

# TAILORING THE DIAGNOSIS FOR THERAPEUTIC AND SURGICAL TREATMENT OF UTERINE FIBROIDS: A COMPREHENSIVE REVIEW

Nikita and Sanjita Das<sup>\*</sup>

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## Abstract

These benign tumors are the most frequent tumors of the female reproductive system. These hormone-responsive tumors can present with a wide range of symptoms, from severe symptoms such as pelvic discomfort, excessive menstrual flow, reproductive dysfunction, and a marked reduction in quality of life, to asymptomatic cases. The clinical relevance of size and quantity concerns, as well as the classification of fibroids by site (subserosal, intramural, submucosal, and cervical), are discussed. Focusing on genetic abnormalities such as MED12 and HMGA2, the effects of estrogen and progesterone, and important risk factors such as ethnicity, reproductive, and environmental variables, this review further clarifies the intricate pathophysiology of fibroids. The therapeutic options are thoroughly reviewed with a focus on fertility-sparing tactics. These include minimally invasive procedures such as MRI-guided focused ultrasound surgery (MRgFUS) and uterine artery embolization (UAE), medical management with hormonal and non-hormonal agents, and surgical options such as myomectomy and hysterectomy. Finally, new pharmacological medicines, minimally invasive technology advancements, genetic and molecular targeting, and the combination of artificial intelligence and personalized medicine to improve treatment are mentioned as future directions in fibroid research and therapy. The purpose of this review is to provide researchers and doctors with a thorough and up-to-date resource to comprehend and address the health issues that uterine fibroids present in women.

**Keywords:** Leiomyoma; Management; Menorrhagia; Minimally Invasive Therapy; Pathophysiology; Uterine Fibroids

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Department of Pharmacy, SMAS, Galgotias University, Plot No. 2, Sector 17-A, Yamuna Expressway, Greater Noida-201310, Uttar Pradesh, India and 9580742455. E-mail: [nikitasinghmconvent@gmail.com](mailto:nikitasinghmconvent@gmail.com), [sanjita8@yahoo.co.in](mailto:sanjita8@yahoo.co.in), ORCID: 0000-0002-9863-9341

<sup>\*</sup> Corresponding author

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## Introduction

Leiomyomas, often known as uterine fibroids, are benign monoclonal tumours that develop from the uterine smooth muscle lining. By the age of 50, these hormone-dependent proliferations typically impact 70-80% of the women, while there can be notable differences based on geographic and ethnic distribution (Baird *et al.*, 2003; Stewart *et al.*, 2017). Although the fact the majority of fibroids are asymptomatic, they can cause reproductive dysfunction, pelvic pain, heavy menstrual flow and pressure symptoms. Worldwide, fibroids are the leading cause of hysterectomy and obviously adversely affect women's quality of life and healthcare (Cardozo *et al.*, 2012). For instance, 80% of women of African descent will have fibroids by the time they are 50 years old, compared to 70% of Caucasian women. They are more likely to have fibroids earlier in life have larger tumours and experience more severe symptoms (Catherino *et al.*, 2020). The necessity for individualised diagnosis and treatment methods that factor into consideration genetic, hormonal and environmental factors is highlighted by these racial and ethnic differences (Bano *et al.*, 2023).

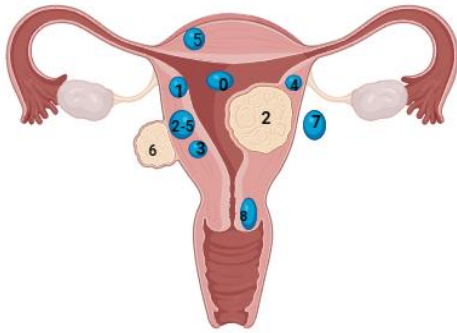
The primary determinant of fibroids classifications is their anatomical position within the uterine wall, which determines their symptomatology and therapeutic strategy. Hysteroscopic surgery is the treatment for this type, which expands into the uterine cavity and is primarily caused by abnormal uterine bleeding, infertility and recurrent pregnancy loss in women (Mascolo *et al.*, 2023). The most common subtype of fibroids is intramural fibroids, which are implanted in the myometrial wall and can cause menorrhagia and pelvic pain by distorting the uterine cavity or affecting contractility (Munro *et al.*, 2011). Bulk symptoms including pelvic pressure, frequent urination and constipation are typically caused by subserosal fibroids, which extend beneath the serosal surface. These fibroids can be pedunculated and are routinely excised by laparoscopic or robotic means (Mascolo *et al.*, 2023). However, the primary facts on FIGO type identification and size-number considerations are included in the methods section to help guide the diagnostics of this review. The remaining eight types of the degree of myometrial and serosal related involvement according to the International Federation of Gynaecology and Obstetrics classification system (Munro *et al.*, 2011).

The factors involved in the pathogenesis of fibroids include, among other of factors, such as chromosomal rearrangements that affect HMGA2

and other loci, acquired somatic mutations (most frequently in the MED12 gene), abnormalities in the Wnt/  $\beta$ -catenin, TGF- $\beta$ , and PI3K/Akt/mTOR signalling networks and massive extracellular matrix deposition (Korczynska *et al.*, 2023). Together estrogen and progesterone promote the formation of fibroids. In contrast to progesterone, which inhibits apoptosis and boost mitotic activity, estrogen increases the expression of the progesterone receptor and proliferative signalling (Bulun, 2013). Environmental and lifestyle factors that affect the risk include obesity, high blood pressure, early menarche and exposure to chemicals that disrupt hormones, inflammation (Bano *et al.*, 2023). The majority of clinicians rely on symptom management and surgical intervention, despite the fact that there has been substantial research into the related molecular mechanisms, with insufficient translation to precision diagnostics and targeted therapies (Khan *et al.*, 2014).

Advances in imaging, particularly magnetic resonance imaging, hysterectomy with saline infusion and high-resolution transvaginal ultrasound made it easier to identify and describe fibroids, providing a precise image of their quantity, size and position (Yang *et al.*, 2022). Artificial intelligence-assisted image interpretation, three-dimensional volumetric analysis and contrast-enhanced ultrasonography are some fascinating research topics that may further increase diagnostic precision and customise treatment strategies (Yang *et al.*, 2022). Medical management with gonadotropin-releasing hormone antagonists and selective progesterone receptor modulators, minimally invasive procedures like uterine artery embolization and MRI-guide focused ultrasound and hybrid therapies that combine medication and local procedures have expanded the range of treatment options beyond surgical interventions only (Stewart *et al.*, 2017). However, algorithms for decision support to particular patient characteristics are lacking and there is not enough comparative evidence to support their long-term use, fertility outcomes and quality of life impact (Stewart *et al.*, 2024).

In all, fibroids high frequency, impact on reproductive health and socioeconomic expenses make them one of the biggest global public health burdens. A significant portion of healthcare spending is related to fibroids, which necessitate operations and long-term medical maintenance. New research into targeted medicines and improved diagnostic techniques are also important.



**Figure 1.** Anatomical overview of the female reproductive system showing common sites of uterine fibroid occurrence. Fibroids can exist at various sites within the uterus-subserosal (outer surface), intramural (within the myometrial wall), and submucosal (underneath the endometrial lining-all of which are accompanied by their own clinical implications regarding pain or bleeding and fertility outcomes). The numbered indicators demonstrate typical fibroid positions within or around the uterus. This schematic is useful for understanding the different presentations of uterine fibroids and their anatomical effect on reproductive function

## Classification of Uterine Fibroids

With important clinical and therapeutic ramifications, uterine fibroids are mostly classified based on where in the uterus they are located anatomically. There are four main categories of fibroids according to the most generally used classification: Figure 1 illustrates the anatomical locations and common types of uterine fibroids within the uterus.

### Types Based on Location

The International Federation of Gynaecology and Obstetrics (FIGO) method is the most widely used classification scheme, and it distinguishes between fibroids in the following ways:

**Submucosal Fibroids:** Less common but frequently linked to heavy menstrual flow, infertility, and repeated pregnancy loss are submucosal fibroids, which are situated slightly below the endometrial lining and project within the uterine cavity. Since they affect the endometrium the most, these fibroids are the main candidates for hysteroscopic resection or surgical excision. Develop into the uterine cavity right below the endometrial layer (Mascolo *et al.*, 2023). Additional classifications for submucosal fibroids include:

Type 0: Pedunculated intracavitary (on a stalk, totally inside the cavity)

Type 1: intramural extension of <50%

Type 2: at least 50% intramural

**Intramural Fibroids:** The most prevalent kind of fibroids are called intramural fibroids, and they are found inside the uterus' muscular wall, or myometrium. Intramural fibroids, depending on their location and size, can cause the uterine cavity to distort, which may result in menorrhagia, pelvic pain, and problems with fertility (De Smit *et al.*, 2025).

These are also sub categorical:

Type 3: fully intramural but has contact with the endometrium

Type 4: completely intramural, with no contact with the serosa or endometrium

**Subserosal Fibroids:** These grow beneath the serosal (peritoneal) layer on the uterus exterior. They are frequently pedunculated and may spread outward into the pelvic region. Bulk sensations such as pelvic pressure are typically caused by subserosal fibroids, which can also affect other organs (Mascolo *et al.*, 2023).

Type 5:  $\geq 50\%$  subserosal and intramural extension

Type 6: less than 50% subserosal and intramural extension

Pedunculated subserosal, or on a stalk outside the uterus, is type seven

Different/Hybrid Types:

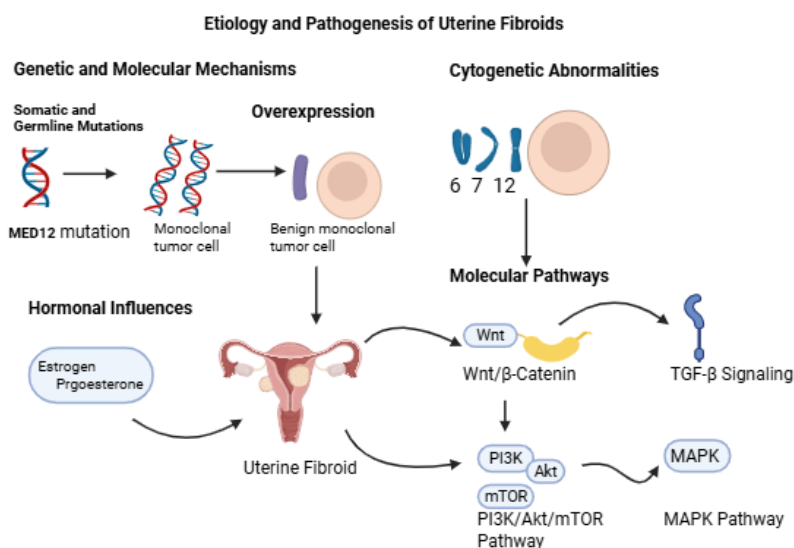
Type 8: Additional sites, include the wide ligament, the cervical region, or parasitic fibroids (which are separated from the uterus)

Hybrid Types : Described by two numerals (e.g., 2-5), these types involve both the serosa and the endometrium.

**Cervical Fibroids:** Cervical fibroids are relatively rare compared to fibroids originating from other uterine locations but may result in symptoms such as dyspareunia or urinary blockage. Surgical management is complicated by their placement. Although they are far less common, they can produce distinct mechanical symptoms because of their position in the cervix (Gluck *et al.*, 2023).

## Etiology and Pathogenesis

The major genetic, molecular, and hormonal mechanism involved in fibroid development are summarized in Figure 2.



**Figure 2.** Etiology and pathogenesis of uterine fibroids. Showing the interaction of genetic (MED12 mutation, cytogenetic abnormalities), molecular (Wnt/β-catenin, PI3K/Akt/mTOR, MAPK, and TGF-β pathways), and hormonal (estrogen and progesterone) mechanisms driving fibroid growth

### Genetic and Molecular Mechanisms

**Somatic and Germline Mutations:** The most frequent genetic alteration in smooth muscle cells is the MED12 mutation, which results in uterine fibroids known as benign monoclonal tumours. 45-90% of fibroids have mutations in the MED12 gene in Xq13; the precise percentage varies by ethnicity and is higher in women of African heritage. These mutations primarily affect exons 1 and 2, with exon 2 mutations being significantly more common and grouped in evolutionary conserved codons 36,43 and 44 (Ishikawa *et al.*, 2023).

A specific and crucial subunit of the significant RNA Polymerase II mediator complex, which is involved in transcription regulation is encoded by the MED12 gene. This specific protein is part of the mediator kinase module, which responsible for the direct binding and activation of cyclin C-CDK8, which leads to the effectiveness of kinase ability to operate is disrupted by pathogenic mutations in the MED12 gene, leading to in altered gene transcription programs and ultimately leads to the development of tumours. Still, the majority of the mutant allele's monoallelic expression is seen in those mutations out of all those in MED12. Accordingly, it shows a pathogenic need for MED12 to change functionally (Mehine *et al.*, 2016).

Chromosome changes that result in overexpression of this high-mobility group protein

are another important class of genetic processes, second only to mutations that alter the HMGA2 gene. Large single fibroids are primarily linked to overexpression of this gene, which is correlated with number of repetitions in the genes promoter region. The concept that MED12 mutations and HMGA2 overexpression are not mutually exclusive is supported by recent data. Approximately 50% of fibroids with MED12 mutations also show upregulated HMGA2. This means these routes interact functionally (Mukherjee, 2025).

Other driver mutations include deletions of COL4A5-COL4A6, which activate insulin receptor substrate-4 (IRS4) signalling pathways and fumarate hydratase (FH) deficiency, which is present in renal cell carcinoma syndrome and hereditary leiomyomatosis. Due to these diverse genetic changes, fibroids may now be molecularly classified into at least four subtypes, each of distinguished by unique gene expression signatures and tumour development pathways (Korczynska *et al.*, 2023).

**Cytogenetic Abnormalities:** 40–50% of fibroids have chromosomal abnormalities, with chromosomes 6, 7, 12, and 14 rearranged. It seems that cytogenetic changes coexist with primary driver mutations, suggesting that they could be incidental factors influencing the development of tumours. Chromosome 12 rearrangements are crucial because they may change HMGA2 expression and deletions

on6p21 and 7q22 may have an impact on other regulator pathways (Medikare *et al.*, 2011).

**Molecular Pathways :** The pathophysiology of fibroids involves dysregulation of a number of interconnected signalling networks. One of these is the Wnt/ $\beta$ -catenin signalling system, which is essential for both tumour initiation and stem cell development. Indeed, when exposed to various treatments of estrogen and progesterone, Wnt will enable the mature myometrial cells and fibroid stem cells to use hormone-dependent paracrine connections that result in nuclear translocation of  $\beta$ -catenin and activation of proliferative target genes (El Sabeh *et al.*, 2021).

TGF- $\beta$  signalling is another important mechanism; fibroids overexpress TGF- $\beta$ , which affects fibrosis and proliferation. Among other things, this route promotes the synthesis of extracellular matrix and anaphasic survival by activating Smad-dependent and independent signalling cascades, PI3K/Akt/mTOR and p38 MAPK pathways (Bariani *et al.*, 2023).

Alterations in cell growth regulation and apoptosis resistance are made possible through mTOR, YAP/TAZ and PI3K/Akt pathways, while aberrant formation of extracellular matrix develops a mechanotransduction environment further assisting in tumor growth (Borahay *et al.*, 2015). Table 1 summarizes the major molecular pathways involved in uterine fibroid pathogenesis and their potential therapeutic targets.

## Hormonal Influences

**Estrogen:** Estrogen promotes the production of fibroids through both genomic and non-genomic mechanisms. It has been demonstrated that fibroids myometrium tissue expresses more aromatase and estrogen receptor- $\alpha$  (ER- $\alpha$ ) than normal myometrium, making fibroids more sensitive to circulating estrogens. By encouraging the development of the progesterone receptor, estrogen's primary action is to increase tissue sensitivity to progesterone. Estrogen promotes cell proliferation through growth factor interaction (mostly with PDGF) by quickly activating the MAPK pathway and causing protein tyrosine phosphorylation. This process is non-genomic. Additionally, estrogens affect the PI3-Akt-mTOR pathway, which is beneficial for cell proliferation and survival (Borahay *et al.*, 2017).

**Progesterone:** More recently, there has been a perception that progesterone plays a major role in the growth of fibroids, which is a direct contradiction to the traditional idea of estrogen dominance. Compared to the surrounding myometrium, these fibroids exhibit significantly greater levels of progesterone receptor expression and it seems that both PR-A and PR-B isoforms are important for tumour development (Ali *et al.*, 2023).

Progesterone is thought to stimulate the synthesis of extracellular matrix, boost cell proliferation in the secretory phase and inhibit apoptosis for the purpose to promote fibroid growth.

**Table 1. Comparative summary of molecular pathways in uterine fibroids and their therapeutic targets**

| Pathway / Mechanism       | Key Molecular Players                       | Role in Pathogenesis                                                                | Potential Therapeutic Targets / Agents                              |
|---------------------------|---------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| Estrogen signaling        | ER- $\alpha$ , Aromatase, PDGF, MAPK        | Promotes proliferation, increases PR expression, enhances ECM synthesis             | SERMs ; aromatase inhibitors ; ER antagonists                       |
| Progesterone signaling    | PR-A, PR-B, PI3K/Akt, MAPK                  | Induces cell proliferation ; ECM accumulation ; inhibits apoptosis                  | SPRMs (e.g. ulipristal acetate) ; antiprogestins ; GnRH antagonists |
| Wnt/ $\beta$ -catenin     | Wnt ligands, $\beta$ -catenin, TCF/LEF      | Maintains fibroid stem cell growth ; hormone-dependent paracrine signaling          | Wnt/ $\beta$ -catenin inhibitors                                    |
| TGF- $\beta$ signaling    | TGF- $\beta$ 1, Smad2/3, PI3K/Akt/mTOR      | Drives fibrosis and ECM overproduction                                              | TGF- $\beta$ receptor antagonists ; Smad inhibitors                 |
| mTOR pathway              | PI3K, Akt, mTOR                             | Increases cell growth, protein synthesis, angiogenesis                              | mTOR inhibitors (e.g. sirolimus, everolimus)                        |
| YAP/TAZ (Hippo pathway)   | YAP, TAZ, TEAD                              | Mediates mechanotransduction, tissue stiffness                                      | YAP/TAZ inhibitors                                                  |
| HMGA2 & MED12 alterations | HMGA2 overexpression ; MED12 mutation       | Alters transcription and mediator complex ; affects proliferation / gene regulation | Gene-targeted silencing ; emerging molecular therapies              |
| ECM remodeling            | Collagen I/III ; fibronectin ; MMPs ; TIMPs | Causes stiffness, promotes growth, ECM accumulation                                 | Anti-fibrotic agents ; MMP modulators                               |

To encourage tumour growth, the hormone passes through a number of signalling channels including PI3K/Akt, MAPK and growth factor pathways. Furthermore, progesterone-dependent development in hormone receptor-deficient stem cells is also encouraged by paracrine signalling from mature fibroids cells (Bulun *et al.*, 2025).

Increase mitotic activity in fibroids during the progesterone-dominated secretory phase provides clinical evidence for the crucial role progesterone and selective progesterone receptor modulators effectively reduce fibroids growth (Al-Hendy *et al.*, 2017).

### Risk Factors and Predisposing Conditions

There are several risk factors that have been found to make women more likely to get fibroid:

**Race and Genetics:** African American women are two to three times more likely than women from other ethnic groups to acquire uterine fibroids. The age at which symptoms appear, the size of the tumours and the intensity of the frequency of surgical treatment vary across European Americans (Stewart *et al.*, 2013).

The myometrial tissue of Black and White women differs molecularly in terms of fibroid tendency, according to recent transcriptome and epigenetic investigations. For instance, differential expression of genes implicated in the stress response (BDNF) suggests that biological sequelae and psychosocial stress are factors that may function at the level of individual differences (Eltoukhi *et al.*, 2014).

**Age:** One of the most significant risk factors for fibroids may be age, as it is more common throughout the reproductive years and peaks in the fifth decade of life. Fibroids typically decrease with postmenopausal estrogen discontinuation, yet some tumours might not go completely (Yang *et al.*, 2022).

**Obesity:** The risk of fibroids disease is increased by obesity in a number of interrelated ways. Increased estrogen synthesis by peripheral aromatisation in adipose tissue is correlated with a higher body mass index, creating a hyperestrogenic environment that promotes the development of fibroid. Additionally, obesity-induced insulin resistance results in hyperinsulinemia, which directly promotes the growth of myometrial smooth muscle cells and increases ovarian hormone production (Harmon *et al.*, 2024).

**Environmental and Lifestyle Factors:** Endocrine-disrupting chemicals (EDCs) are

important risk factors that can be changed and are variously linked to the development of fibroids. They have a number of groups, including dioxins, phthalates and bisphenol a, which can interfere with regular hormonal signalling and induce cancer by modification of the epigenetic code (Katz *et al.*, 2016). The hypothalamic-pituitary-adrenal (HPA) axis is activated by stress, particularly psychosocial stress, which leads to the formation of fibroids (Vines *et al.*, 2010). Progesterone synthesis rises as a result of chronic stress regulation of cortisol, which promotes fibroidal growth.

### Clinical Presentation and Impact

**Symptomatology:** While the fact that 70% of uterine fibroids are asymptomatic and are unintentionally found during other imaging tests, they can present with a variety of clinical symptoms. The size, position and quantity of fibroids as well as the individual traits of each patient, determine the clinical presentation. Reproductive dysfunction, pelvic pain, pressure symptoms and menorrhagia are the four main ways these symptoms present (Stewart *et al.*, 2024).

**Menorrhagia (Heavy Menstrual Bleeding):** Women with symptomatic fibroids are mostly likely to experience heavy blood loss during their periods, which occurs in approximately 30% of cases. The most common causes of heavy menstrual bleeding linked to submucosal fibroids are disturbances in normal endometrial haemostasis and an increase in the surface area of bleeding (Lumsden *et al.*, 2015). This illness typically manifests as abnormal bleeding patterns with increased menstrual volume and duration resulting in iron deficiency anaemia and exhaustion. As an effect of blood loss during periods longer than seven days, some women may need to change their pads every hour during periods of high flow (Ju *et al.*, 2020).

**Dysmenorrhea (Painful Periods):** The relationship between pelvic pain and dysmenorrhea is complicated; approximately 25-35% of women with fibroids experience both. Given the bulk effect and uterine anatomical deformation caused by big intramural fibroids, they might induce pelvic pain over time. Pregnancy-related red degeneration of the fibroid degeneration of the fibroid causes abrupt, severe pain that may resemble an acute abdomen and demand for additional testing (Leal *et al.*, 2024).

**Pressure Symptoms:** The mass effect of growth on proximal pelvic organs can cause this sequence of symptoms. When anterior or larger fibroids put pressure on the bladder, this may manifest in symptoms including frequency, urgency

and nocturia. Posterior fibroids can outcome in constipation, rectal pressure and elimination difficulties. Very big fibroids might cause pelvic heaviness, early satiety and abdominal distension (Medikare *et al.*, 2011).

### Impact on Fertility and Pregnancy Outcomes

**Reproductive Dysfunction:** Submucosal fibroids are the most harmful type of uterine fibroids, accounting for 5-10% of female infertility. The uterine cavity is mechanically distorted the endometrium's receptivity is changed and sperm transmission is compromised. In comparison to normal women without fibroids, submucosal fibroids also increase the rate of miscarriages by 68% and decrease clinical pregnancy rates by 63% (Pritts *et al.*, 2009).

According to recent molecular research, fibroids reduce endometrial receptivity by changing the expression of implantation markers such as leukemia inhibitory factor (LIF), HOXA10, and HOXA11. Further reducing reproductive outcomes are the obstruction of uterine peristalsis and the alteration of the local hormonal milieu (Rackow and Taylor, 2010, Sinclair *et al.*, 2011; Ikhen and Bulun, 2018).

**Pregnancy Complications:** Pregnant women with fibroids are at risk of experiencing miscarriages (10-24%), placenta previa (16% incidence), placental abruption, fetal malpresentation (16-20%), and preterm labor incidences. They have a cesarean section proportion of 36-86% as compared to the average of 17% in the population in general. Neonatal complications include low birth weight (26-30%), preterm birth (30%), and NICU admissions (30%) (Metwally *et al.*, 2012).

### Quality of Life Impact

**Physical and Psychological Burden:** Symptomatic fibroids impair health-related quality of life considerably in various domains. Physical symptoms such as bleeding, pain, and fatigue limit functional capacity and productivity at work. Increased depression about 1.12 times higher, anxiety, and psychological impact can often be attributed to symptom unpredictability and perceived loss of control (Behairy *et al.*, 2024).

Body image disturbance, sexual disturbances, and social limitations arising from halting episodes of heavy bleeding only add to the decline in quality of life. The Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire has become a valid standard for evaluating treatment outcomes with respect to symptom burden (Spies *et al.*, 2002).

**Economic Impact:** In the United States, the economic cost of uterine fibroids increased from \$34.4 billion in 2010 to \$42.2 billion in 2022. Medical management, surgery, and diagnostic imaging are examples of direct healthcare expenditures; absenteeism and lost productivity are examples of indirect healthcare costs. Healthcare expenses for women with symptoms average \$21,993 per year, compared to \$16,491 for those without symptoms (Cardozo *et al.*, 2012; Soliman *et al.*, 2015).

### Diagnostic Approaches

#### Imaging Modalities (Ultrasound, MRI)

**Transvaginal Ultrasound:** The best first-choice imaging modality for diagnosing fibroids is transvaginal ultrasonography due to its ease of use, affordability and reasonable accuracy. Fibroids as small as 5 mm can be detected and precisely located in relation to the uterine cavity using high-resolution TVS. The visualization of submucosal fibroids and endometrial cavity distortion is improved by saline infusion sonohysterography (SIS) (Ducholm, 2006; Peitsidis *et al.*, 2014).

**Magnetic Resonance Imaging MRI:** The most precise way to evaluate the uterus is via magnetic resonance imaging (MRI), which can identify additional uterine abnormalities and provide comprehensive details about the size, location, number, and blood supply of leiomyomas (Lipson and Hricak, 1996). It is an extremely expensive operation, but it provides a better picture of individual myomas. It is useful for surgical planning because of its nearly 100% sensitivity and specificity (Liao *et al.*, 2023).

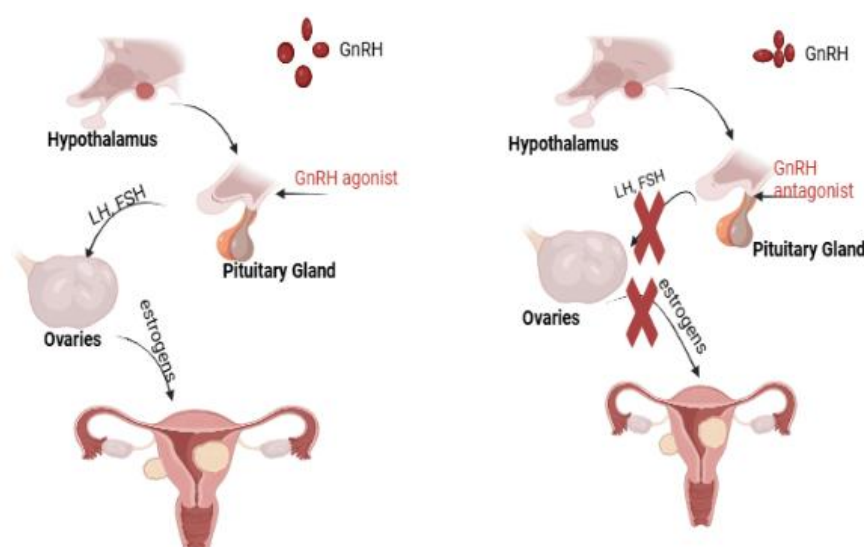
**Emerging Diagnostic Technologies:** The use of three-dimensional ultrasonography and contrast-enhanced ultrasound is increasing diagnostic accuracy through volumetric analysis and improved tissue characterization. Additionally, AI-assisted imaging holds promise for improving diagnostic consistency and reducing interpretation time for the detection and classification of fibroids (Flower *et al.*, 2020; Navarro *et al.* 2021).

**Differential Diagnosis:** The two main differentiating diagnoses are endometrial polyps, which show up on imaging as pedunculated and echogenic rather than hypoechoic, and adenomyosis, which shows diffuse uterine enlargement and a thicker junctional zone (>12 mm) on MRI. In the appropriate clinical settings, ovarian masses and uterine sarcoma should be taken into consideration (Mindjuk *et al.*, 2015).

**Pathophysiological Impact on Endometrial Function:** There are several mechanisms by which the fibroids may adversely affect reproductive outcomes, beyond mechanical distortion. Molecular deviations include dysregulated expression of implantation factors (HOXA10, HOXA11, LIF) and altered integrin profiles for the embryo-endometrial interaction. Vascular changes include aberrant angiogenesis and focal ischemia that jeopardize the endometrial preparation for implantation. Immunological alterations may impair the function

of uterine natural killer cells and macrophages critical for maternal-fetal tolerance (Rackow and Taylor, 2010; Sinclair *et al.*, 2011).

Clinical evidence exists in favor of effective resolution of cavity-distorting fibroids, which has proved to significantly increase the rates of implantation and live birth especially for submucosal and select intramural fibroids. The above effect even advocates therapeutic efficacy out to the intervention for any fibroids



**Figure 3. Mechanisms of action of GnRH agonists and antagonists in hormonal regulation.** GnRH agonists directly stimulate pituitary GnRH receptors to begin with, inducing a short-lived release of LH and FSH before desensitizing the receptor, leading to cessation of estrogen production - these are the “flare and fall”. On the contrary, GnRH antagonists directly competitively inhibit GnRH receptors, leading to an immediate and complete reduction in LH and FSH without an initial flare. Ongoing would be both effective in the reduction of fibroid size as well as symptoms severity in hormone-dependent uterine disorders.

**Table 2. Pharmacological Therapies for Uterine Fibroids**

| Drug Class                                                      | Mechanism of Action                                              | Clinical Efficacy                                     | Adverse Effects / Limitations                                          |
|-----------------------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------------|------------------------------------------------------------------------|
| GnRH Agonists (Leuprolide acetate, Triptorelin)                 | Initial receptor stimulation → desensitization → hypoestrogenism | 35-65% fibroid volume reduction; bleeding control     | Bone loss, vasomotor symptoms, recurrence post-therapy                 |
| GnRH Antagonists (Elagolix, Relugolix)                          | Competitive receptor blockade → rapid hypoestrogenism            | 35-65% fibroid volume reduction; rapid symptom relief | Dose-dependent hypoestrogenism; long-term safety remains unestablished |
| Selective Progesterone Receptor Modulators (Ulipristal acetate) | Selective progesterone receptor modulation                       | Amenorrhea in 82-89%; fibroid shrinkage               | Hepatotoxicity risk: restricted use in EU                              |
| Aromatase Inhibitors (Letrozole, Anastrozole)                   | Peripheral estrogen suppression                                  | Modest volume reduction (20-30%)                      | Bone density loss; limited data on long-term outcome                   |
| Non-Hormonal (Tranexamic Acid)                                  | Antifibrinolytic → reduces menstrual blood loss                  | 40-50% reduction in bleeding                          | Limited clinical data                                                  |

for patients with reproductive goals (Metwally *et al.*, 2012).

## Therapeutic Approaches

### Medical Management: Hormonal and Non-Hormonal Agents

The main goals of uterine fibroid care are symptom relief, fibroid volume reduction and quality of life enhancement which opens the door to surgical intervention. Treatment selection would take into account the patient's risk profile, fibroid features, reproductive goals and symptom severity (Bulun *et al.*, 2025). Table 2 presents the pharmacological therapies currently used in the management of uterine fibroids.

### Hormonal Therapies: Comparative Efficacy and Safety Controversies

#### GnRH Agonists vs. GnRH Antagonists:

Traditional GnRH antagonists, such as goserelin and leuprolide, produce hypoestrogenism by first stimulating the receptor, which may be followed by desensitisation. This results in a typical 'flare effect' that makes symptoms worse for a short time. On the other hand, antagonists block competitive receptors right away without requiring an initial stimulus infusion (Ali *et al.*, 2017 ; Schlaff *et al.*, 2020). The mechanisms of action of GnRH agonists and antagonists are illustrated in Figure 3.

According to clinical investigations, GnRH antagonists provide faster symptom relief than GnRH agonists (1–2 weeks versus 4–8 weeks for agonists). They also don't increase bleeding because of flare-effects, which happen in 10-15% of women using agonists. Global studies comparing longevity, however, showed similar efficacy in bleeding control and fibroid volume reduction and fibroid volume reduction (35-65% for both classes). Though long-term safety on bone has not been as well proven, the main issue concerns the effect on bone density. They both cause hypoestrogenism, but it may be feasible to dose antagonist more carefully to prevent bone loss (Donnez and Dolmans, 2016).

**Selective Progesterone Receptor Modulators SPRMs:** Selective progesterone receptor modulators, principally ulipristal acetate (UPA), represented a major advance in the medical management of fibroids until safety issues came into play. The PEARL trials established UPA as more effective than GnRH agonists, achieving amenorrhea in 82–89% of women, compared with 39 percent in the case of leuprolide, with lasting effects seen up to 6 months after treatment (Donnez *et al.*, 2012).

The many reports of severe hepatotoxicity, some of which required liver transplantation, were the rationale behind the withdrawal of UPA from the market in several countries. This case highlights the assessment of risk and benefit in fibroid management. While UPA provided a unique method for non-surgical management of fibroids, the risk of a serious liver injury, at 1 in 2,000, was deemed too great with the disease being benign in nature. This has prompted the recent development of next-generation SPRMs, which are believed to have improved safety profiles, namely vilaprisan and linzagolix (Whitaker and Critchley, 2016).

**Aromatase inhibitors:** Although theoretically promising, the clinical evidence for the aromatase inhibitors letrozole and anastrozole does not remain strong. A systematic review of six randomized trials revealed modest fibroid volume reduction (20-30%) compared to GnRH agonists (40-60%). The reduction also featured large variability in response. The controversy hinges on whether peripheral estrogen suppression provides enough therapeutic gain to outweigh side effects such as arthralgias, mood changes, and potential cardiovascular risks (Yang *et al.*, 2022).

### Non-Hormonal Agents

**Tranexamic Acid:** Recent studies suggest that tranexamic acid has a favorable safety profile and can decrease menstrual blood loss by 40%–50% via anti-fibrinolytic action. However, the application of tranexamic acid into the context of treatment of heavy menstruation with hormonal therapies is still under discussion. For example, some argue that hormonal therapies that shrink fibroids offer more long-term benefits compared to tranexamic acid, which is recommended by a number of international groups as the first-line treatment for HMB (Lukes *et al.*, 2010).

Recent studies suggest that tranexamic acid is probably best for those using their own judgment in choosing among effective therapies to achieve rapid symptom control with minimal side effects. Hormonal therapies can be recommended to women who want to reduce fibroid volume (Lethaby *et al.*, 2018).

## Minimally Invasive Techniques

**MR-guided Focused Ultrasound (MRgFUS) or Uterine Artery Embolization (UAE):** When it comes to the clear clinical dilemma of choosing between UAE and MRgFUS in women wishing to preserve their fertility and hence to consider future

**Table 3. Comparative Surgical Outcomes for Fibroids treatment**

| <b>Surgical Approach</b>    | <b>Technique</b>             | <b>Advantages</b>                                    | <b>Limitation</b>                                     |
|-----------------------------|------------------------------|------------------------------------------------------|-------------------------------------------------------|
| Laparoscopic Myomectomy     | Minimally invasive           | Reduced recovery time, less blood loss               | Technical difficulty with large fibroids              |
| Robotic Myomectomy          | Robotic-assisted laparoscopy | Improved ergonomics, 3D vision                       | Higher cost ; no clear superiority vs. Laparoscopy    |
| Power Morcellation          | Fragmentation for removal    | Enables minimally invasive removal of large fibroids | Risk of sarcoma dissemination ; FDA warning           |
| Uterine Artery Embolization | Vascular occlusion           | Minimally invasive ; effective symptom control       | Fertility concerns ; miscarriage risk increase        |
| MRgFUS                      | Focused ultrasound ablation  | Non-invasive ; preserves uterus                      | Limited volume treated ; efficacy decreases over time |

pregnancy, considerable controversy remains (Xu *et al.*, 2021). Table 3 compares the outcomes, advantages, and limitations of major surgical approaches for fibroid treatment.

#### **Comparison of Fertility Outcomes:**

Concerns have been raised that UAE may adversely affect fertility, as non-selective ischemia may affect blood supply to normal myometrium, as well as that to the ovary. However, recent larger cohort studies show that pregnancy rates post-UAE are 45-65%, with live birth rates stated to be between 40% and 55%. Complications include increased risk of miscarriage (25% vs. 15% in controls) and abnormal placenta (Gupta *et al.*, 2008).

In theory, MRgFUS preserves fertility by performing a precise thermal ablation without vascular compromise. Although fertility data remain limited, state a pregnancy rate of 50% to 70% post-treatment but with a less-established evidence base than that of UAE. A significant disadvantage is that MRgFUS treats only 60% to 80% of fibroid volume in most patients, whereas in UAE, 90% to 95% devascularization is achieved (Leal *et al.*, 2024).

#### **Long-Term Efficacy Controversy**

Divergent findings arise from the 5-year follow-up : While UAE maintains symptom relief in 75% to 85% of women, efficacy of MRgFUS declined to 55% to 65% due to regrowth of fibroids from incompletely treated tissues. However, MRgFUS permits repeated treatments without cumulative morbidity, while repeat procedures of UAE will risk compromising ovarian reserves (Lumsden *et al.*, 2015; Stewart *et al.*, 2017).

#### **Patient selection Algorithms: Molecular Profiling Integration**

New data suggests that the characteristics of fibroid molecular findings were incorporated into treatment selection beyond size and location. For example, fibroids that have the MED12 mutation respond much better to progesterone receptor

modulators than to other alternatives, while anti-angiogenic approaches are superior to others in managing HMGA2-overexpressing fibroids (Bedaiwy *et al.*, 2017).

#### **Surgical Management: Minimally Invasive Evolution**

**Myomectomy Approaches: Technology and Outcomes Laparoscopia vs. Robotic Controversy:** Robotic myomectomy is increasingly adopted, though it remains unclear if it is better than conventional laparoscopy in randomized trials. Meta-analyses indicate that both interventions have comparable operative times and blood losses as well as similar complication rates ; robot-based surgery incurs double to triple the financial charges. Its acceptance is currently surrounded by issues of whether a marketing-driven adoption is, in fact, evidence-based practices, with some institutions reporting as much as 80% of robotic myomectomies performed without clear clinical justification (Advincula *et al.*, 2007).

**Concerns of Morcellation safety:** After the reports of dissemination of undiagnosed leiomyosarcoma, using power morcellation saw a paradigm shift in surgical practice following the 2014 FDA warning. While the actual risk of sarcoma is 1 in 350-500 (lower than previously estimated risk of 1 in 350), morcellation techniques are now performed with great containment. This has resulted in longer surgical time and greater technical difficulty, with some surgeons abandoning the minimally invasive route for larger fibroids altogether (Stewart *et al.*, 2017).

#### **Future Directions**

Precision medicine approaches will continue to advance rapidly into the therapy of uterine fibroids in the future by combining molecular characterisation, artificial intelligence and

customised treatment algorithms to improve patient outcomes. AI-aided treatment planning will be transformative, with machine learning algorithms demonstrating better predictive accuracy (80-85%) than traditional clinical assessment (65-70%) through analysis of multi-parametric datasets encompassing the patient demographics, fibroid character, molecular markers and advanced imaging features (Xu *et al.*, 2021). These predictive models will enable response prediction for medical therapies according to hormonal profiles and genetic markers, surgical complexity scoring considering three-dimensional imaging analysis for myomectomy planning, as well as recurrence risk stratification, based on molecular subtypes and treatment history.

Molecular-targeted therapeutics-si, even now, emerging as replacement alternatives to similar conventional approaches : for example, phase ii studies showed that antiangiogenic agents such as bevacizumab will cause about a 30 and 40 percent reduction in the volume of very vascularized fibroids (Bulun *et al.*, 2025), while mTOR-driven autophagy modulators hold promise in treating MED12-mutated fibroids (El Sabeh *et al.*, 2021). Epigenetic therapies, including histone deacetylase (HDAC) inhibitors, are in ongoing investigation for specific molecular signatures in fibroids (Catherino *et al.*, 2020). All this is progressively feeding into the personalized treatment algorithm, which will define the molecular profile that decides the target therapy, the pharmacogenomic testing that predicts responses and drug metabolism, and the AI-assisted decision support for sequencing treatment, and finally the patient-reported outcome measures to mature the entire quality of life management (Ciebia *et al.*, 2025).

This precision medicine framework will have as its components genetic testing for MED12/HMGA2 status, guiding medical therapy selection, imaging volumetrics for procedural planning, hormone profiling in optimizing timing and sequencing of interventions, and comprehensive quality of life assessments in prioritizing patient-centered outcomes (Mukherjee, 2025). This evolution from standard empirical treatment selection to evidence-based individualized care is indeed transformational in the approach toward precision fibroid management concerning molecular characteristics, patient preferences, and long-term reproductive goals (Stewart *et al.*, 2024). By so doing, the transformation will hopefully lead to better therapeutic efficacy and reduced treatment failures, giving women suffering from this common gynecology disease a better quality of life.

## Conclusions

The most common benign tumour of the female reproductive system, uterine fibroids continue to have a significant negative impact on women's health worldwide. The intricate interactions between inherited, molecular, related to hormones, and environmental elements that influence their development and growth have become obvious as the study of their origin has advanced. From asymptomatic cases to severe symptoms such as excessive monthly flow, pelvic pain, reproductive dysfunction, and major effects on quality of life, fibroid illness has a wide range of clinical manifestations.

However, the number, volume, and intrauterine location of nodes are largely determined by clinical characteristics. The potential effects of uterine fibroids on the subendometrial myometrium and endometrium surroundings, and in turn, are not yet well understood. Submucosal nodes are linked to significant clinical symptoms. The "endometrial-subendometrial myometrium unit disruption disease" had been suggested a novel condition they should be differentiated from adenomyosis. The abnormal or unhealthy thickness of the subendometrial myometrium which may be the location of formation of intramural and submucosal fibroids, is the manifestation of this disorder. According to recent research, they are pathogenetic similarities within adenomyosis and myomatosis, including an excess inflammation, elevated endothelial nitric oxide generation with upregulated MMP, and inflammatory cytokines like TNF- $\alpha$  and interleukin-1.

The development of submucosal and intramural myomas, uterine haemorrhage, and infertility associated with fibroid may all be significantly impacted by disturbance of the endometrial junction. Uterine fibromatosis's physiological and psychological impacts are growing, and there is a noticeable trend these days to postpone conception. More research is required for determining the etiopathogenesis of this disorder and develop novel, efficient treatments. A multidisciplinary, patient-centred strategy that combines molecular science, technology advancement, and holistic care is the way of the future for managing uterine fibroids. The objective is always to provide safe, efficient, and customized therapies that maintain reproductive health to improve the impacted women's quality of life, even while research into the intricate biology of fibroids continues to shed light on treatment approaches.

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