**Uterine fibroid management: from the present to the future**

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**ABSTRACT**

Uterine fibroid is a leiomyoma (benign tumour of smooth muscle tissue) originating from the uterus's smooth muscle layer (myometrium). According to a recent study, it is estimated that about 70 to 80% of women worldwide suffer from uterine fibroid disease over their lifetime. It is most common in 30-to 40-year-old women but can occur at any age. Fibroids can grow as a single nodule or in clusters. Clusters of fibroids can range in size from 1 mm to more than 20cm (8 inches) in diameter or even larger. In comparison, they can get as large as a watermelon. This growth can develop within the uterine lining, inside the main organ, or even on the outer surface. Symptoms of uterine fibroid are followed by a painful, heavy menstrual flow, a pressure in the lower abdominal region, frequent urination, chronic vaginal discharge, infertility, and anaemia. The aetiology is unknown. There are many more surgical and medical treatments available, but these therapies are complicated and expensive. These are a direct burden on women who have the condition. This paper provides a thorough overview of recent developments in uterine fibroids research, concentrating on risk factors, the genesis of the condition's development, pathogenetic pathways, and available therapies. In addition, we outline the latest management approaches.

**Keywords:** Uterine fibroid, leiomyoma, nodule, genesis, managemental approach.

1. **INTRODUCTION**

The most prevalent type of benign uterine tumors is uterine fibroids, commonly known as leiomyomas or myomas[1]. having a 20%–40% estimated incidence in females during their reproductive years [2] The prevalence rises with age, reaching its peak in females in their 40s. [3] According to their location and size, uterine fibroids present a variety of symptoms in 30–40% of patients. They may result in heavy & painful menstrual bleeding, anemia, which could be fatal [4], mass in the pelvis, pain in the pelvic region, infertility, bulk symptoms, and obstetric issues [5] Our paper aims to examine the existing knowledge on uterine fibroids with a focus on current facts for management. in females

1. **Epidemology**

according to recent American research. More than 80% of women of African heritage and those with Asian ancestry have fibroids diagnosed by ultrasound. At the age of 50.6 years, nearly 70% of white women [6] Undiagnosed fibroids are present in 43–59% of premenopausal women aged 35–49, according to a cross-sectional study conducted in the US [7]. The probable incidence of UFs ranges from 20 to 77%; the estimated prevalence among women under the age of 35 is between 40 and 60%; and the estimated prevalence among women over the age of 50 is between 70 and 80%. Additionally, a previous study found that American black women have a higher likelihood of developing this condition (59%) [8].

Although fibroids are a possibility for all women of reproductive age, black women are more likely than women of other racial groups to have them. Additionally, more severe symptoms are more likely to affect black women, have more or larger fibroids, and experience their symptoms at a younger age along with their advantages, disadvantages, and indications [9].

1. **Risk factors**

**Age**

#### Age poses a considerable risk for the emergence of fibroids. Pathologically confirmed, there is a greater prevalence of fibroids as people get older, peaking at age 50. Before puberty, myomas do not develop, and as menopause approaches, their frequency declines. Pregnant women who had early pregnancy screening provided the data on young (19–35-year-old) women [10]. According to a US study, uterine fibroids affect African-American women at a rate of 60% by age 35, rising to >80% by age 50, compared to Caucasian women at a rate of 40% by age 35, rising to 70% by age 5 [1].

#### Obesity

Obesity is a chronic disease that today causes a large amount of disability worldwide and is a big public health issue. Premenopausal women with excessive body fat may develop UFs due to a number of reasons, like decreased production of sex hormone-binding globulin, changes in the metabolism of sex hormones, and systemic inflammation. An earlier study examined the positive relationship between obesity and the prevalence and risk of UF’s [11].

**Vitamin D deﬁciency/insufﬁciency**

Three main studies demonstrated that vitamin D levels are much lower in the sera of uterine fibroid patients, suggesting vitamin D may be linked to the pathogenesis of uterine fibroids. [12] According to earlier studies, low vitamin D levels were associated with UL in white people but not in black ones. These findings could be explained by differences in sun exposure, racial variances, and personal characteristics [13]. Calcium hemostasis is thought to be mostly regulated by vitamin D. Several studies have indicated that 1,25-dihydroxyvitamin D is an effective anti-tumour drug that suppresses the growth of leiomyoma cells in culture and reduces the size of uterine leiomyomas in live animal models [14].

**Parity and pregnancy**

# Although a direct protective benefit of pregnancy has been shown, the mechanism is poorly understood. There have been some hypotheses that tiny lesions may undergo selective apoptosis during postpartum uterine remodelling. Ischemia has also been suggested as a possible mechanism during parturition. This suggests that fibroid tissue may be particularly vulnerable to ischemia during both parturition and remodelling [2].

# Caffeine, tobacco and alcohol

The BWHS is the first prospective cohort study to examine the causes of uterine leiomyomas in a large population of US black women. Current alcohol use, particularly beer intake, was positively linked with uterine leiomyomata risk. Cigarette smoking and caffeine consumption were unrelated to overall risk overall.[15] The precise processes by which drinking alcohol raises the possibility of myoma remain a mystery. The following are hypothesised, but as of yet unidentified, mechanisms through which increased alcohol consumption may favour the growth of myomas associated with hormones: an increase in endogenous oestrogen levels through a reduction in oestrogen metabolism and an interaction with a luteinizing hormone, with subsequent modulation of ovarian estradiol release [16].

**Genetic factor**

In accordance with the latest findings, up to 40% of uterine fibroids have some chromosomal abnormalities. Genetic changes that result in the overexpression of HMGA2, disruption of the locus, and biallelic deletion of FH, which codes for the tricarboxylic acid cycle enzyme fumarate Shydratase, have been linked to a proportionately decreased percentage of uterine fibroids [5].

**Hypertension**

The previous meta-analysis revealed a significant association between UFs and the prevalence of hypertension [pooled OR = 1.44, 95% CI: 1.17–1.75, P = 0.0004; I2 = 68%]. Thus, UFs may be associated with the prevalence of hypertension. (17) In a prospective cohort analysis, we discovered that pregnant women with uterine fibroids had higher longitudinal SBP and DBP. Women with uterine fibroids diagnosed before the 20th week of pregnancy had a greater risk for HDP during pregnancy than those without fibroids. These findings might help identify women who are at high risk for HDP early on. [18].

**Hormonal factors**

The Swan study investigated the relationship between uterine fibroids and hormonal imbalance, and they addressed midlife women who had never previously reported having fibroids. Estradiol (E2) was linked to an increased chance of incident fibroids. Conversely, in women with high E2, the likelihood of recurring fibroids was reduced [19]

**Uterine infection**

A previous study explored the correlation between RTIs and fibroid size, quantity, and overall volume. Self-identified fibroids and respiratory tract infections did not seem to have any clear connections. For a deeper comprehension of relationships between RTIs and fibroids, studies using serology, a biological indicator of prior infection, are required [20].

Genetic factor

Obesity & Hypertention

Tobacco, Alcohol & caffine

Parity and pregnancy

hormonal factors

Uterine Infections

Vitamin D deﬁciency

**Figure 1 : Uterine fibroid risk factors**

**Figure 1: Uterine fibroids risk factors**

1. **Pathophysiology of uterine fibroid**

Another theory for uterine fibroids is that they arise because of an increase in exposure to circulating oestrogens. In actuality, leiomyomas have more oestrogen receptors than the surrounding myometrium does. By boosting the formation of extracellular matrix at lower concentrations than the endometrium, this oestrogen may nonetheless aid in the growth of tumours. As opposed to that, progesterone raises young women's myomas' mitotic activity. It might promote tumour growth by decreasing apoptosis in the fibroids. [21,3] There can be one or several myomas, and they can differ in size, location, and perfusion. In general, myomas are divided into three subgroups according to where they are found: subserosal (projecting outside the uterus), intramural (inside the myometrium), and/or submucosal (projecting into the uterine cavity) [3].

**Table 1: Key pathways involved in the pathophysiology of uterine fibroids targeted by certain**

**substances.[12]**

|  |  |  |
| --- | --- | --- |
| **Compound** | **Family** | **Molecular effects** |
| Leuprolide acetate, Goserelin | GnRH agonist | ECM and TGF-β inhibition, tumor shrinkage |
| Ulipristal acetat | SPRM | Apoptosis induction, proliferation inhibition, ECM inhibition |
| Vitamin D | Natural compound | DNA repair induction, Wnt/β-catenin pathway inhibition, TGF-βinduced inhibition of ECM production, anti-inflammatory |
| EGCG (green tea) | Natural compound | COMT suppression, apoptosis induction, proliferation inhibition |
| Tranilas | Anti-allergic compound | ECM inhibition, inhibit proliferation, cell cycle arrest, induction of miR-29c and miR-200c expression |
| Curcumin | Natural compound | Inhibition of ECM production, inhibition of UF proliferation, antiinflammatory effect |
| 2-methoxyestradio | Estradiol metabolite | PI3K/Akt/mTOR inhibition, ECM inhibition |
| Letrozole | Aromatase inhibitor | Apoptosis induction, inhibition of proliferation |
| All-trans retinoic acid | Active metabolite of vitamin A | TGF-β-induced inhibition of ECM production |
| Methyl jasmonate | Natural compound | Wnt/β-catenin pathway inhibition, apoptosis induction, inhibition of proliferation |
| Apicidin | Class I HDAC inhibitor | Inhibition of Wnt/β-catenin pathway, apoptosis induction, inhibition of proliferation |
| ICG-001 | β-catenin inhibitor | Inhibition of Wnt/β-catenin pathway, inhibition of proliferation |
| Resveratrol | Natural compound | Inhibition of ECM production, apoptosis |
| Collagenase | Proteolytic enzyme | ECM degradation |
| Simvastatin | Statin drug | ECM, apoptosis, ER-α palmitoylation and degradation |
| Verteporfin | YAP inhibitor | Anti-proliferation, -fibrosis and -mechanotransduction |
| Nintedanib | YAP inhibitor | Anti-fibrotic effect |
| 5-Aza | Hypomethylation drug | Fibroid stem cell differentiation and PGR signaling |

Abbreviations: Akt, protein kinase B; COMT, Catechol-O-methyltransferase; ECM, extracellular matrix; EGCG, epigallocatechin gallate; GnRH, gonadotropinreleasing hormone; HDAC, histone deacetylase; miR, microRNA; mTOR, mechanistic target of rapamycin; PI3K, phosphoinositide 3-kinase; SPRM, selective progesterone receptor modulator; TGF-β, transforming growth factor beta; PGR, progesterone receptor; UF, uterine fibroids.

**Symptoms:**

**Figure 2 : Symptoms of uterine fibroid**

1. **MANAGEMENT**

|  |
| --- |
| Medicinal treatment |

|  |
| --- |
| Surgical treatment |

|  |
| --- |
| Radiological tratment |

* GnRH agonist and antagonist
* SPRM
* NSAIDS
* Tranexamic acid
* Aromatase inhibitor
* Oral contraceptives
* Iron suppliment
* Hysterectomy
* Levonorgestrel-intrauterine device
* Magnetic resonance guided focused ultrasound surgery
* Myomectomy
* magnetic resonance guided focused ultrasound
* uterine artery embolization

**Figure 3 : Management of Uterine fibroids**

1. **Medicinal treatment**

**GnRH agonist and antagonist**

GnRH agonists, particularly adjuvant preoperative medical therapy, have been the subject of most research on how Symptomatic uterine fibroids should be treated. The Cochrane Systematic Review examined 26 randomised controlled trials to ascertain the effectiveness of GnRH agonists prior to myomectomy or hysterectomy [22].

mechanism:

When a GnRH agonist binds to the GnRH receptor, it initially increases gonadotropin secretion.

Then, the GnRH agonist desensitises the receptor, resulting in a decrease in the release of gonadotropin, which in turn lowers the oestrogen level as a result of the decreased ovarian stimulation by gonadotropin. Additionally, it was discovered that GnRH agonists directly inhibited fibroid proliferation. GnRH agonists can currently be used as a treatment for UF prior to surgery thanks to FDA approval. However, due to the high frequency of side effects, its use is typically restricted to 6 months. [,3,23] In most research, the use of GnRH agonists, particularly adjuvant preoperative medical therapy, has been given for the treatment of symptomatic uterine fibroids. In order to assess the effectiveness of GnRH agonists prior to hysterectomy or myomectomy, the Cochrane Systematic Analysis, a systematic analysis of 26 randomised controlled trials, revealed considerable therapeutic benefits [22]. Current modes of delivery of GnRH agonists include injection, medication-releasing implants, and nasal spray [24].

The second-most recent member of the GnRH analogue class, after the GnRH agonist, is the GnRH antagonist. It works by competing for GnRH receptors, lowering the levels of oestrogen and progesterone as a result. It does not cause the early rise of luteinizing hormone and follicle-stimulating hormone, unlike GnRH agonists. The use of elagolix, a GnRH inhibitor, in conjunction with estradiol and norethindrone acetate for the purpose of treating uterine fibroid received FDA approval in 2020 (FDA, 2020). Relugolix, the most recent GnRH antagonist, is currently undergoing a clinical trial to treat uterine fibroid, and it has the advantage of only requiring a once-daily dosage as opposed to elagolix's twice-daily requirement. Relugolix was given the go-ahead to be marketed as a remedy for UF symptoms in Japan in 2019. Due to the serious risk of bone loss, the FDA recommends using Egolilix only for a 24-month period [23].

**progesterone receptor modulators(SPRM)**

Another family of drugs frequently used in UF is the elective progesterone receptor modulator, which has a combination of progesterone receptor agonist and antagonist actions. Mifepristone (a pure antagonist) and ulipristal acetate are the two most often employed SPRM that have been shown to be successful against Regrettably, the EMA's Committee for Pharmacovigilance Risk Assessment has established very tight indications for the SPRM ulipristal acetate. In January 2021, the European Commission came to the conclusion that 5 mg should be implemented if fibroid embolisation and/or surgical treatment are not suitable options or have failed to alleviate the moderate-to-severe adult uterine fibroids symptoms in women who have not achieved menopause. This comes after an EMA examination of five cases of liver damage that necessitated transplantation in 2018 [4]. Mifepristone, asoprisnil, vilaprisan, and telapristone acetate are other SPRM that have shown effectiveness in lowering fibroid-associated symptoms in randomized controlled studies; however, clinical research on these medications is now on hold [26].

**Non-steroidal anti-inflammatory agents**

NSAIDs are used as the first line of treatment for AUB and dysmenorrhea brought on by fibroids because of their affordability, lack of adverse effects, and wide availability[6]. Non-steroidal anti-inflammatory medicines (NSAIDs), which are used to decrease uterine bleeding, are another non-hormonal treatment. By blocking the cyclooxygenase enzyme, NSAIDs lower prostaglandin synthesis. Endometrial It is known that prostaglandin receptors encourage the development of new vasculature in tumours, which may result in irregular bleeding. As a result, NSAIDs diminish menstrual bleeding by inhibiting the formation of prostaglandin **[**27].

**Tranexamic acid**

A synthetic lysine derivative has antifibrinolytic properties, tranexamic use of acid to lessen blood loss, and the requirement for blood transfusions during surgical procedures. [2,3] It is prohibited for individuals with color blindness, current bleeding, a history of intravascular clotting, or hypersensitivity to the drug due to its uncommon and minor side effects, which include gastrointestinal and musculoskeletal complaints [3].

**Aromatase inhibitor**

The drug is used to inhibit the activity of the enzyme aromatase, which converts androstenedione into oestrogen and causes increased cell proliferation and fibrosis. Letrozole and anastrozole are the two aromatase inhibitors that have been extensively researched for UF. Both therapies were shown to be effective in reducing the myoma volume and symptoms in a randomised controlled trial evaluating the effect of aromatase inhibitors and GnRH agonists on UF. While aromatase inhibitor side effects are often moderate and increase in frequency with continued usage, it has been observed that using them reduced hot flushes when compared to using a GnRH agonist [23].

**Combined hormonal contraceptives**

In order to treat AUB, including uterine fibroids in females, combined oestrogen-progesterone contraceptives such as pills, vaginal devices, or transdermal patches, used cyclically or continuously, are frequently used. They primarily have a tendency to maintain a thin endometrium and reduce the amount of endometrial loss throughout the menstrual cycle. Women who took oral contraceptives in combination showed improvements in fibroids-related AUB, haemoglobin level, and quality of life when compared to placebo, although they were less effective than intrauterine devices that release progesterone (IUD) [6]. Contraceptive use decreases the probability of, particularly among women, uterine fibroids in patients between 30 and 40 years of age. After using oral contraceptives, the risk of myomas due to a favourable family history can also be reduced [28].

**Iron suppliment**

In the Eastern Zone of India, fibroid uterus cases with microcytic hypochromic anaemia were shown to be more likely to have vitamin D insufficiency than fibroid uterus cases without anaemia. Since exposure to sunshine was generally sufficient in both study groups, serum ferritin and haemoglobin played a crucial role in determining blood vitamin D values [29].

1. **Surgical Management techniques:**

**Hysterectomy**

A hysterectomy involves the uterus's surgical removal and, most likely, the cervix. A hysterectomy could include the removal of nearby organs and tissues, including the fallopian tubes and ovaries, depending on the purpose of the procedure [30]. The first successful selected hysterectomy operation was performed in 1813 by Conrad Langenbeck via the vaginal approach (2305015 hysterectomies were conducted overall throughout the research period, according to German studies from 2005 and 2006), and the hysterectomy rate for benign diseases of the genital tract among women aged 20 or older (3.6 out of 1000 women) was higher than in Sweden but lower than in the US or Australia. The hysterectomy can be done in different ways. These procedures can be performed using one of three main approaches: laparoscopic hysterectomy (LH), abdominal hysterectomy (AH), or vaginal hysterectomy (VH**).** abdominal hysterectomy [31].

**Types surgical approaches in Hysterectomy**

Laparoscopic hysterectomy Abdominal hysterectomy vaginal hysterectomy

Complete removal of the uterus and with/or without cervix with/or without removal of ovaries. Lymph nodes, ovaries and fallopian tubes can also be removed in this situation.

Removal of the uterus, cervix, upper vagina, and parametrium. Lymph nodes, ovaries and fallopian tubes can also be removed in this situation.

Removal of the uterus, cervix with/or without removal of ovaries

**Figure 4 : Types surgical approaches in Hysterectomy**

**Myomectomy**

For women who want to keep their uterus regardless of whether they want to get pregnant, myomectomy is an alternative to hysterectomy. If fibroids are suspected of being related to heavy menstrual flow, pelvic discomfort and/or pressure symptoms, and occasionally reproductive problems, removal should be taken into consideration [3]. Age, uterine size, the number of fibroids present before surgery, the presence of additional diseases, and childbearing following myomectomy are all connected with the risk of recurrence [32].

**Hysteroscopic myomectomy**

Hysteroscopic myomectomy is the conventional treatment for intramural and subserosal fibroids. Compared to open myomectomies, This process is related to reduced post-operative pain, less blood loss and morbidity, and shorter hospital stays [9]. A prospective study with 235 patients undergoing laparoscopic myomectomy for symptomatic fibroids showed no conversions to laparotomy, and in 3 years, only 1.2% of patients had a second laparoscopic myomectomy for recurrent fibroids. By 48 hours after surgery, 86.3% of the patients were discharged [3]. Patients who desire to maintain their fertility may benefit from a laparoscopic myomectomy. The laparoscopic approach is regarded as the best surgical technique in this area because of benefits like little postoperative discomfort, quick recovery, acceptable aesthetic results, and successful reproductive outcomes. In multiple studies, the results of pregnancy outcomes following laparoscopic myomectomy have been discussed. These investigations have revealed varying degrees of increases in pregnancy rates [33].

**Levonorgestrel-intrauterine device**

The LNG-IUD has been considered a locally acting and effective agent with minimal hormonal side effects in the pharmacological treatment of menorrhagia associated with uterine leiomyoma. A reduction in the frequency of bleeding disturbances at 6 and 12 months following LNG-IUD insertion was observed. Breast tenderness and pelvic pain were mostly reported in the first 3 months after LNG-IUD insertion but resolved spontaneously without treatment. Previous research has shown that the LNG-IUD can serve as an effective contraceptive for women of reproductive age with uterine leiomyoma. Furthermore, the medication effectively controls leiomyoma-related menorrhagia while having no effect on leiomyoma growth or uterine volume [34].

1. **Radiological tratment**

**MRI-guided focused ultrasound surgery**

MRgFUS is a thermal ablation method that the Food and Drug Administration (FDA) of the United States approved for ExAblate 2000 in 2004. The technique involves using MRI to focus ultrasonic radiation on a specific spot inside a fibroid, leading to tissue necrosis with little harm to neighbouring tissue. It is feasible that MRgFUS may be the therapy of choice for individuals wishing for future fertility; however, more research is required. A durable, minimally invasive method of treating uterine fibroids, MRgFUS can improve both fibroid size and quality of life[35].

**Uterine artery embolization**

In comparison to surgical methods (both hysterectomy and myomectomy), embolisation of uterine arteries is a secure and less invasive therapy that produces the same outcomes in terms of patient satisfaction. Although there have been fewer reports of minor complications, the likelihood that a new surgical treatment will be required in the next 2 to 5 years is higher than it is for surgeries like myomectomy and hysterectomy (15%–32%) vs. 7%. Additionally, the potential compromise of healthy myometrium and ovarian reserve opposes its use prior to pregnancy. In our opinion, UAE is recommended for patients who want to save their uterus because, in our experience, the consequences are significantly more painful and uncomfortable than a hysterectomy[36].

**MR-guided focused ultrasound**

The first clinical MRg-FUS device for treating uterine fibroids was the ExAblate 2000. Although the short-term efficacy of MRg-FUS case series ranging from 51 to 359 patients has been documented, problems such as skin burns have occurred in up to 7% of patients, and at least one intestinal perforation has been observed. The MRg-FUS technique has drawbacks such as a high exclusion rate, the requirement of MR equipment, a lengthy treatment period (minutes to hours), the treatment of one fibroid at a time, and the ablation of fibroids centrally while fibroids appear to proliferate peripherally[3].

**Table 2 : Possible benefits and drawbacks of surgical and pharmacological treatments**

|  |  |  |
| --- | --- | --- |
| Therapy | Benefits | Drawbacks |
| Gonadotropin-releasing hormone agonist | * Greater fibroid and uterine volume reduction than SPRM * Reduce blood loss during surgery * Fewer postoperative complications * Uterus is preserved | * Greater adverse effects, especially hot flushes and bone loss on prolonged use * Risk of disease recurrence |
| Selective Progesterone Receptor Modulator | * Less hot flushes than GnRH agonist * Reduce uterine or fibroid volume * Increase preoperative hemoglobin * Reduce blood loss during surgery | * Progesterone receptor modulator-associated endometrial changes * Risk of disease recurrence |
| Aromatase Inhibitor | * Reduce fibroid size Uterus is preserved * Fewer vasomotor adverse effect than GnRH agonist * Rapid onset of action than GnRH agonist | * Bone loss on prolonged use |
| Levonorgestrel-intrauterine device | * Most effective for reducing blood loss * Most effective for reducing blood loss * Reduce fibroid and/or uterine volume | * Irregular bleeding * Increase risk of device expulsion |
| Non-steroidal antiinflammatory drugs | * Reduce pain and blood loss from fibroids | * Do not decrease fibroid volume; gastrointestinal adverse effect |
| Oral contraceptives | * Reduce blood loss from fibroids * ease of switching to alternative therapy in the event of failure | * Do not decrease fibroid volume |
| Tranexamic acid (cyklokapron) | * Reduces blood loss from fibroids ease of conversion to alternate therapy | * Does not decrease fibroid volume; medical contraindications |
| Hysterectomy | * Definitive treatment * An increase in satisfaction and quality of life | * Increase risk of blood loss, postoperative fever, and surgical site infection * Uterus is removed |
| Myomectomy | * Able to preserve fertility * Lower rate of complication | * Risk of myoma recurrence * Risk of bleeding |
| Focused ultrasound surgery | * Noninvasive * Shorter duration of hospitalization * Less morbidity | * Risk of skin burn, weakness, or numbness of the lower limbs * Risk of myoma recurrence and reintervention |
| Uterine artery embolization | * Minimally invasive; avoids surgery short hospitalization | * Recurrence rate is less |

1. **FUTURE DIRECTIONS AND DISCUSSIONS**

Uterine fibroids are extremely common in females who are fertile, and if women continue to put off having children, more patients will need fertility-preserving treatment alternatives. In addition to the chance to preserve fertility, medical therapy for uterine fibroids may provide relief from symptoms connected to uterine fibroids. There are currently many options accessible, some of which need additional analysis. The best data now supports SPRMs and agonists of GnRH as the most efficient medicinal treatments for reducing fibroid volume and symptomatically improving menstrual bleeding. The choice of therapy is determined by the patient's individual treatment objectives as well as the effectiveness and necessity of follow-up interventions. Future clinical trials should concentrate on prevention methods, such as avoiding recurrence following surgery in high-risk women and preventing incidence in women genetically susceptible to this illness.

1. **ABREVATION**

|  |  |
| --- | --- |
| US | United State |
| UFs | Uterine Fibroids |
| HMGA2, | High mobility group A2 |
| TCA | Tricarboxylic acid |
| SBP | Systolic blood Pressure |
| DBP | Diastolic blood pressure |
| HDP | Hypertensive disorders of pregnancy |
| E2 | Estradiol |
| RTIs | Reproductive tract infections |
| GnRH | Gonadotropin releasing hormone |
| FDA | Food and Drug Administration |
| UPA | Ulipristal acetate |
| SPRM | Selective progesterone receptor modulator |
| EMA | European Medicines Agency |
| NSAIDs | Non- steroidal anti- inflammatory drugs |
| AUB | abnormal uterine bleeding |
| (LNG- IUD | Levonorgestrel releasing intrauterine devices |
| (IUD | intrauterine devices |

**REFERENCES**

[1]Jacques Donnez , Marie-Madeleine Dolmans, “Uterine fibroid management: from the present to the future,”  Human Reproduction Update, Volume 22, Issue 6, 20 November 2016, Pages 665–686, <https://doi.org/10.1093/humupd/dmw023>.

1. Khan A, Shehmar M, Gupta J. “Uterine fibroids: current perspectives. “ Int J Womens Health. 2014;6:95-114, <https://doi.org/10.2147/IJWH.S51083>.
2. George A. Vilos, Catherine Allaire, Philippe-Yves Laberge and Nicholas Leyland, “The Management of Uterine Leiomyomas,” 2015;37(2):157–178
3. Dolmans M-M, Cacciottola L, Donnez J. Conservative Management of Uterine Fibroid-Related Heavy Menstrual Bleeding and Infertility: Time for a Deeper Mechanistic Understanding and an Individualized Approach. Journal of Clinical Medicine. 2021; 10(19):4389. <https://doi.org/10.3390/jcm10194389>.
4. Vitthal Agrawal , Deepika Deewani and Arpita Jaiswal Singham, “Management of Uterine Fibroid,” Journal of Research in Medical and Dental Science, Volume. 11, Issue 01, JANUARY-2023 (J Res Med Dent Sci, 2023, 11 (01):049-054)
5. Giuliani, E., As-Sanie, S. and Marsh, E.E. (2020), Epidemiology and management of uterine fibroids. Int J Gynecol Obstet, 149: 3-9. <https://doi.org/10.1002/ijgo.13102>

#### Holly R. Harris, Jessica L. Petrick, Rosenberg , “The epidemiology of uterine fibroids: Where do we go from here? ,” Fertility and Sterility, Volume 117, Issue 4, 841 - 842

1. Cheng L-C, Li H-Y, Gong Q-Q, Huang C-Y, Zhang C and Yan J-Z, “ Global, regional, and national burden of uterine fibroids in the last 30 years: Estimates from the 1990 to 2019 Global Burden of Disease Study,” Front. Med. 9:1003605, Volume 9 – 2022, doi: 10.3389/fmed.2022.1003605.
2. [https://www.mayoclinic.org/diseases-conditions/uterine-fibroids/symptoms-causes/syc- 20354288](https://www.mayoclinic.org/diseases-conditions/uterine-fibroids/symptoms-causes/syc-%20%20%20%20%20%2020354288)
3. Dora Pavone, Sara Clemenza, Flavia Sorbi, Massimiliano Fambrini, Felice Petraglia,Epidemiology and Risk Factors of Uterine Fibroids, Best Practice & Research Clinical Obstetrics & Gynaecology, Volume 46, 2018, Pages 3-11, <https://doi.org/10.1016/j.bpobgyn.2017.09.004>.
4. Qin H, Lin Z, Vásquez E, Luan X, Guo F, Xu L. Association between obesity and the risk of uterine fibroids: a systematic review and meta-analysis ,J Epidemiol Community Health 2021;75:197-204.
5. Qiwei  Yang, Michal  Ciebiera,Maria  Victoria  Bariani, Mohamed  Ali, Hoda Elkafas, Thomas G. Boyer,and Ayman Al-Hendy, Comprehensive Review of Uterine Fibroids: Developmental Origin, Pathogenesis, and Treatment, Endocrine Reviews, Volume 43, Issue 4, August 2022, Pages 678–719, <https://doi.org/10.1210/endrev/bnab039>
6. Ramin Mohammadi1 , Reza Tabrizi , Kamran Hessami1,3, Hoda Ashari , Peyman Nowrouzi-Sohrabi, Mahnaz Hosseini-Bensenjan and Nasrin Asadi Correlation of low serum vitamin-D with uterine leiomyoma: a systematic review and meta-analysis. Reprod Biol Endocrinol 18, 85 (2020). <https://doi.org/10.1186/s12958-020-00644-6>
7. Brakta S, Diamond JS, Al-Hendy A, Diamond MP, Halder SK. Role of vitamin D in uterine fibroid biology. Fertil Steril. 2015 Sep;104(3):698-706. doi: 10.1016/j.fertnstert.2015.05.031. Epub 2015 Jun 13. PMID: 26079694; PMCID: PMC4561014.
8. Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, Adams-Campbell LL, Rosenberg L. Risk of uterine leiomyomata in relation to tobacco, alcohol and caffeine consumption in the Black Women's Health Study. Hum Reprod. 2004 Aug;19(8):1746-54. doi: 10.1093/humrep/deh309. Epub 2004 Jun 24. PMID: 15218005; PMCID: PMC1876785.
9. Tinelli A, Vinciguerra M, Malvasi A, Andjić M, Babović I, Sparić R. Uterine Fibroids and Diet. Int J Environ Res Public Health. 2021 Jan 25;18(3):1066. doi: 10.3390/ijerph18031066. PMID: 33504114; PMCID: PMC7908561.
10. Chen Y, Xiong N, Xiao J, Huang X, Chen R, Ye S, Tan X. Association of uterine fibroids with increased blood pressure: a cross-sectional study and meta-analysis. Hypertens Res. 2022 Apr;45(4):715-721. doi: 10.1038/s41440-022-00856-w. Epub 2022 Feb 15. PMID: 35169279.
11. Chen, Yequna,∗; Lin, Mengyuea,b,∗; Guo, Pic,∗; Xiao, Jiaxina; Huang, Xirua,b; Xu, Land; Xiong, Nianlinga,b; O’Gara, Mary Claree; O’Meara, Michaelf; Tan, Xueruia. Uterine fibroids increase the risk of hypertensive disorders of pregnancy: a prospective cohort study. Journal of Hypertension 39(5):p 1002-1008, May 2021. | DOI: 10.1097/HJH.0000000000002729
12. Wong JY, Gold EB, Johnson WO, Lee JS. Circulating Sex Hormones and Risk of Uterine Fibroids: Study of Women's Health Across the Nation (SWAN). J Clin Endocrinol Metab. 2016 Jan;101(1):123-30. doi: 10.1210/jc.2015-2935. Epub 2015 Dec 15. PMID: 26670127; PMCID: PMC4701845.
13. Moore KR, Cole SR, Dittmer DP, Schoenbach VJ, Smith JS, Baird DD. Self-Reported Reproductive Tract Infections and Ultrasound Diagnosed Uterine Fibroids in African-American Women. J Womens Health (Larchmt). 2015 Jun;24(6):489-95. doi: 10.1089/jwh.2014.5051. Epub 2015 Apr 22. PMID: 25901468; PMCID: PMC4490779
14. Jason Y. Y. Wong, Ellen B. Gold, Wesley O. Johnson, and Jennifer S. Lee, Circulating Sex Hormones and Risk of Uterine Fibroids: Study of Women's Health Across the Nation (SWAN), The Journal of Clinical Endocrinology & Metabolism, Volume 101, Issue 1, 1 January 2016, Pages 123–130, <https://doi.org/10.1210/jc.2015-2935>
15. [Geum Seon Sohn](https://www.ogscience.org/articles/search_result.php?term=author&f_name=Geum%20Seon&l_name=Sohn)1,2, [SiHyun Cho](https://www.ogscience.org/articles/search_result.php?term=author&f_name=SiHyun&l_name=Cho)1,2, [Yong Man Kim](https://www.ogscience.org/articles/search_result.php?term=author&f_name=Yong%20Man&l_name=Kim)3, [Chi-Heum Cho](https://www.ogscience.org/articles/search_result.php?term=author&f_name=Chi-Heum&l_name=Cho)4, [Mee-Ran Kim](https://www.ogscience.org/articles/search_result.php?term=author&f_name=Mee-Ran&l_name=Kim)5, [Sa Ra Lee](https://www.ogscience.org/articles/search_result.php?term=author&f_name=Sa%20Ra&l_name=Lee)6; Current medical treatment of uterine fibroids, Obstetrics & Gynecology Science 2018;61(2):192-201.
16. Arip M, Yap VL, Rajagopal M, Selvaraja M, Dharmendra K and Chinnapan S (2022) Evidence-Based Management of Uterine Fibroids With Botanical Drugs-A Review. Front. Pharmacol. 13:878407. doi:10.3389/fphar.2022.878407
17. Saleh FL, Taylor HS. Clinical applications of gonadotropin-releasing hormone analogues: a broad impact on reproductive medicine. F S Rep. 2023 Feb 2;4(2 Suppl):83-87. doi: 10.1016/j.xfre.2023.01.008. PMID: 37223759; PMCID: PMC10201293.
18. Rozenberg, S., Praet, J., Pazzaglia, E., Gilles, C., Manigart, Y., and Vandromme, J. (2017). The Use of Selective Progestin Receptor Modulators (SPRMs) and More Specifically Ulipristal Acetate in the Practice of Gynaecology. Aust. N. Z. J. Obstet. Gynaecol. 57, 393–399. doi:10.1111/ajo.12641
19. Sukhbir S. Singh, Liane Belland, Nicholas Leyland, Sarah von Riedemann, Ally Murji,The past, present, and future of selective progesterone receptor modulators in the management of uterine fibroids,American Journal of Obstetrics and Gynecology,Volume 218, Issue 6,2018,

Pages 563-572.e1,ISSN 0002-9378,https://doi.org/10.1016/j.ajog.2017.12.206.

1. Narvella Sefah , Sithembinkosi Ndebele , Lillian Prince , Elizabeth Korasare , Michael Agbleke , Annabella Nkansah , Humphrey Thompson , Ayman Al-Hendy and Andrews Akwasi Agbleke , Uterine fibroids — Causes, impact, treatment, and lens to the African perspective, Frontiers in Pharmacology, VOLUME=13 , 2023, https://www.frontiersin.org/articles/10.3389/fphar.2022.1045783 DOI=10.3389/fphar.2022.1045783
2. Kwas K, Nowakowska A, Fornalczyk A, Krzycka M, Nowak A, Wilczyński J, Szubert M. Impact of Contraception on Uterine Fibroids. Medicina (Kaunas). 2021 Jul 16;57(7):717. doi: 10.3390/medicina57070717. PMID: 34356998; PMCID: PMC8303102.
3. Kumari S, Swetha P, Krishnan R S, Nayak S, Singh S. The Association Between Ferritin and Vitamin D Levels in Premenopausal Fibroid Uterus Cases With Anemia. Cureus. 2021 Feb 17;13(2):e13392. doi: 10.7759/cureus.13392. PMID: 33758693; PMCID: PMC7977030.
4. <https://my.clevelandclinic.org/health/treatments/4852-hysterectomy>
5. Stang A, Merrill RM, Kuss O. Hysterectomy in Germany: a DRG-based nationwide analysis, 2005-2006. Dtsch Arztebl Int. 2011 Jul;108(30):508-14. doi: 10.3238/arztebl.2011.0508. Epub 2011 Jul 29. PMID: 21904583; PMCID: PMC3165925.
6. Garcia CR. Management of thesymptomatic fibroid in women older than 40 years of age: hysterectomy or myomectomy? ObstetGynecol Clin North Am 1993;20:337–48.)
7. Dumitrașcu Mihai Cristian, Nenciu Cătălin-George, Nenciu Adina-Elena, Călinoiu Amalia, Neacșu Adrian, Cîrstoiu Monica, Șandru Florica , Laparoscopic myomectomy – The importance of surgical techniques, Frontiers in Medicine , (10)2023 URL=https://www.frontiersin.org/articles/10.3389/fmed.2023.1158264 DOI=10.3389/fmed.2023.1158264 ISSN=2296-858X
8. Xie ZW, Zhang YN, Wan S, Xu WZ, Chen J. Levonorgestrel-releasing intrauterine device is an efficacious contraceptive for women with leiomyoma. J Int Med Res. 2012;40(5):1966-72. doi: 10.1177/030006051204000538. PMID: 23206480.
9. Clark NA, Mumford SL, Segars JH. Reproductive impact of MRI-guided focused ultrasound surgery for fibroids: a systematic review of the evidence. Curr Opin Obstet Gynecol. 2014 Jun;26(3):151-61. doi: 10.1097/GCO.0000000000000070. PMID: 24751998; PMCID: PMC4137489.
10. Mas A, Tarazona M, Dasí Carrasco J, Estaca G, Cristóbal I, Monleón J. Updated approaches for management of uterine fibroids. Int J Womens Health. 2017 Sep 5;9:607-617. doi: 10.2147/IJWH.S138982. PMID: 28919823; PMCID: PMC5592915.