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A Multifaceted Approach to Uterine Fibroids: Understanding Causes and Treatment Options

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ABSTRACT

Uterine fibroids are benign tumors that arise from the smooth muscle of the uterus, affecting a significant proportion of women during their reproductive years. This review explores the pathophysiology, risk factors, and epidemiology associated with fibroid development, emphasizing the role of genetic predisposition, hormonal influences, and environmental exposures. Studies indicate that factors such as age, obesity, and certain lifestyle choices may increase fibroid risk. The pathogenesis of uterine fibroids involves complex interactions between estrogen, progesterone, and growth factors, which promote cellular proliferation and extracellular matrix remodeling. This review also addresses the link between environmental exposures, such as endocrine-disrupting chemicals, and the incidence of fibroids. Medical treatment options, including hormonal therapies and novel agents like ulipristal acetate, offer symptom relief but may have limitations in fibroid size reduction. Surgical options, ranging from myomectomy to hysterectomy, remain definitive treatments, though minimally invasive techniques, such as laparoscopic myomectomy and uterine artery embolization, have gained popularity for their reduced recovery times and complications. Acute uterine bleeding, a common symptom associated with fibroids, can significantly impact quality of life. This review outlines the clinical management strategies for acute bleeding episodes, integrating both medical and surgical approaches. The discussion concludes with a comprehensive overview of treatment options, emphasizing the importance of individualized care based on patient preferences and clinical circumstances. Further research is needed to fully elucidate the underlying mechanisms of fibroid formation and develop targeted therapies for effective management.

KEYWORDS: Uterine fibroids, Hormonal Therapy, Myomectomy, Acute Uterine Bleeding.

INTRODUCTION:

Uterine fibroids, scientifically known as leiomyomas, were first referred to as "fibroids" in the 1860s. These non-cancerous tumors are prevalent in the pelvic area of women during their reproductive years, affecting over 70% of the global female population. While benign, uterine fibroids can grow rapidly and significantly. They may lead to various symptoms, including irregular and heavy menstrual bleeding, which can cause severe anemia, as well as dysmenorrhea, pelvic pain and pressure, infertility, preterm labor, and recurrent pregnancy loss[(1)].

The exact cause of leiomyomas remains unknown, but they are thought to arise from changes in myometrial cells under specific physiological and pathological conditions. Most of these tumors are monoclonal and estrogen-dependent, primarily impacting women of reproductive age[(2)].

Historically, many fibroids were undiagnosed due to their often asymptomatic nature. Contemporary diagnostic practices concentrate on patients with symptoms, yielding a clearer picture of their true prevalence through targeted diagnostic testing. Initially, surgical intervention was the primary treatment for symptomatic fibroids, with the first hysterectomy performed to address this issue. To reduce the effects of surgery, various minimally invasive techniques, such as mini-laparotomy-assisted vaginal surgery, have been developed. The development of uterine myomas is linked to a range of risk factors, genetic mechanisms, and other influencing factors[(3)].

Pathophysiology of uterine fibroids:

Uterine fibroids are monoclonal tumors that arise from the smooth muscle tissue of the uterus, specifically the myometrium. These benign growths are composed of disorganized myofibroblasts surrounded by a rich extracellular matrix, which constitutes a large part of the tumor's volume. The cells within fibroids have a moderate proliferation rate, and their growth is regulated by the ovarian hormones estrogen and progesterone, leading to a reduction in size after menopause. Estradiol, a biologically active form of estrogen, promotes the synthesis of progesterone receptors (PR) through the action of ER-alpha. These receptors are essential for the fibroid tissue's response to progesterone produced by the ovaries. Both progesterone and PR are critical for tumor growth, as they stimulate cell proliferation, enhance cell survival, and increase the production of the extracellular matrix. In the absence of progesterone and PR, the presence of estrogen and ER-alpha alone does not suffice for the growth of fibroids.

Myomas are classified into three types based on their location: subserosal (extending outside the uterus), intramural (located within the myometrium), and submucosal (projecting into the uterine cavity)[(4)].

Risk factors and Epidemiology:

The occurrence of uterine fibroids is increasing, especially among African American women. Many of these tumors are asymptomatic or exhibit mild symptoms, often leading to undiagnosed cases. Research indicates that only about 25% to 30% of women report experiencing symptoms related to uterine fibroids. The development of these fibroids is influenced by the levels and metabolism of estrogen and progesterone. In one study, researchers used MRI technology to examine the growth patterns of fibroids in both Black and White women with clinically significant tumors. Notably, each tumor displayed a unique growth rate, and the growth appeared to be unrelated to characteristics such as size and location. Uterine fibroids are linked to heavy menstrual bleeding and reduced uterine receptivity, which can lead to infertility—two common reproductive issues impacting millions of women worldwide. These conditions arise from endometrial dysfunctions caused by fibroids, with the severity of dysfunction related to the size and position of the fibroids. The presence of fibroids increases the endometrial surface area, contributing to menstrual bleeding and altering the shape of uterine cells, which affects gene expression and function. Recent studies have shown that fibroids not only affect the nearby endometrium but also have an impact on the entire uterus[(5)].

Uterine fibroids can be influenced by several significant risk factors. These include obesity, deficiencies in vitamin D, high levels of vitamin E, and imbalances in the reproductive tract microbiome. Additionally, exposure to endocrine-disrupting chemicals such as organophosphate esters and plasticizers, along with adverse environmental influences experienced early in life, can contribute to their formation. Lifestyle factors like smoking and alcohol consumption also play a role. Notably, having multiple risk factors increases the likelihood of developing uterine fibroids (6).

Age:

Advancing age is a notable risk factor for uterine fibroids, especially in premenopausal women and those over 40. Among African American women aged 35 to 49, approximately 60% report having fibroids, with this figure rising to 80% for those 50 and older. In comparison, around 40% of White women under 35 and 70% of those over 50 develop fibroids. Uterine fibroids are rarely identified in adolescents, and the causes for early development remain unclear. Although biochemical pathways show minimal differences, fibroids typically do not present in younger women. For those in menopause, there is a reduction in fibroid lesions and sex hormone levels. However, hormonal replacement therapy can lead to the regrowth of these lesions and may trigger initial symptoms associated with uterine fibroids[(7)].

Race and Ethnicity:

The risk of developing uterine fibroids differs significantly among various racial and ethnic groups. Medical records and self-reports using the U.S. Census's five racial categories indicate that Black women, the largest racial minority in the country, have the highest incidence of uterine fibroids. Symptoms tend to be more severe in this group, although the exact reasons for this increased prevalence remain unclear. One contributing factor may be vitamin D deficiency, which affects African American women at rates 5 to 10 times higher than their White counterparts(White American). This disparity is likely due to reduced absorption of ultraviolet (UV) radiation, which is crucial for vitamin D metabolism[(8)].

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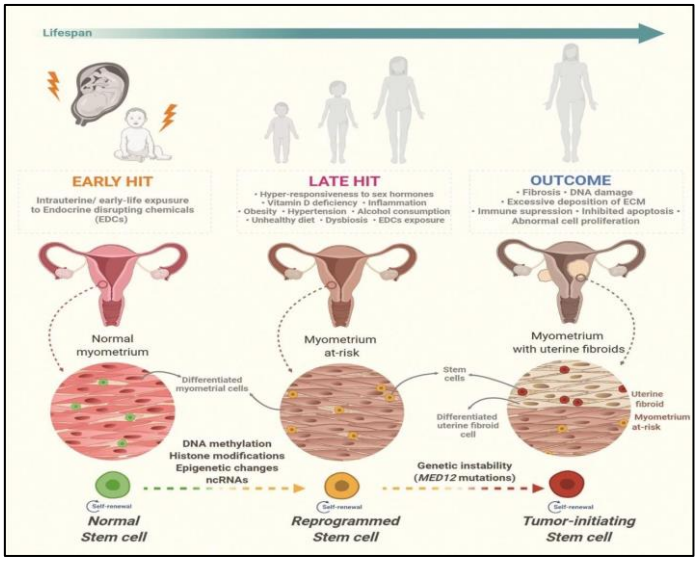

Figure 1. Developmental Origin of Fibroids from Myometrial Stem Cells:

This diagram illustrates the developmental pathway through which fibroids arise from myometrial stem cells. The process begins with exposure to harmful environmental factors, particularly endocrine-disrupting chemicals during intrauterine development and early life. Such exposures can reprogram normal myometrial stem cells, exploiting the epigenome's inherent plasticity. This vulnerability can lead to further adverse exposures later in life, resulting in mutations that transform these cells into tumor-initiating stem cells[9].

The growth and progression of fibroids are characterized by several key features, including abnormal cell proliferation, resistance to apoptosis (programmed cell death), DNA instability, excessive buildup of extracellular matrix (ECM), and the activation of essential biological pathways. Key abbreviations used include ECM for extracellular matrix, MED12 for the subunit 12 of the RNA polymerase II transcriptional mediator complex, and ncRNAs for non-coding RNAs. This comprehensive representation underscores the intricate molecular and cellular mechanisms underlying the origin and development of fibroids, highlighting their complex and multifaceted nature[10].

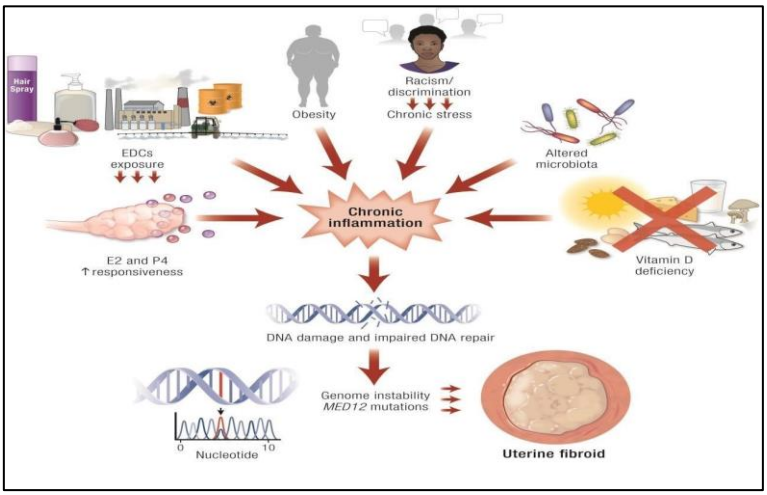

Figure 2. Risk Factors for Uterine Fibroids: Inflammation, DNA Damage Pathways, and Genetic Instability:

This diagram outlines the key risk factors contributing to uterine fibroids, with a focus on their impact on inflammation, DNA damage pathways, and genetic instability. External and internal factors, including exposure to endocrine-disrupting chemicals (EDCs), heightened responsiveness to sex steroid hormones, obesity, vitamin D deficiency, and alterations in the reproductive tract microbiome, collectively contribute to chronic systemic inflammation. The interplay of these factors creates an inflammatory environment, with EDC exposure and vitamin D deficiency further promoting DNA damage and the accumulation of mutations.

Subsequently, these genetic events may activate pathways associated with cell proliferation, the inhibition of apoptosis, and remodeling of the extracellular matrix (ECM). These processes culminate in the initiation and growth of fibroids. Abbreviations used include E2 for estrogen, EDCs for endocrine-disrupting chemicals, MED12 for RNA polymerase II transcriptional mediator complex subunit 12, and P4 for progesterone. This visual representation highlights the intricate connections between various risk factors and the molecular pathways involved in the development of uterine fibroids, underscoring the complex nature of their etiology.

Obesity:

Obesity, associated with increased caloric intake and reduced physical activity, ranks as the fifth leading cause of death. Numerous studies have highlighted obesity as a significant risk factor for developing uterine fibroids, largely due to the metabolic functions of adipose tissue. This tissue secretes cytokines and growth factors that influence various physiological and pathological processes, including immune responses and inflammation. Particularly, excess visceral fat may lead to decreased production of sex hormone-binding globulin (SHBG), disrupting hormonal activity and affecting the delicate hormonal balance in the body. Each kilogram of excess body weight is linked to an increased risk of uterine fibroid development. Furthermore, obese women with type 2 diabetes are at a heightened risk for fibroids, with insulin resistance contributing to their development.

Parity:

Epidemiological studies consistently indicate an inverse relationship between parity (the number of childbirths) and the risk of developing uterine fibroids, suggesting a protective effect of having children. Nulliparous women—those who have not given birth—are more frequently affected by uterine fibroids compared to those who have had multiple pregnancies, with each childbirth potentially reducing the risk of fibroid formation. This protective effect may be attributed to the exposure to steroid hormones during pregnancy and the significant remodeling of uterine tissues that occurs after each childbirth, both of which may contribute to a lower likelihood of fibroid development[11].

Hypertension:

There is a direct correlation between arterial hypertension and the development of uterine fibroids, with elevated diastolic blood pressure linked to an increased risk, regardless of antihypertensive medication use. Women with hypertension are five times more likely to develop fibroids. The chronic damage to the myometrium, resulting from increased blood flow and cytokines released by injured myometrial cells, plays a significant role in the formation of fibroid lesions[12].

Vitamin D Deficiency and Diet:

Vitamin D is a fat-soluble steroid compound with diverse effects in the human body, synthesized in the skin upon exposure to sunlight. It is transported by vitamin D-binding protein to the liver and kidneys, where it is convertedinto 25-hydroxyvitamin D [25(OH)D] and 1,25dihydroxyvitamin D [1,25(OH)D], which then act on target tissues. Inefficient absorption of sunlight can result in vitamin D deficiency, which tends to worsen with age. Sufficient vitamin D levels can be achieved through diet or supplementation. Higher concentrations of vitamin D have been linked to a reduced risk of issues such as prolonged menstrual cycles, infertility, hyperandrogenism, insulin resistance, and polycystic ovary syndrome (PCOS). Additionally, lifestyle factors, including a diet rich in green vegetables, fruits, and fish—rather than red meat are associated with a lower incidence of uterine fibroids[13].

Environmental Exposure and Pathogenesis of Uterine Fibroids:

Air Pollution:

Air pollution is a significant contributor to various chronic diseases and is closely linked to the development of uterine fibroids. Particulate matter (PM), which includes a mix of small particles and gaseous components such as organic chemicals, smoke, soot, sulfates, nitrates, and acidic substances, may play a role in fibroid etiology. Additionally, exposure to ozone (O3) has been associated with an increased risk of developing these tumors[14].

Alcohol Consumption:

Alcohol consumption is recognized as a risk factor for uterine fibroids. Although the exact mechanisms are not fully understood, studies indicate that alcohol intake can elevate steroid hormone levels in premenopausal women. It also alters the levels of growth

factors and cytokines, which are crucial in the pathogenesis of uterine fibroids. Furthermore, alcohol can induce DNA damage, particularly double-stranded breaks, potentially leading to chromosomal rearrangements in stem cells[15].

Cigarette Smoking:

The relationship between smoking and uterine fibroids remains contentious. Some studies report an inverse correlation, suggesting that smoking may lower the risk due to reduced estrone and estradiol levels in smokers. However, other research has found no significant association. Components of cigarette smoke may also have estrogen-like effects on the uterus, which could promote cell proliferation[16].

Evaluation:

Diagnosis of uterine fibroids often involves a physical examination that may reveal an enlarged, mobile uterus with an irregular contour, typically corresponding to a weight of approximately 300 g or the size of a 12-week pregnancy. Ultrasonography, particularly transabdominal and transvaginal approaches, as well as contrast Sono hysterography, is commonly employed due to its accessibility, ease of use, and cost-effectiveness. While CT scans have limited utility, MRI is considered the most accurate imaging modality for assessing the uterus and adnexa, providing detailed information on the size, location, number, perfusion of leiomyomas, and other uterine conditions[17].

Medical Treatment of Uterine Fibroids

- **Monitoring Asymptomatic Fibroids:**

For individuals with asymptomatic uterine myomas who do not wish to become pregnant, specific treatment is often unnecessary. Regular monitoring is generally sufficient. A systematic review of medical treatments in 2016, which analyzed 75 randomized controlled trials, found the overall quality of evidence to be very low, leading to insufficient support for recommending medical treatments for fibroid management. Conversely, another review that evaluated 52 studies suggested the potential efficacy of certain agents, indicating possible medical alternatives to surgical interventions.

Oral Contraceptives:

There is no evidence that low-dose oral contraceptives stimulate the growth of benign fibroids, and they are not contraindicated for women with uterine fibroids. Oral contraceptives have been shown to effectively reduce menstrual bleeding in the short term and may even prevent the development of fibroids[18].

- **Progestins and Levonorgestrel Intrauterine System (LNG-IUS):**

Progestogens, whether natural or synthetic, have dual effects on fibroid growth. While natural progesterone may stimulate growth by enhancing epidermal growth factor, it can also inhibit growth by downregulating insulin-like growth factor-1. Progestogens can decrease both estrogen and progesterone receptor expression in fibroids, thereby modulating their biology. The LNG-IUS significantly reduces menstrual blood loss and uterine volume in women with menorrhagia, though it may not significantly impact fibroid size. When comparing the LNG-IUS to combined oral contraceptives for fibroid-related menorrhagia, the LNG-IUS is more effective at reducing menstrual blood loss, despite similar rates of treatment failure. Evidence suggests that oral progestogens are less effective than GnRH agonists in reducing fibroid size[19].

- **Gonadotropin-Releasing Hormone (GnRH) Agonists:**

GnRH agonists can shrink fibroids by up to 50% in three months. However, treatment duration is generally limited to 3-6 months due to the risk of fibroid regrowth, which typically occurs within 12 weeks post-treatment. Long-term use, particularly when combined with estrogen add-back therapy, requires careful consideration of risks and benefits[20].

Surgical Options

- **Hysterectomy:**

The type of hysterectomy abdominal, laparoscopic, or vaginal should align with the surgeon's experience and clinical guidelines. While abdominal hysterectomy may raise concerns about sexual and urinary function, supracervical hysterectomy can reduce blood loss and complications.

- **Myomectomy:**

For women desiring to preserve their uterus, myomectomy is an option. Indications include heavy menstrual bleeding and reproductive issues. Although myomectomy presents higher risks for blood loss and longer operative time compared to hysterectomy, it has a recurrence rate of about 15%, with factors such as age and the number of fibroids influencing this.

Minimally Invasive Approaches

- **Hysteroscopic Myomectomy:**

Effective for treating abnormal uterine bleeding due to symptomatic intracavitary fibroids, hysteroscopic myomectomy has failure rates of 14.5%-30% within three to four years. It is particularly suitable for submucous myomas up to 4-5 cm.

- **Laparoscopic Myomectomy:**

This method offers advantages like less blood loss and quicker recovery. The choice of approach laparotomy, mini-laparotomy, or laparoscopy should depend on fibroid characteristics and surgeon expertise.

- **Robotic-Assisted Laparoscopy:**

Though popular, robotic-assisted procedures may lead to increased blood loss and longer operative times compared to standard laparoscopic approaches, with no significant benefits in benign cases[21].

- **Preoperative Evaluation**

Thorough preoperative assessment is essential. Correcting anemia and reducing uterine volume can significantly influence surgical outcomes. Pharmacological agents, including iron supplementation, should be used to manage anemia effectively. Research indicates that ulipristal acetate can help reduce uterine fibroid size and correct anemia before surgery[22].

Intraoperative Adjuncts for Uterine Surgery:

The selection of intraoperative adjuncts in myomectomy aims to minimize blood loss, reduce the need for transfusions, and enhance surgical outcomes. The choice of specific techniques may depend on the surgeon's preference, patient characteristics, and clinical scenarios, warranting further research to establish consistent efficacy across different interventions.

i. Misoprostol

Misoprostol, a prostaglandin E1 analogue, has demonstrated benefits in uterine surgeries by reducing blood flow and enhancing myometrial contractions, which can lead to decreased blood loss. Evidence suggests that preoperative administration of misoprostol before abdominal myomectomy significantly lowers operative time, blood loss, postoperative hemoglobin drop, and the need for blood transfusion. However, its use in hysterectomy remains limited and conflicting.

ii. Oxytocin

Emerging studies indicate that oxytocin receptors are present in uterine myomas, but the evidence regarding its effectiveness as an intraoperative adjunct is mixed. Some studies show that intraoperative oxytocin can reduce blood loss and transfusion rates during laparoscopically assisted vaginal hysterectomy, while systematic reviews for myomectomy do not consistently support benefits regarding operative bleeding.

iii. Vasopressin

Vasopressin, known for its vasoconstrictive and uterotonic properties, should be used with caution due to potential cardiovascular risks. One trial found that vasopressin injection during abdominal hysterectomy led to a 40% decrease in total blood loss. However, a systematic review of myomectomy interventions showed no significant differences in transfusion needs, surgery duration, or pregnancy rates postoperatively. Recent studies with dilute vasopressin during laparoscopic myomectomy have shown promising results in reducing blood loss[23].

iv. Bupivacaine and Epinephrine

In laparoscopic myomectomy, a combination of bupivacaine (0.25%) and epinephrine (1 mg/mL) has been shown to be more effective than placebo in reducing intraoperative bleeding, total operative time, and subjective surgical difficulty. Additionally, the use of bupivacaine has been associated with a reduced need for analgesics postoperatively.

v. Antifibrinolytics - Tranexamic Acid

Tranexamic acid, a synthetic lysine derivative with antifibrinolytic properties, has shown limited effectiveness in abdominal myomectomy. While intravenous administration has been linked to reduced blood loss, the results have not reached statistical significance.

vi. Gelatin-Thrombin Matrix

This hemostatic sealant, composed of bovine-derived gelatin and thrombin, can be applied to bleeding sites during abdominal myomectomy. Studies indicate it results in less intraoperative and postoperative blood loss, along with a lower need for blood transfusions compared to controls[24].

vii. Intraoperative Uterine Artery Occlusion (UAO)

The use of laparoscopic UAO during myomectomy is controversial. While some studies found no significant difference in blood loss with or without UAO, others noted longer operative times but reduced blood loss and no need for transfusions in the UAO group.

viii. Peri-cervical Tourniquet

Trials have shown that occlusion of the uterine artery, with or without the ovarian arteries, can significantly reduce blood loss during myomectomy and decrease transfusion requirements.

ix. Anti-adhesion Barriers

These barriers are applied post-myomectomy to minimize adhesion formation. While evidence supports a reduction in adhesions, no adjunct has shown a definitive improvement in fertility or pregnancy outcomes[25].

Special Considerations:

Acute Uterine Bleeding in the Context of Uterine Fibroids:

Definition:

Acute uterine bleeding unrelated to pregnancy is defined as bleeding of a volume deemed sufficient by the treating clinician to require urgent or emergent intervention.

Challenges in Evaluation:

Patient instability, excessive bleeding, and/or blood clots may limit endometrial biopsy, sonographic, and hysteroscopic evaluations of the uterine cavity.

Approach to Investigation and Treatment:

The approach to acute uterine bleeding, whether associated with fibroids or not, should be the same. After resuscitation, ruling out other causes, including history, physical examination, and preliminary imaging, is crucial[26].

Treatment Options for Managing Acute Bleeding Due to Fibroids:

1. Tranexamic Acid:

Administered either intravenously or orally, typically at a dosage of 1 g over 10 minutes, three times daily for 5 to 7 days. This treatment has proven effective in managing heavy menstrual bleeding in patients with fibroids and has a low risk of thromboembolic events (under 1%).

2. Ulipristal Acetate:

Among the hormonal therapies, ulipristal acetate stands out for its rapid onset of action in controlling bleeding. In clinical studies, 80% of women reached a Pictorial Blood Assessment Chart score of less than 75 within a week. Treatment is often initiated at the start of regular menstrual cycles[27].

3. Intrauterine Foley Catheter:

This method is employed as a temporary measure to manage bleeding until other medical treatments take effect. The Foley balloon can be left inflated for a period ranging from 1 to 48 hours, depending on the suspected cause of the bleeding.

4. Myoma Extraction:

Removing fibroids, particularly those that have prolapsed through the cervix, is often effective in stopping bleeding. Submucous fibroids may cause significant bleeding and can protrude after treatments like GnRH agonist therapy or uterine fibroid embolization.

5. Emergency Endometrial Ablation and Hysteroscopic Myomectomy:

These emergency interventions are considered for acute bleeding associated with submucous fibroids, although they can be technically challenging due to visibility issues during the procedure.

6. Uterine Artery Embolization (UAE):

This procedure is an option for severe bleeding that does not respond to conservative treatments. The availability of UAE can influence treatment decisions.

7. Emergency Hysterectomy:

In cases of life-threatening bleeding that do not improve with other interventions, an emergency hysterectomy may be necessary[26].

CONCLUSION:

In conclusion, uterine fibroids represent a significant health concern for many women, with their development influenced by a complex interplay of genetic, hormonal, and environmental factors. While various medical and surgical treatment options are available, the choice of therapy should be personalized, taking into account individual patient needs and preferences. This review is essential to deepen our understanding of the mechanisms underlying fibroid formation, which could lead to more effective and targeted treatment strategies. Ultimately, improving management approaches for uterine fibroids is crucial for enhancing patient quality of life and addressing the challenges posed by this condition.

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