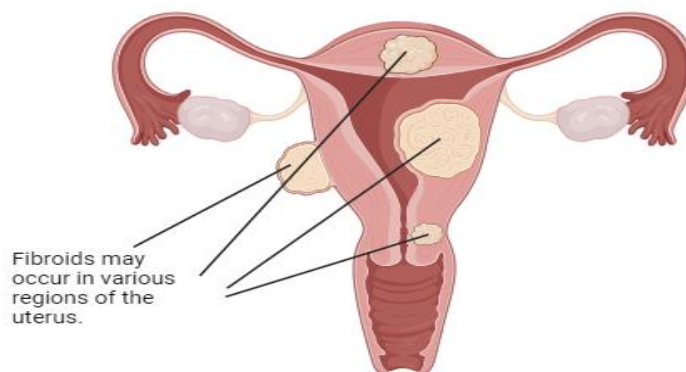


Figure 2. Uterine fibroids.

2. Pathogenesis:

The incidence of UFs declines after menopause. Its incidence increases with age, peaking in the early 40s. However, this could be a result of previously asymptomatic fibroids becoming more noticeable

after years of growth and exposure to endogenous steroid hormones. The main risk factors for uterine fibroids are age and race (6). Lifestyle choices can have a significant impact on the risk of fibroid development. Obesity, dietary habits, sedentary lifestyle, and smoking have shown associations with the incidence of uterine fibroids. Additionally, diet and physical activity have been connected to uterine fibroid occurrence, although the extent to which they influence body weight and whether they independently constitute risk factors are subjects that require further clarification (10, 19).

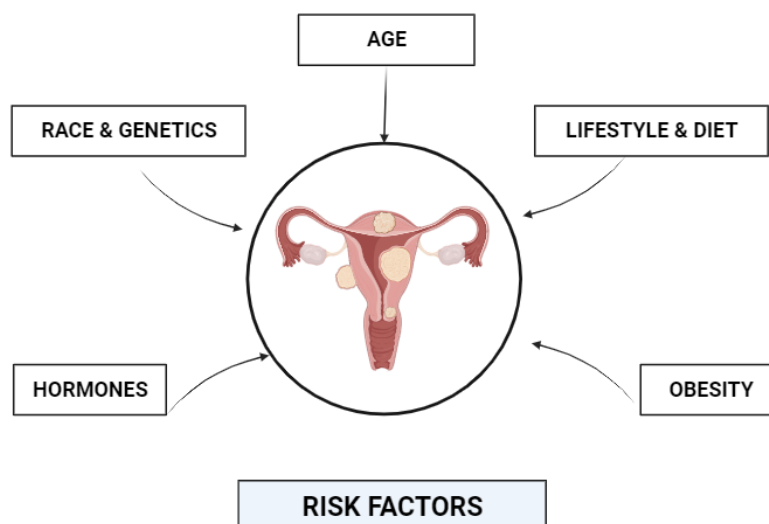


Figure 2. Uterine fibroid risk factors

2.1. Age

Age is a significant risk factor for the development of fibroids, because Estrogen and progesterone, two hormones that play a role in fibroid development, are most active during a woman's reproductive years. Related to age, fibroids usually do not occur in pre-pubertal girls, but are seen to develop in teenage girls having the start of puberty and its incidence increases as the age increases till menopause, typically occurring between the ages of 30 and 50 (4). The incidence of uterine fibroids by age 35 was found to be 60% among African American women, increasing to >80% by age 50, whereas Caucasian women have an incidence of 40% by age 35 and almost 70% by age 50. Advancing age increases the incidence and the number of fibroids manyfold and is thus expected to be diagnosed in greater numbers in older age (20). Although fibroids might decrease in size or exhibit reduced symptoms after menopause due to decreased hormone levels, they can persist in certain instances. Hence, age continues to play a role in managing fibroids after menopause. As women age, fibroids have the potential to enlarge, potentially resulting in more pronounced symptoms (21).

2.2. Race and Genetics

African-American women tend to have a higher prevalence of fibroids compared to women of other racial backgrounds. When talking about race, the Incidence of UFs is more common in black women, than in white women, approximately 2-3 times higher, but the reason is unknown, also black women have more severe symptoms than white women (7). Screening studies show that there is a 10-year age gap in developing UFs between black and white women. It appears in a higher percentage of women of African-American descent. African American women have a higher incidence, larger tumors at diagnosis, more severe symptoms, and earlier age at diagnosis than white, Hispanic, or Asian American women (19). The incidence of UFs by age 50 is more than 80% among African American women, compared with 70% in Caucasian women (21).

A family history of fibroids also increases the risk of uterine fibroids. Women with a family history of uterine fibroids have three times more risk of developing UFs than those with no history. Likewise,

women having hypertension have five times more risk of developing UFs. Inherited genetic factors can enhance the vulnerability to developing fibroids across generations (22). The genetic landscape of uterine fibroids is intricate, encompassing a network of genes and pathways. The interplay between genetic variations and hormonal factors can impact the initiation, growth, and clinical manifestations of fibroids. Studies into somatic genetic alterations revealed that 50% of fibroids have chromosomal abnormalities. Genetic alterations have been described in 12 out of 26 chromosomes (23). The hereditary defects in the fumarate hydratase FH, Birt-Hogg-Dube BHD, and tuberous sclerosis complex 2 TSC2 genes mainly contribute to the development of this tumor. It is estimated that 40% to 50% of uterine fibroids have cytogenetic abnormalities that are tumor-specific. Several studies reported different genetic alterations, such as deletions of chromosomes, trisomy of chromosomes, reciprocal translocation of chromosomes, and monosomy of chromosomes (18) (24).

2.3. Hormones

Uterine fibroids are sensitive to sex steroid hormones, especially estrogen, for growth and development (21). UFs are typically found in the reproductive years, which led to the assumption that estrogen is the main feeder of uterine fibroids. A more accurate analysis has revealed that progesterone action is also required for the full development and proliferation of fibroid cells. UFs can become symptomatic starting after puberty, when endogenous estrogen levels rise, and UFs regress after menopause. UFs have higher concentrations of estradiol, aromatase, progesterone receptor PR, and estrogen receptor- α ER- α . ER is abundantly expressed in uterine fibroids, which ensures considerable responsiveness to the circulating estrogens (11). Regarding PR, studies have found increased expression levels in fibroids compared to matched myometrial samples. Estrogen acts primarily by increasing cell responsiveness to progesterone. UFs also grow in response to progesterone, which typically has a suppressive effect on the myometrium. Serum levels of estrogen and progesterone are similar in women with and without UFs (25). However, African American women have 18% higher estradiol levels compared with Caucasians and no difference in progesterone levels. The exact role of progesterone in UF's pathogenesis is still poorly understood. However, estrogen is essential for UF cell growth. During gestation, uterine leiomyomas may be expected to grow in response to the very high levels of circulating estrogens and progesterone of placental origin (19).

2.4. Obesity

Obesity impacts various pathways that contribute to the development of uterine fibroids. Higher body mass index BMI is associated with a modest increase in the risk of fibroids. Obesity is associated with an increase in estrogen production. Because estrogen is produced by adipose tissues, due to obesity adipose tissues increase and it increases the production of estrogen, which eventually promotes fibroid growth (26). Obesity can also result in elevated insulin levels due to reduced responsiveness of cells to insulin, and increased insulin levels have a stimulating effect on fibroid growth. Hyperinsulinemia can influence the development of fibroids by promoting myometrial smooth muscle cell proliferation and increasing circulating levels of ovarian hormones (21). A higher incidence of surgically treated fibroids has been found in women who gained >20 kg compared with women who gained <10 kg and a reduced risk has been found in those who lost weight. Inflammatory mediators can also be released by adipose tissue or fat cells that influence fibroid growth (26, 27).

2.5. Lifestyle and diet

Maintaining a healthy weight is very important in reducing the risk of fibroids. Physical activity, stress, diet, smoking, alcohol, and caffeine consumption seem to modulate molecular mechanisms that are involved in the development and growth of fibroids (28). Exercise may be protective for fibroids because it can help regulate hormonal levels and also improve insulin sensitivity which can influence fibroid risk. In women who perform regular exercise, the risk of fibroid seems to be lower than in women who do not exercise (21). Stress is a potential fibroid risk factor. Stressful experiences have been associated with high BMI, obesity, alcohol consumption, and elevated blood pressure, all

factors that increase the risk of myoma. Stress also influences hypothalamic-pituitary-adrenal and gonadal axes, thus affecting the bioavailability of estrogen and increasing the risk for fibroid development (7). Diet also plays a role in the risk of developing fibroids. There is a 70% increased risk of fibroids with a diet heavy in red meat because such diets can contribute to inflammation, insulin resistance, and hormonal imbalances, all of which can lead to fibroid growth. whereas green vegetable and fruit intake reduces the risk of fibroids, because of the high number of antioxidants in them. Sufficient dietary fiber intake can also help in the removal of excess estrogen from the body. Fruits and vegetables contain various nutrients that may decrease fibroid risk through inhibition of proliferation, apoptosis, or hormone-dependent pathways sexually transmitted infections also develop the risk of fibroids (13).

3. Clinical presentation

Myomas, or uterine fibroids, can appear as solitary or multiple growths in the uterus, with varying sizes and locations. They are categorized into subgroups: Sub serosal myomas grow on the outer uterine surface, potentially causing pelvic discomfort. Intramural myomas, the most common, form within the uterine muscle and can lead to an enlarged uterus and menstrual issues. Submucosal myomas project into the uterine cavity, causing abnormal bleeding and fertility problems. Pedunculated fibroids, attached by a stalk, can be sub serosal or submucosal, posing risks like pain and torsion. These subtypes demonstrate the diversity and clinical implications of myomas(1, 29, 30). The clinical presentation of uterine fibroids is diverse and varies from woman to woman. Up to 70% of fibroids are asymptomatic and may be incidentally diagnosed during radiologic procedures conducted for other indications. The clinical presentation of Symptomatic uterine fibroids depends on size, location, and number of fibroids, as well as on individual patient characteristics (5). The four major complications associated with fibroids are menorrhagia, pelvic pain, pressure symptoms, and infertility. While others are abdominal enlargement, painful intercourse, anemia, urinary retention, leg swelling, and back pain. Several studies have shown that women with fibroids have a higher risk of developing emotional distress, depression, and anxiety, which can strongly impact their quality of life. The presence of uterine fibroids can lead to various clinical challenges (6). The most common symptom of uterine leiomyoma is abnormal uterine bleeding AUB. The mechanism of leiomyoma associated AUB is unknown. Abnormal or excessive menstrual bleeding i.e., menorrhagia may cause prolonged periods and anemia. Pelvic discomfort or pain occurs, especially if fibroids are large. Larger fibroids can also exert pressure on adjacent organs, leading to urinary frequency, urinary urgency, and other bowel disturbances. Those fibroids which are present within the uterine cavity, can interfere with implantation and increase the risk of miscarriages, affecting fertility and pregnancy (31) (15).

4. Diagnosis

Diagnosis depends on a combination of medical history, physical examination, and imaging studies such as ultrasound or MRI. Diagnostic methods commonly used for uterine fibroids are (2, 32):

4.1. Clinical Examination

The clinical examination provides the physical characteristics of the uterus. It involves **the** thorough medical history of the patient to understand the symptoms and severity of the condition, including menstrual patterns, reproductive history, and any other medical conditions if present (17). Visual Inspection is done to inspect the external genitalia, for any visible abnormalities, like the enlarged uterus. A pelvic examination is done to check the internal reproductive organs and to assess the size, shape, and condition of the uterus (1).

4.2. Imaging Studies

4.2.1 Ultrasound

Ultrasound serves as the frequently utilized initial non-invasive radiological technique for visualizing uterine fibroids because it can provide information about the number, size, location, and

characteristics of fibroids and is generally sufficient for their diagnosis (18). It allows us to determine whether fibroids are submucosal, intramural, or sub serosal (8). Transvaginal ultrasound, also known as abdominal ultrasound, is often the initial imaging method used to detect fibroids. It is the most commonly utilized technique due to its widespread availability, user-friendliness, and cost-effectiveness. It is especially beneficial for evaluating the expansion of myomas, to confirm the diagnosis and exclude the possibility of ovarian neoplasm (1, 33).

4.2.2 Magnetic Resonance Imaging MRI

MRI stands out as the most precise technique for evaluating the uterus, offering comprehensive details regarding the dimensions, position, quantity, and blood supply of leiomyomas, in addition to identifying the presence of other uterine abnormalities (5). It gives a better visualization of individual myomas, but it is a very costly procedure. Its sensitivity and specificity is close to 100%, so it is valuable for surgical planning (6, 34)

4.3.3 Computerized Tomography CT scan

CT imaging offers restricted utility in clearly depicting the positioning of myomas about the endometrium or myometrium. Utilizing X-ray technology, CT scans produce detailed cross-sectional images. However, they are not the predominant imaging method employed for this purpose, primarily due to the widespread availability of more appropriate techniques like MRI and ultrasound (1) (35). Hysteroscopy is a less invasive endoscopic technique utilized to observe the interior of the uterus. It facilitates direct observation of the uterine cavity, enabling healthcare professionals to evaluate the existence, positioning, and attributes of fibroids (36). In the hysteroscopy procedure, a thin lighted tube hysteroscope is inserted through the vagina and cervix to visualize the inside of the uterus. It is particularly helpful for diagnosing submucosal fibroids (37, 38).

Laparoscopy is a minimally invasive surgical procedure. A small camera is inserted through a small incision near the navel to view the pelvic organs. It helps to identify fibroids on the outer surface of the uterus i.e. sub serosal fibroids but it may not be ideal for diagnosing submucosal fibroids (39) (18).

5. Management

Medical treatment is initially used to relieve heavy menstrual bleeding. It improves a woman's quality of life and reduces subsequent surgical morbidity. Medical treatment is also reducing the uterine volume which can facilitate surgical management (23). The primary aim of this is to decrease abnormal uterine bleeding AUB which occurs due to fibroids. A range of medical management strategies are available for the treatment of symptomatic fibroids, and it is classified into two major categories, hormonal and non-hormonal (40). Hormonal therapies include combined hormonal contraceptives, gonadotropin-releasing hormone GnRH agonists, GnRH antagonists, progestins, selective progesterone receptor modulators SPRMs, and aromatase inhibitors. Non-hormonal options are tranexamic acid, NSAIDs (6).

5.1. Hormonal therapies

5.1.1 Combined hormonal contraceptives

Combined hormonal contraceptives contain both estrogen and progestin. They are used primarily for contraception but also can be beneficial for uterine fibroids by decreasing bleeding. They are commonly used for the treatment of AUB, including in women with uterine fibroids (32). They work by keeping the endometrium thin and decreasing the amount of endometrial shedding during the menstrual cycle. Reduced endometrial thickening can ultimately lead to lighter blood loss, but it is not suitable for all women with fibroids (6).

5.2.2 GnRH agonist

Gonadotropin-releasing hormone GnRH agonists are effective medical therapies for uterine fibroids and are generally used preoperatively for 3–6 months in combination with iron therapy to facilitate

endoscopic or transvaginal surgery (18). GnRH agonists are used for managing myomas or fibroids. They decrease the production of estrogen and progesterone hormone (7). They work by first increasing the release of gonadotropins i.e. follicle stimulating hormone FSH and luteinizing hormone LH, which is followed shortly by desensitization and downregulation, leading to decreased production of gonadotropins which subsequently reduces the level of estrogen and progesterone hormone, and this produces a state clinically resembling the menopause (1, 41). These agents significantly reduce uterine size, generally 35% to 65%, and cause amenorrhea in most women. However, after discontinuation, there is rapid resumption of menses and return to pretreatment uterine volume. Thus, GnRH agonists are primarily used to allow a woman to prepare for surgery by shrinking fibroids and reducing anemia related to uterine bleeding (36, 42).

5.2.3 GnRH antagonist

GnRH antagonists have the added advantage of the rapid onset of clinical effects without the flare effect as compared to GnRH agonists. GnRH antagonists compete with GnRH for receptors on gonadotropic cell membranes, inhibit GnRH-induced signal transduction, and, consequently, inhibit the secretion of GnRH (33). Thus, the initial flare effect seen with GnRH agonists does not occur with these drugs. Currently, however, GnRH antagonists are only licensed for ovulation induction protocols and long-acting preparations are not available (18). While GnRH agonists work by downregulation and desensitization of the GnRH receptors, GnRH antagonists act by competitive blockage mechanism of the GnRH receptors in the pituitary gland. It causes a rapid and reversible decrease in the production of LH and FSH hormones, leading to fibroid shrinkage and a decrease in heavy menstrual bleeding, pelvic pain, and pressure. They are only used for short-term symptom relief because the use of GnRH antagonists as a treatment for fibroids requires further evaluation (5, 43).

5.3.3 Progestins

Progestins are synthetic forms of progesterone hormone. The most common progesterone-only treatments for AUB involve the use of oral progestins i.e. norethindrone acetate 5 to 10 mg daily; medroxyprogesterone acetate 10 mg daily; megestrol 40 mg daily and progesterone-releasing IUDs (5). They bind to progesterone receptors and modulate the effects of progesterone, by altering the uterine lining, affecting the growth of fibroids (32). They are used to treat dysfunctional uterine bleeding associated with fibroids by reducing endometrial hyperplasia. Both natural progesterone and synthetic progestins decrease menstrual blood loss in women with fibroids (23, 44).

5.3.4 Selective Estrogen Receptor Modulators SERMs

Selective Estrogen Receptor Modulators SERMs are nonsteroidal estrogen receptor ligands with both agonist and antagonist effects depending on the tissue. They are primarily known for their use in breast cancer treatment, for example, tamoxifen is the widely used SERM in breast cancer gives an antagonist effect but has agonist properties on the uterus (45). While raloxifene exerts antiestrogenic effects in fibroids by reducing cell proliferation and has no endometrial agonist activity, it is the most studied SERM for the treatment of leiomyomata. However the use of SERMs for uterine fibroids is still being studied, and there are no specific SERMs approved solely for fibroid treatment (1, 43).

5.3.5 Androgens

Danazol is a synthetic androgen, most commonly used for the medical treatment of endometriosis, and it can be useful by inducing amenorrhea to control anemia due to myoma-related menorrhagia (46). Danazol is chemically related to 17- α ethinyl testosterone. It acts by competing with natural androgens, like progesterone, and glucocorticoids in receptor binding. Danazol causes a reduction in fibroid volume by 20% to 25%. Although the use of danazol for the shrinkage of uterine fibroids has been described in cohort studies, a systematic review did not find any randomized trials comparing its efficacy with placebo or other treatments (7).

5.3.6 Estrogen receptor antagonists

Estrogen receptor antagonists block the effects of estrogen by binding to estrogen receptors, they are primarily used in the treatment of receptor-positive breast cancer, but estrogen receptor antagonists like Fulvestrant also have a potential role in managing uterine fibroids. Fulvestrant promotes degradation and down-regulation of estrogen receptors in the uterus and slows down fibroid growth. However, Fulvestrant was not as effective as the GnRH agonist goserelin in reducing fibroid and uterine volume and inducing amenorrhea (1).

5.2. Non-hormonal therapies

5.2.1 Aromatase inhibitors

Aromatase inhibitors are primarily used in the treatment of hormone receptor-positive breast cancer by inhibiting the enzyme aromatase, which converts androgens into estrogens. By reducing estrogen levels, they indirectly impact the growth of estrogen-dependent tissues, including fibroids (45). Aromatase inhibitors such as letrozole 2.5 or 5 mg orally once a day and anastrozole 10 mg once a day, induce a hypoestrogenic state and result in thinning of the endometrial lining and reduced menstrual bleeding(47). This class of agents is better tolerated than GnRH agonists, with a lower incidence of serious short-term anti-estrogenic adverse effects. The use of letrozole reduced fibroid volume by 46% and the use of a GnRH agonist by 32% after 12 weeks of treatment, although these results were not statistically significant (5, 48).

5.2.2 Selective progesterone receptor modulators SPRMs & Anti progestins

Selective progesterone receptor modulators SPRMs & and progestins are Progesterone receptor ligands having agonist, antagonist, or mixed activity. They act at the level of the peripheral progesterone receptors by inducing apoptosis, inhibiting cellular proliferation of the fibroid, and thinning the endometrial lining (45, 49). Several clinical trials have investigated the efficacy and safety of SPRMs, showing that mifepristone, UPA, asoprisnil, and telapristone acetate are all effective in reducing fibroid and uterine volume. Fibroid volumes are reduced by 17%–57% and uterine volume by 9%–53% following treatment. SPRMs control tumor volume for a prolonged period of up to 6 months after discontinuation of treatment. They suppress bleeding more rapidly than GnRH analogs in women with fibroids (23, 41). SPRMs are rapidly becoming the standard medical option for fibroids and are used preoperatively and as a short-term medical therapy in most of the world. They are particularly useful for women who want to avoid the estrogen-related effects of other hormonal therapies (18, 44).

5.2.3 Tranexamic acid

Heavy menstrual bleeding associated with uterine fibroids is at least partly due to local fibrinolysis, therefore, antifibrinolytics are also useful agents. The synthetic lysine derivative, tranexamic acid, is an antifibrinolytic agent and it promotes the formation of blood clots. It is one of the oldest and most globally available treatments of AUB (50). Moreover, tranexamic acid is well tolerated and has a favorable safety profile. It prevents fibrin degradation at the level of the plasminogen lysine receptor site, which leads to a reduction in menstrual blood flow and improvement of symptoms (51). It is associated with rare and mild adverse effects including gastrointestinal and musculoskeletal symptoms, and it is contraindicated for patients with color blindness, active bleeding, a history of intravascular clotting, or hypersensitivity to the medication. It can be particularly helpful for women who prefer non-hormonal treatment options (46).

5.2.4 non-steroidal anti-inflammatory agents

Non-steroidal anti-inflammatory Drugs NSAIDs are commonly used to relieve pain and reduce inflammation. While NSAIDs are not a specific treatment for uterine fibroids themselves, they can help manage some of the symptoms associated with fibroids. NSAIDs work by inhibiting the enzyme cyclooxygenase and lowering the production of pro-inflammatory prostaglandins (17). They have been shown to decrease the painful menses and heavy menstrual bleeding associated with fibroids

(48). They are also inexpensive and are available without a prescription. The most commonly used agents are ibuprofen and naproxen which are most efficacious when started a day or two before the onset of menses and continued for the duration of menstruation (6). However, they are less effective in reducing menstrual bleeding than tranexamic acid and combined hormonal contraceptives. They provide symptomatic relief and do not directly affect fibroid growth. NSAIDs should be avoided in women with known hypersensitivity to this class of medications, active gastric or peptic ulcers, or renal disease (50).

5.3. Surgical interventions

Various surgical options are available for treating uterine fibroids, depending on the patient's needs, fibroid characteristics, and desire for fertility preservation. Surgical approaches for treating uterine fibroids are:

5.3.1 Hysterectomy

Hysterectomy is the only definitive surgical treatment as a permanent solution for symptomatic fibroids because it eliminates both the symptoms and the chance of recurrence. This is an appropriate procedure for those women who have completed childbearing and inappropriate for those who simply wish to retain their uterus or desire future pregnancies (3, 37). Following hysterectomy, the majority of women report a significant improvement in quality of life and symptomatology as early as 3 months after surgery. The selection and method of performing a hysterectomy, whether through the abdominal, laparoscopic, or vaginal route, should be determined by the surgeon's expertise, experience, and comfort level, as well as by adherence to clinical practice guidelines. Whenever possible, the most minimally invasive approach should be utilized. Abdominal hysterectomy is done through an abdominal incision and it is often recommended for larger fibroids (18). Vaginal hysterectomy is the removal of the uterus through the vaginal canal. The vaginal approach has the advantages that the patient will have no abdominal scar, decreased post-operative discomfort, decreased hospital stays, decreased risk of infection, and overall decreased cost. Vaginal hysterectomies are not recommended for the patient who has a uterus that is larger than 10 to 14 weeks gestational size (5). Laparoscopic or Robotic-Assisted hysterectomy is a minimally invasive procedure using small incisions and specialized instruments. Vaginal and laparoscopic hysterectomies are recommended as a first line because they are associated with shorter hospital stays, faster recovery, and better patient satisfaction. Overall, hysterectomies are associated with a relatively low number of complications, including a 0.4% incidence of major complications (6). Although the rates of hysterectomy are decreasing, the lifetime prevalence in the United States is 45%. The main advantages of hysterectomy include the elimination of the risk of the growth of new fibroids, in addition to treating other diseases including adenomyosis, and a remarkable improvement in quality of life over the following 10 years. However, long-term health consequences can be associated with hysterectomy, including cognitive impairment and dementia, even with ovarian conservation (1, 52).

5.3.2 Myomectomy

Myomectomy involves removing the fibroids but leaving the uterus intact, an alternative to hysterectomy for women who wish to retain their uterus. It is most often offered to patients who desire future fertility but is also considered by those who have completed childbearing but wish to retain their uterus (10). Myomectomy provides a temporary reduction in uterine volume and improvement of symptoms in up to 80% of women but approximately 27% risk associated with recurrence after removal of a single fibroid, and greater than 50% in the case of multiple fibroids. Overall Myomectomies are associated with a low rate of complications only 1%–5% (53). Different approaches such as open / Abdominal, hysteroscopic, and laparoscopic can be undertaken to remove the fibroids. Open myomectomy is a traditional surgery with a larger abdominal incision for the removal of the fibroid. Hysteroscopic myomectomies are the procedure of choice for the removal of smaller type submucosal fibroids. Laparoscopic myomectomy should be the standard procedure for intramural and sub serosal fibroids. This approach is associated with lower blood loss and morbidity,

shorter hospital stays, and less post-operative pain than open myomectomies (5). The disadvantage of myomectomy is the risk that new myomas will form. Thus, myomectomy successfully relieves the symptoms of myomas, but it does not affect the underlying process. Abdominal myomectomy also permits healthy pregnancies after surgery. The risk of uterine rupture after myomectomy is very low 0.02 %. For women with uterine size of 16 weeks or less and a small number of sub serosal or intramural fibroids, laparoscopic myomectomy may be an option (18, 54).

5.3.3 Uterine-artery Embolization UAE

Uterine-artery embolization UAE is a novel technique for the treatment of myomas. It is a non-surgical procedure in which tiny particles are injected into the uterine arteries to block blood flow to the fibroids, which causes them to shrink (9). A catheter is introduced through a minor incision, frequently located in the groin region, and skillfully navigated to the uterine arteries with the aid of imaging methods. Subsequently, minute embolic particles are introduced into these arteries, leading to the obstruction of blood flow to the fibroids. Initial studies show that UAE is useful in controlling menorrhagia and provides a more variable response in reducing uterine volume (55). Serious complications including major sepsis or death are rare, but may not be suitable for all women, particularly those desiring future pregnancies (7, 56).

5.3.4 Myo lysis

Myo lysis is a variation on the technique of myomectomy in which the fibroid tissue is coagulated rather than removed. It involves using heat, freezing, or electric current to destroy fibroid tissue, causing the targeted destruction or removal of fibroid tissue (46). It can be performed through different approaches, including laparoscopy or hysteroscopy. It may be suitable for women who want to preserve their fertility or avoid extensive surgery (10). Although this technique is easier to master than removal, localized destruction without repair may also increase the chance of uterine rupture and adhesion formation (5).

5.3.5 Endometrial ablation

Endometrial ablation is a minimally invasive surgical technique used for the destruction of the endometrial lining and can be used in women who do not want future pregnancies. It is not a treatment for fibroids themselves but is used to manage heavy menstrual bleeding associated with fibroids (6). It can be used either in combination with hysteroscopic myomectomy or alone in women with or without submucosal fibroids (10). Endometrial ablation is less preferable because the procedure cannot be reversed and does not provide contraception, women are at risk for extrauterine pregnancies following endometrial ablation. It is indicated for those patients with leiomyomas who have small submucosal fibroids less than 2 cm in diameter (18). This method is contraindicated for patients with multiple submucosal fibroids greater than 2 cm in diameter, or for patients desiring to maintain future fertility. It is associated with up to 90% satisfactory improvement of uterine bleeding and a low rate of complications i.e. 1%–2% including uterine perforation and bleeding (9, 45).

6. Impact on fertility

Uterine fibroids can significantly influence fertility and the outcomes of pregnancy. Fibroids situated within the uterine cavity i.e., submucosal fibroids can hinder the successful implantation of embryos, diminishing the likelihood of a successful pregnancy. Similarly, large fibroids have the potential to modify the configuration of the uterine cavity, impacting embryo implantation and elevating the risk of miscarriage (57). These fibroids can also disrupt the normal blood flow to the uterus and endometrium, posing a barrier to implantation and causing fertility issues. While not all women with fibroids encounter fertility challenges, there is evidence suggesting that fibroids could contribute to lower fertility rates compared to those without fibroids (58).

Moreover, the presence of submucosal fibroid is linked to an increased chance of miscarriage during the early stages of pregnancy (58). When fibroids are large or located near the cervix, they may increase the probability of preterm labor and preterm birth. Depending on where they are situated,

fibroids can lead to complications like placental abruption, where the placenta detaches prematurely, or placenta previa, characterized by the placenta covering the cervix. Notably, larger fibroids might even obstruct the birth canal, necessitating a delivery via cesarean section C-section (59).

7. Future directions

There could be many future directions and research avenues in the field of uterine fibroids. The future of fibroid treatment may involve a more personalized approach. Researchers are likely to continue investigating the genetic and molecular factors that contribute to fibroid development. This knowledge may lead to targeted therapies based on a patient's specific genetic profile. Advances in non-surgical approaches to treating fibroids may include the development of new medications, hormonal therapies, or targeted therapies that can shrink fibroids without the need for surgery (20). To investigate the genetic and molecular mechanisms that are involved in the development and growth of uterine fibroids. Identification of specific genetic markers associated with fibroids could lead to targeted therapies. To examine the role of estrogen and progesterone hormone, and their influences also give rise to more effective hormonal treatments. Immune therapies can also offer new treatment options, because of the potential involvement of the immune system in the development of fibroids (18). Personalized medicine based on a patient's genetic profile and the specific characteristics of their fibroids could lead to more effective therapies. Non-invasive or minimally invasive treatment options such as focused ultrasound, uterine artery embolization, and radiofrequency ablation aim to reduce the need for surgery, future developments may focus on refining these techniques and making them even less invasive. New medical therapies can also be developed that target specific pathways to avoid the side effects. To identify strategies for prevention from those lifestyle and dietary factors that may contribute to the development of fibroids. Healthcare systems may conduct more cost-effectiveness studies to determine the best approaches to fibroid management and treatment (60) (45).

8. CONCLUSION

Uterine fibroids, benign neoplasms of uterine smooth muscle, are influenced by various risk factors, including age, race, genetics, hormones, and lifestyle. They can lead to symptoms such as heavy menstrual bleeding, pelvic pain, and infertility. Diagnosis involves a comprehensive approach, including medical history, physical examination, and imaging. Treatment options range from medical, minimally invasive to surgical interventions, with an evolving landscape in fibroid research. Personalized treatments based on genetics, non-surgical alternatives, and strategies for prevention are on the horizon. These advancements aim to offer women more precise and less invasive care, ultimately enhancing their well-being. Understanding the complex mechanisms underlying fibroid development is key to providing effective care for these common gynecological tumors.

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