UTERINE FIBROID: MANAGEMENT OPTIONS

Abstract

Uterine fibroid is leiomyoma (non-cancerous tumor) originating from the uterus's smooth muscle layer (myometrium). According to a recent study, it is anticipated that about 70 to 80% of females worldwide will be affected by uterine fibroid disease over their lifetime. It is most common in 30 to 40-year-old women but can occur at any age. Fibroids grow as clusters in single nodules. 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, pressure in the lower abdominal region, frequent urination, chronic vaginal discharge, infertility, and anemia. The etiology 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, and the genesis of the condition's development, pathogenesis pathways, and available therapies. In addition, we outline the latest management approaches.

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

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I. 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]With age, the prevalence increases, hitting its peak in 40-year-old women. [3]Uterine fibroids present a variety of symptoms in 30–40% of patients depending on their location and size. They may result in heavy & painful menstrual bleeding, anemia, which could be fatal [4], pelvis mass, pelvic pain, infertility, and obstetric problems [5] Our paper aims to examine the existing knowledge on uterine fibroids with a focus on current facts for management. in females

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

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

2. **Risk Elements**

- **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].In contrast to Caucasian women, who experience uterine fibroids at a rate of 40% by age 35 and 70% by age 5, African-American women experience uterine fibroids at a rate of 60% by age 35 and >80% by age 50 [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 (Uterine Fibroids) due to several reasons, like decreased production of sex hormone, changes 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:** Vitamin D levels were shown to be significantly lower in the sera of uterine fibroid individuals in three major investigations, suggesting that vitamin D may be connected to the etiology of uterine

fibroids. [12] According to earlier studies, low vitamin D levels are 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-tumor drug that suppresses the growth of fibroids in culture and reduces the size of uterine leiomyomas in animal models [14].

- **Parity and Pregnancy:** The exact mechanism of pregnancy was poorly understood. There have been some hypotheses that tiny lesions may undergo selective apoptosis during postpartum uterine remodeling. Ischemia has also been suggested as a possible mechanism during parturition. This suggests uterine fibroid tissue may be vulnerable to ischemia during both remodeling &parturition [2].

- **Coffee, Tobacco and Alcohol:** The black women's health study is the cohort study to examine the causes of leiomyomas in a majority of US black women. Current alcohol use, particularly beer intake, was positively linked with uterine leiomyomata risk [15] the precise processes by which drinking alcohol raises the possibility of myoma remain a mystery. The following are hypothesized, but as of yet unidentified, increased alcohol consumption can favor the growth fibroid associated with hormones: an increase in endogenous estrogen levels through a reduction in estrogen metabolism and subsequent rises of ovarian estradiol release [16].

- **Genetic factor:** Following the latest findings, up to 40% of uterine fibroids have some chromosomal abnormalities. Genetic changes that result in the over-expression of HMGA2(High mobility group A2), disruption of the locus, and balletic deletion of FH, which codes for the tricarboxylic acid cycle enzyme fumarate Hydratase, 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 Thus, UFs are associated with the occurrence of hypertension. (17) In a prospective cohort analysis, we discovered that pregnant women with uterine myomas had higher longitudinal systolic and diastolic blood pressure Women with uterine fibroids diagnosed before the 20th week of pregnancy had a greater risk for hypertension disorder during pregnancy than those without fibroids. These findings may aid in the early detection of women who have the risk of hypertensive disorders of pregnancy [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 reproductive tract infections (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 the relationships between RTIs and fibroids, studies using serology, a biological indicator of infection, are required [20].

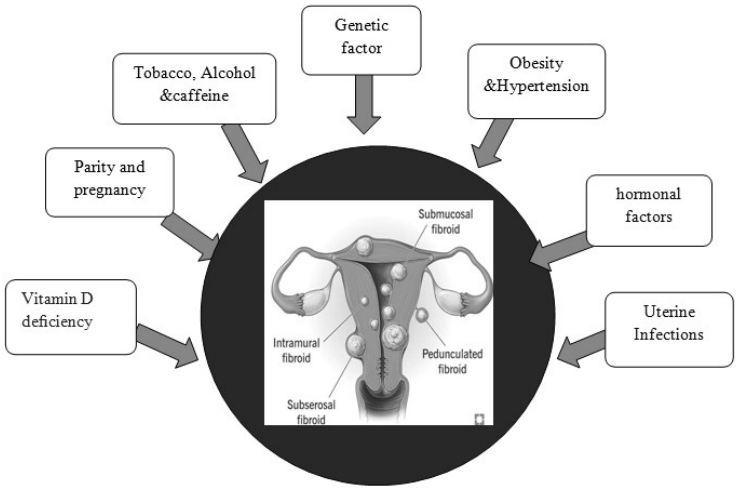

Figure 1 : Uterine fibroid risk factors

3. Symptoms

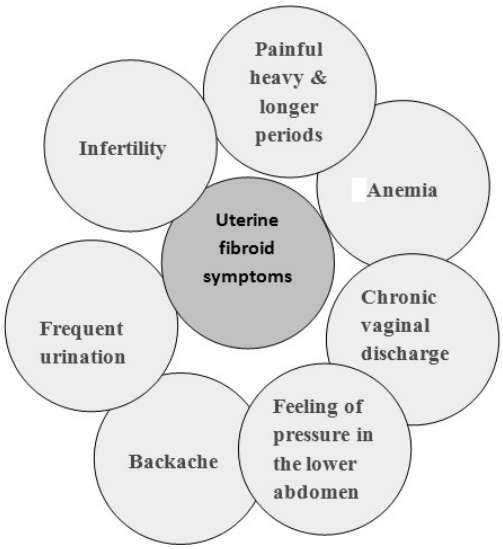

Figure 2: Symptoms of uterine fibroid

4. **Pathophysiology of Uterine Fibroid:** Although leiomyomas have more estrogen receptors than the surrounding myometrium, this estrogen may still contribute to tumor growth by increasing the formation of extracellular matrix at lower concentrations than the endometrium. In contrast, progesterone increases the mitotic activity of young women's myomas, which may also contribute to tumor growth [21, 3]According to their location, myomas can be classified generally into three subgroups: subserosa (projecting outside the uterus), intramural (found inside the myometrium), and/or submucosal (imposing into the uterine cavity) [3].

II. MANAGEMENT

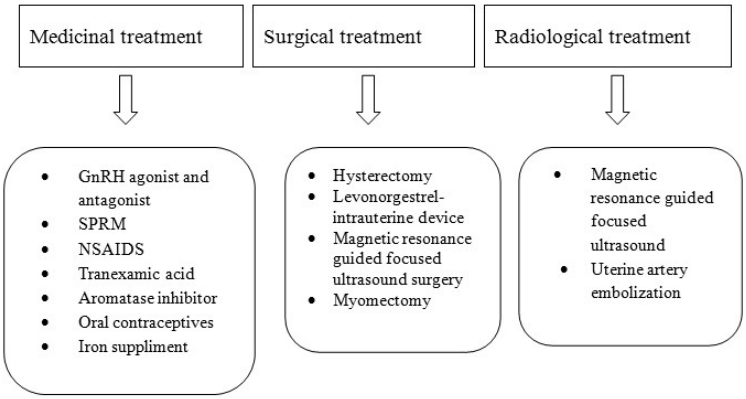

Figure 3: Management of Uterine fibroids

1. Medicinal Treatment

- **Gnrh Agonist and Antagonist (GnRH):** GnRH agonists, particularly adjuvant preoperative medical therapy, have been the subject of most research on how symptomatic uterine fibroids should be treated. The cochrane review examined 26 randomized controlled trials to ascertain the effectiveness of agonists of GnRH before myomectomy or hysterectomy [22].

  When an agonist of GnRH binds to the GnRH receptor, it initially increases gonadotropin secretion. Then, the GnRH agonist desensitizes the receptor, decreasing the gonadotropin release as a result, which in turn lowers the estrogen 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 before 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 treatment of symptomatic UFs. To check the effectiveness of GnRH agonists before hysterectomy or myomectomy, the Cochrane Systematic Analysis, a systematic analysis GnRH agonists are currently given via injection, implanted medications, and nasal spray [24]. The second-most recent member of the GnRH analog class, after the GnRH agonist, is the GnRH antagonist. It works by competing for GnRH receptors, lowering the levels of estrogen 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 to treat 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 elagolixs only for 24 months [23].

- **Selective 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 are successful against Regrettably, the EMA's (European Medicines Agency) Committee for Pharmacovigilance Risk Assessment has established very tight indications for the SPRM and ulipristal acetate. In January 2021, the European Commission concluded that 5 mg should be implemented when fibroid embolization and or surgical treatment is not suitable or has failed to alleviate the severe to moderate adult UFs 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)**:** NSAIDs are used as the initial course of treatment for abnormal uterine bleeding and dysmenorrhea brought on by fibroids because of their affordability, lack of adverse effects, and wide availability [6]. NSAIDs, used to decrease abnormal 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 tumors, 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 as an acid used in 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 estrogen and causes increased cell proliferation and fibrosis. Letrozole and anastrozole are the aromatase inhibitors that have been extensively researched for UF. Both therapies were shown to be effective in the reduction of fibroid volume and symptoms in a randomized 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 reduces hot flushes when compared to using a GnRH agonist [23].

- **Combined Hormonal Contraceptives:** To treat abnormal uterine bleeding, including uterine fibroids in females, combined estrogen-progesterone contraceptives

such as pills, vaginal devices, or transdermal patches, used cyclically or continuously, are frequently used. They primarily tend 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 abnormal uterine bleeding, hemoglobin level, and quality of life when compared to placebo, although they were less effective than intrauterine devices that release progesterone (IUD) [6]. Uterine fibroids are less likely to develop in people between the ages of 30 and 40, especially among women. Oral contraceptives can also lower the incidence of myomas brought on by a favorable family history [28].

- **Iron Supplement:** In the Eastern Zone of India, fibroid uterus cases with anemia were shown to be more likely in case of vitamin D insufficiency than fibroid uterus cases without anemia. Since exposure to sunshine was generally sufficient in both study groups, serum ferritin and hemoglobin played a crucial role in determining blood vitamin D values [29].

2. Surgical Management Techniques:

- **Hysterectomy:** In a hysterectomy, the uterus and, most likely, the cervix are surgically removed. Depending on the goal of the treatment, a hysterectomy may involve the removal of surrounding organs and tissues, such as the ovaries and fallopian tubes [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].

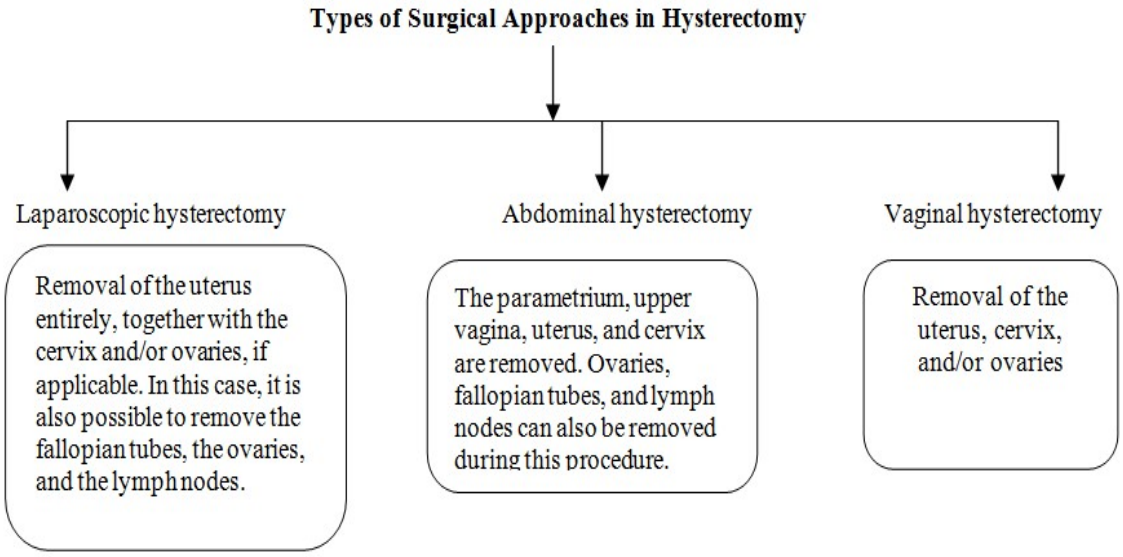

Figure 4: Types of surgical approaches in Hysterectomy

- **Myomectomy:** Myomectomy is an option to hysterectomy for women who want to maintain their uterus regardless of whether they desire to become pregnant. Removal might be considered if fibroids are thought to be connected to heavy menstrual flow, pelvic pressure and/or pain symptoms, and occasionally reproductive issues [3]. Age, uterine size, fibroids present before surgery, the presence of additional diseases, and childbearing following myomectomy are all connected with the recurrence of fibroid [32].

- **Hysteroscopic Myomectomy:** Hysteroscopic myomectomy is a conventional treatment in the case of intramural and subserosal fibroids. Compared to open myomectomies, this process is related to reduced post-operative pain, less blood loss 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 considered the best surgical technique in UFs treatment 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 (LNG-IUD):** In the pharmacological treatment of menorrhagia related to uterine leiomyoma, the LNG-IUD has been regarded as a locally acting and efficient drug with low hormonal side effects. At 6 and 12 months after LNG-IUD insertion, a decrease in the incidence of bleeding disturbances was noted. Most often reported in the first three months following LNG-IUD installation, breast soreness and pelvic pain eventually went away on their own without the need for therapy. Previous studies have demonstrated that women of reproductive age with uterine leiomyoma can use the LNG-IUD as a reliable method of contraception. Additionally, the drug successfully manages menorrhagia brought on by leiomyoma while having no impact on the development of the tumor or the size of the uterus [34].

3. Radiological Treatment

- **MRI-Guided Focused Ultrasound Surgery (MRgFUS):** 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 neighboring tissue. MRgFUS may be a good therapy 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 lifestyle quality [35].

- **Uterine Artery Embolization (UAE):** In comparison with surgical procedures (both hysterectomy and myomectomy), embolization 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 hysterectomy and myomectomy hysterectomy (15%–32%) vs. 7%. Additionally, the potential compromise of healthy myometrium and ovarian reserve opposes its use before pregnancy. In our opinion, because the outcomes are, in our opinion, much more painful and uncomfortable than a hysterectomy, UAE is advised for patients who want to preserve their uterus [36].

- **MR-Guided Focused Ultrasound (MRg-FUS-Device):** The first clinical MRg-FUS device for treating uterine fibroids was the Ex Ablate 2000. Although the short-term efficacy of MRg-FUS case series ranging from 51 to 359 patients has been documented, up to 7% of patients have experienced issues like skin burns, and at least one intestinal perforation has been noted. One fibroid must be treated at a time, and the MRg-FUS procedure has limitations such as a high exclusion rate, the need for MR equipment, a lengthy treatment duration (minutes to hours), and the ablation of fibroids in the center while they appear to spread peripherally [3].

Table 2: Potential advantages and disadvantages of surgical and pharmaceutical interventions

Therapy	Advantages	Disadvantages
Gonadotropin-releasing hormone agonist	Reduction in fibroid volume than SPRM, reduce blood loss during surgery, postoperative complicationsis preserved.	Prolong use may cause hot flushes bone loss and risk of recurrence
Selective Progesterone Receptor Modulator (SPRM)	Fewer hot flushes than with GnRH agonist reduce in fibroid and uterine volume, increase preoperative hemoglobin reduce blood loss during surgery.	Progesterone release associated changes in endometrial Risk of recurrence
Aromatase Inhibitor	Shrink the size of the uterus, Fewer adverse effect than GnRH agonist, rapid therapeutic action than GnRH agonist.	Bone loss on prolonged use
Levonorgestrel-intrauterine device	Effective in reducing in blood loss, and reduce size of fibroid and uterus.	Irregular bleeding Chances of device expulsion are more.
Non-steroidal anti-inflammatory drugs	Reduce blood loss & pain.	Enable to decrease fibroid volume; adverse effect on GIT
Oral contraceptives	Effectively reduce blood loss .	Do not decrease fibroid volume
Tranexamic acid	Reduction in blood loss from fibroids.	Not able to reduce fibroid volume

Hysterectomy	Definitive treatment, an increase satisfaction and quality of life.	risk of postoperative fever, blood loss and surgical site infection Uterus is removed
Myomectomy	Able to preserve fertility rate of complication is lesser.	Chances of myoma recurrence Risk of bleeding
Focused ultrasound surgery	Noninvasive Shorter duration hospitalization, Less morbidity.	Shows adverse effect like skin burn, weakness, complications in lower limbs, Risk of fibroid recurrence
Uterine artery embolization	Minimally invasive, surgery is avoided short term hospitalization.	Rate of recurrence is less

III. FUTURE DIRECTIONS AND DISCUSSIONS

Uterine fibroids are extremely common in fertile females, 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 effective medicinal treatments for reduction in fibroid volume and improving menstrual bleeding. The options of therapy are 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

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/dmw23.
[2] 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
[3] George A. Vilos, Catherine Allaire, Philippe-Yves Laberge and Nicholas Leyland, “The Management of Uterine Leiomyomas,” 2015;37(2):157–178
[4] 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.
[5] Vitthal Agrawal, Deepika Deewani and Arpita Jaiswal Singham, “Management of Uterine Fibroid,” Journal of Research in Medical and Dental Science, Volume. 11, Issue 01, jan 2023 (J Res Med Dent Sci, 2023, 11 (01):049-054)
[6] Giuliani, E., As-Sanie, S. and Marsh, E.E. (2020), Epidemiology and management of uterine fibroids. Int J GynecolObstet, 149: 3-9. https://doi.org/10.1002/ijgo.13102
[7] 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
[8] 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.
[9] https://www.mayoclinic.org/diseases-conditions/uterine-fibroids/symptoms-causes/syc- 20354288
[10] 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.

[11] 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 Feb 1;75(2):197-204
[12] 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
[13] 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).
[14] 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.
[15] 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.
[16] 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.
[17] 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.
[18] Chen, Yequn[a,*]; Lin, Mengyue[a,b,*]; Guo, Pi[c,*]; Xiao, Jiaxin[a]; Huang, Xiru[a,b]; Xu, Lan[d]; Xiong, Nianling[a,b]; O'Gara, Mary Clare[e]; O'Meara, Michael[f]; Tan, Xuerui[a]. Uterine fibroids increase the risk of hypertensive disorders of pregnancy: a prospective cohort study. Journal of Hypertension 39(5):p 1002-1008, May 2021.
[19] 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.
[20] 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.
[21] 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.
[22] Geum Seon Sohn[1,2], SiHyun Cho[1,2], Yong Man Kim[3], Chi-Heum Cho[4], Mee-Ran Kim[5], Sa Ra Lee[6]; Current medical treatment of uterine fibroids, Obstetrics & Gynecology Science 2018;61(2):192-201.
[23] 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.
[24] 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.
[25] 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.
[26] 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.
[27] NarvellaSefah ,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, Vol.13 , 2023, https://www.frontiersin.org/articles/10.3389/fphar.2022.1045783.
[28] 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.
[29] 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.
[30] https://my.clevelandclinic.org/health/treatments/4852-hysterectomy
[31] Stang A, Merrill RM, Kuss O. Hysterectomy in Germany: a DRG-based nationwide analysis, 2005-2006. DtschArztebl Int. 2011 Jul;108(30):508-14.
[32] Garcia CR. Management of the symptomatic fibroid in women older than 40 years of age: hysterectomy or myomectomy? Obstet Gynecol Clin North Am 1993;20:337–48.)

[33] Dumitrașcu Mihai Cristian, Nenciu Cătălin-George, Nenciu Adina-Elena, Călinoiu Amalia, Neacșu Adrian, Cîrstoiu Monica, ȘandruFlorica , Laparoscopic myomectomy – The importance of surgical techniques, Frontiers in Medicine , (10)2023 URL=https://www.frontiersin.org/articles/10.3389/fmed.2023.1158264.
[34] 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.
[35] Clark NA, Mumford SL, Segars JH. Reproductive impact of MRI-guided focused ultrasound surgery for fibroids: a systematic review of the evidence. CurrOpinObstet Gynecol. 2014 Jun;26(3):151-61.
[36] Mas A, Tarazona M, Dasí Carrasco J, Estaca G, Cristóbal I, Monleón J. Updated approaches for management of uterine fibroid. Int J Womens Health. 2017 Sep 5;9:607-617.

