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ETIOLOGY, LIFESTYLE FACTORS, AND MODERN MANAGEMENT STANDARDS FOR UTERINE FIBROIDS AND THEIR IMPACT ON PATIENTS' QUALITY OF LIFE: A REVIEW

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ABSTRACT

Background: This article is a literature review aimed at providing a comprehensive analysis of the current state of medical knowledge regarding uterine fibroids. The study discusses in detail the etiopathogenetic mechanisms of the condition and highlights the role of lifestyle factors.

Methods: This paper is a narrative review of the current medical literature. A comprehensive literature search was conducted across electronic databases including PubMed, MEDLINE, Embase. Studies included in the analysis comprised randomized controlled trials, cohort studies, clinical guidelines, systematic reviews, and meta-analyses.

Results: Based on the literature review, somatic mutations in the MED12 gene are present in 70–80% of uterine fibroid cases, acting as a primary driver of clonal proliferation. Central obesity, vitamin D3 deficiency, and high red meat consumption stimulate extracellular matrix accumulation. In terms of therapeutics, next-generation oral GnRH antagonists, effectively control heavy menstrual bleeding in 70–80% of patients. Minimally invasive treatments achieve a 40–60% reduction in fibroid volume.

Conclusions: The main conclusion of the paper demonstrates that contemporary treatment of patients with uterine fibroids necessitates abandoning the purely surgical dogma in favor of individualized pharmacological and minimally invasive therapies. Clinical success is no longer evaluated exclusively by the reduction of tumor volume, but by a multidimensional enhancement of the patient's quality of life and the mitigation of socio-economic costs.

KEYWORDS

Uterine Fibroids, MED12 Mutation, Lifestyle Factors, GnRH Antagonists, Hormonal Fluctuations, Infertility.

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1. Introduction

Uterine fibroids (*leiomyomata uteri*) represent the most common type of benign mesenchymal neoplasms of the female reproductive system [14]. These monoclonal tumors, arising from the smooth muscle cells of the myometrium, are diagnosed in over 70% of women before the age of 50, with the peak incidence occurring during the perimenopausal period [14]. Although a significant proportion of cases remain asymptomatic, approximately 25–50% of patients experience a range of distressing clinical symptoms [14]. The most prevalent of these include abnormal and heavy uterine bleeding (AUB/HMB), which leads to secondary iron-deficiency anemia, dysmenorrhea, chronic pelvic pain, and bulk symptoms resulting from pressure on adjacent organs, manifesting as urinary frequency or constipation [14]. Furthermore, depending on their size and topography, uterine fibroids can be a major cause of infertility and obstetric complications, such as recurrent miscarriages and preterm labor [2].

Despite such high prevalence, the exact etiopathogenesis of *leiomyomata uteri* remains a subject of intensive research and has not yet been fully elucidated [1]. It is well-established that the development of these lesions is multifactorial, with genetic predispositions and hormonal imbalances—particularly hyperestrogenism and the dysregulation of progesterone receptors—playing a pivotal role [1, 2]. However, increasing attention in the scientific literature is being directed toward environmental factors and modifiable lifestyle choices [5]. Epidemiological and epigenetic studies unequivocally indicate that factors such as a Western diet, obesity, low physical activity, chronic stress, and micronutrient deficiencies (including vitamin D3) can significantly stimulate the proliferation of fibroid cells [4, 5].

For decades, the gold standard of uterine fibroid management was surgical intervention, which was very frequently radical in nature (hysterectomy) [9]. Contemporary gynecology, however, is undergoing a profound evolution toward personalized and minimally invasive medicine [9]. Modern therapeutic standards encompass innovative pharmacotherapies, such as oral GnRH antagonists administered as combination therapy (add-back therapy) [8], as well as advanced organ-preserving techniques—ranging from laparoscopic and hysteroscopic myomectomy [10] and uterine artery embolization (UAE) [10] to non-invasive thermal ablation using magnetic resonance-guided focused ultrasound (MRgFUS) or high-intensity focused ultrasound (HIFU) [11].

All these facets—from debilitating physical symptoms to the necessity of making difficult therapeutic choices—exert a profound impact on patients' quality of life (QoL) [12, 14]. Uterine fibroids are not merely a strictly medical issue, but rather a phenomenon with broad psychosocial and economic dimensions, deeply affecting women's psychological well-being, intimate relationships, procreative plans, and professional productivity [13].

2. Methodology

This study was designed as a comprehensive narrative review of the contemporary medical literature concerning uterine fibroids (*leiomyomata uteri*). Given the multi-disciplinary nature of the topic—encompassing molecular genetics, lifestyle medicine, innovative pharmacology, and minimally invasive gynecology—a descriptive synthesis approach was utilized to gather, evaluate, and integrate existing clinical data and scientific insights.

A systematic and thorough literature search was conducted across major electronic medical databases, including PubMed, MEDLINE, Embase, and Google Scholar, covering publications up to December 2024. To ensure a highly sensitive and specific search outcome, combinations of Medical Subject Headings (MeSH) terms and free-text keywords were employed using Boolean operators (AND, OR). The primary search strings included the following terms: *uterine fibroids*, *leiomyomata uteri*, *MED12 mutation*, *lifestyle factors*, *diet*, *vitamin D3 deficiency*, *obesity*, *physical activity*, *GnRH antagonists*, *relugolix combination therapy*, *LNG-IUS*, *uterine artery embolization*, *HIFU*, *MRgFUS*, *myomectomy*, *quality of life*, *UFS-QOL*, *socioeconomic burden*, *absenteeism*, and *presenteeism*.

The literature selection followed a multi-stage screening process: initial title and abstract screening, followed by a full-text eligibility assessment. Data from the selected eligible papers were carefully extracted with a focus on core themes corresponding to the study's chapters:

- **Molecular and Endocrine Pathogenesis:** Data on the prevalence of the *MED12* mutation, the synergism of estrogen and progesterone signaling, and extracellular matrix (ECM) accumulation [1, 2, 3].
- **Epidemiological and Lifestyle Correlates:** Quantitative metrics regarding the impact of physical activity, visceral adiposity, and micronutrient deficiencies [4, 5, 6, 7].
- **Therapeutic Efficacy and Safety Profile:** Clinical trial endpoints for next-generation oral GnRH antagonists, radiologic interventions (UAE), and non-invasive technologies (HIFU/MRgFUS) [8, 9, 10, 11].
- **Psychosocial and Macroeconomic Impact:** Findings regarding female sexual dysfunction, infertility, psychosocial distress, and corporate productivity losses (absenteeism and presenteeism) [12, 13, 14].

3. Etiopathology of Uterine Fibroids: Current Molecular and Clinical Insights

3.1. Genetic and Epigenetic Determinants

Although uterine fibroids (*leiomyomata uteri*) are benign tumors, their pathogenesis is fundamentally rooted in disruptions at the cellular genome level. Cytogenetic studies unequivocally demonstrate that approximately 40–50% of these fibroid lesions exhibit recurrent chromosomal aberrations [1]. Among the most frequently described are translocations between chromosomes 12 and 14 [t(12;14)(q15;q24)], deletions within the long arm of chromosome 7 [del(7)(q22q32)], as well as trisomy 12 [1].

A pivotal discovery of recent years in the molecular biology of these neoplasms was the identification of mutations in the *MED12* gene, located on the X chromosome [1]. These mutations occur in nearly 70–80% of all uterine fibroid cases globally [1]. The *MED12* gene encodes a protein that is a component of the Mediator complex, which regulates the transcription of RNA polymerase II-dependent genes [1]. Somatic mutations in this region lead to the dysregulation of downstream signaling pathways (including the Wnt/ β -catenin pathway) and drive the uncontrolled proliferation of smooth muscle cells [1]. Interestingly, research suggests that tumors harboring the *MED12* mutation tend to be smaller in size but occur significantly more frequently as multiple lesions [1].

In addition to classical genetic mutations, epigenetic alterations—defined as modifications in gene expression that do not involve changes to the underlying DNA sequence—play a fundamental role in the pathogenesis of *leiomyomata uteri* [1]. These phenomena serve as a direct bridge between biological predispositions and environmental influences [1]. Histopathological and molecular analyses of fibroids reveal global DNA hypomethylation alongside hypermethylation of specific tumor suppressor genes [1]. Furthermore, the dysregulation of non-coding RNA molecules (microRNAs, such as miR-21 and miR-200) represents a critical element, as they control the translation of proteins responsible for apoptosis, angiogenesis, and extracellular matrix (ECM) synthesis [1].

3.2. Hormonal Regulations

Uterine fibroids are classic hormone-dependent neoplasms [2]. Their growth and development are absolutely driven by ovarian steroids—specifically estrogen and progesterone [2]. Clinical confirmation of this thesis is supported by the fact that these tumors develop almost exclusively in women of reproductive age, tend to enlarge during pregnancy, and naturally undergo involution after menopause [2, 14]. For decades, estrogen was considered the sole and primary factor stimulating fibroid development [2]. Neoplastic tissue exhibits a significantly higher concentration of estrogen receptor alpha (ER- α) compared to healthy myometrium [2]. Estradiol stimulates cellular division by activating local growth factors [2]. Furthermore, fibroid cells demonstrate an overexpression of aromatase—the enzyme responsible for converting androgens into estrogens [2]. This implies that the tumor is capable of local, autonomous estrogen production, rendering it partially independent of cyclic ovarian function [2].

An increasing body of medical knowledge redefines the role of progesterone, indicating that it is at least as critical—and in certain phases, essential—for tumor growth as estrogen [2]. Acting through its receptors (PR-A and PR-B), progesterone directly mediates fibroid cell divisions during the luteal phase of the menstrual cycle [2]. This hormone blocks apoptosis and stimulates the synthesis of growth factors as well as extracellular matrix proteins [2, 3]. It is precisely this progesterone dependence that served as the conceptual foundation for

developing modern therapeutics, such as selective progesterone receptor modulators (SPRMs) used in the management of this condition [2, 9].

Estrogen and progesterone do not act in isolation; rather, they exhibit a potent synergy [2]. Estradiol is indispensable for "sensitizing" the tissue, as it drives the overexpression of progesterone receptors, thereby enabling progesterone to exert its full proliferative effect [2].

3.3. Growth Factors and Extracellular Matrix (ECM) Involvement

A key element in the pathomechanism of uterine fibroid formation is not only the excessive proliferation of myocytes themselves, but also the pathological and uncontrolled deposition of intercellular substance [3]. The tissue comprising fibroids is characterized by the presence of an abundant, structurally altered extracellular matrix (ECM), which can account for over 50% of the total tumor mass [3]. It is precisely this excessive production of collagen (primarily types I and III), proteoglycans, and fibronectin that is responsible for the characteristically firm and fibrous consistency of these neoplasms [3].

This process is tightly regulated by signaling cascades mediated by local growth factors, which are previously stimulated by the aforementioned steroid hormones [2, 3]. The most critical mediators include:

- **Transforming Growth Factor-beta (TGF-β):** Regarded as the primary driver of fibrosis [3]. An overexpression of TGF-β and its receptors is consistently observed in fibroid cells [3]. This factor directly induces the synthesis of ECM components and blocks the activity of enzymes responsible for their degradation, namely matrix metalloproteinases (MMPs) [3].

- **Basic Fibroblast Growth Factor (bFGF) and Platelet-Derived Growth Factor (PDGF):** Potent mitogens that stimulate cell division and enhance angiogenic processes, thereby securing the supply of oxygen and nutrients to the tumor [3].

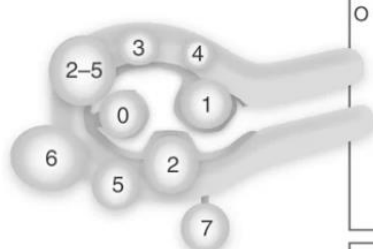
- **Insulin-like Growth Factor-I (IGF-I):** Acts synergistically with estradiol, blocking apoptotic pathways and promoting the hypertrophy of myometrial cells [3, 5].

The accumulation of ECM generates high hydrostatic pressure and mechanical stress within the tumor [3]. These physical stimuli are detected by cell surface mechanoreceptors, which transmit feedback signals that stimulate even greater ECM production [3]. Consequently, this establishes a self-perpetuating feedback loop driving fibroid growth [3].

3.4. The FIGO Clinical Classification System

From the standpoint of clinical practice, the absolute size of a fibroid is often less critical than its precise anatomical location within the uterine structure. It is the specific topography of the tumor that dictates the clinical manifestation of symptoms (e.g., its impact on heavy bleeding or fertility) and guides the selection of the optimal surgical or procedural technique.

The current, universally accepted global standard is the FIGO (International Federation of Gynecology and Obstetrics) classification system, which operates as a core component of the broader PALM-COEIN framework for abnormal uterine bleeding. This system replaces traditional descriptive terminology with a precise numerical categorization (categories 0 through 8) based on the tumor's relationship to the endometrium, myometrium, and serosa:



SM - Submucosal	0	Pedunculated intracavitary
	1	>50% intramural
	2	≥50% intramural
O - Other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (specify e.g., cervical, parasitic)
Hybrid leiomyomas	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

Table 1. The official FIGO leiomyoma subclassification framework

FIGO Class	Category Type	Topographical Description & Relationship to Uterine Layers	Clinical & Surgical Implications
Type 0	Submucous	Pedunculated intracavitary lesion; located entirely within the uterine cavity.	Highly symptomatic (HMB); prime candidate for Transcervical Resection of Myoma (TCRM).
Type 1	Submucous	Less than 50% of the tumor volume invades the surrounding myometrium.	Readily accessible via hysteroscopic approach; strongly associated with subfertility.
Type 2	Submucous	50% or more of the tumor volume extends deep into the myometrium.	Demands advanced hysteroscopic skills or a combined laparoscopic approach.
Type 3	Intramural	Contacts the endometrium directly; 100% intramural with no protrusion into the cavity.	Distorts the internal architecture; compromises embryo nidation and perfusion.
Type 4	Intramural	Purely intramural; entirely surrounded by myometrium without mucosal or serosal extension.	Triggers bulk symptoms and dysmenorrhea; suitable for laparoscopic myomectomy or UAE.
Type 5	Subserous	50% or more of the tumor volume is embedded deep within the myometrium.	Can cause pelvic pressure; addressed via laparoscopic approach if symptomatic.
Type 6	Subserous	Less than 50% of the tumor volume invades the myometrium.	Exerts minimal impact on the endometrium; primarily produces mechanical bulk symptoms.
Type 7	Subserous	Pedunculated subserous lesion attached exclusively to the external surface of the uterus.	High risk of torsion; easily managed via standard or robotic laparoscopy.
Type 8	Other	Ectopic/Extracorporal locations (e.g., cervical, parasitic, or within the broad ligament).	Atypical presentation; requires highly individualized, customized surgical planning.
Type 2–5	Hybrid	Transmural lesions impacting both the endometrium and serosa across the entire wall thickness.	Associated with severe clinical morbidity and socioeconomic burden; ideal for GnRH analogs pre-op.

4. The Significance of Lifestyle and Environmental Factors in the Development and Prevention of Uterine Fibroids

4.1. Diet and Dietary Habits

Contemporary epidemiological and nutrigenomic studies provide growing evidence that dietary patterns exert a significant influence on the risk of development and the growth rate of uterine fibroids [5]. Diet can modulate hormonal balance, inflammatory processes, and angiogenesis, acting either as a stimulatory or protective factor on myometrial cells [5].

The Role of Red and Processed Meat: High consumption of red meat (particularly beef and pork) and processed meats is strongly correlated with an increased incidence of *leiomyomata uteri* [5]. This mechanism is linked to a high content of saturated fatty acids, which exacerbate systemic inflammation and stimulate the synthesis of endogenous estrogens [5]. Furthermore, commercially farmed meat may contain trace amounts of exogenous hormones and estrogen-like compounds [5].

The Significance of Vitamin D3: Deficiency of calcitriol (the active form of vitamin D3) is currently recognized as a major environmental risk factor [4]. Vitamin D3 acts as a potent transcriptional regulator with prominent anti-proliferative and pro-apoptotic properties [4]. *In vitro* studies have demonstrated that calcitriol directly inhibits the growth of neoplastic cells, downregulates the expression of estrogen receptor alpha (ER- α) and progesterone receptors (PR), and reduces the synthesis of metalloproteinases and extracellular matrix (ECM) components [4]. It has been proven that patients with optimal serum 25(OH)D levels exhibit lower tumor growth dynamics [4].

The Impact of Polyphenols and Cruciferous Vegetables: Phytochemicals contained in plants display robust protective effects [5]. Epigallocatechin gallate (EGCG)—the primary polyphenol found in green tea—merits particular attention [5]. EGCG exhibits anti-angiogenic properties (by inhibiting VEGF expression) and induces apoptosis in fibroid cells without adversely affecting healthy uterine cells [5]. A similar protective effect is observed with cruciferous vegetables (e.g., broccoli, cauliflower) rich in indole-3-carbinol, which promotes favorable hepatic estrogen metabolism (favoring the formation of the safer 2-hydroxyestrone over the genotoxic 16 α -hydroxyestrone) [5].

Glycemic Index (GI): A high-GI diet, rich in simple carbohydrates, leads to chronic hyperinsulinemia [5]. Insulin and free somatomedin C (IGF-1) act as potent mitogens, stimulating receptors within the myometrium and directly driving the proliferation of tumor cells [5].

4.2. Obesity and Metabolic Syndrome

Obesity, particularly the visceral (abdominal) phenotype, and its co-occurring metabolic syndrome, constitute independent risk factors for the initiation and progression of uterine fibroids [5]. This relationship relies on three primary pathophysiological pillars: hormonal alterations, adipokine activity, and chronic inflammation [5].

Peripheral Aromatization (Hyperestrogenism): Adipose tissue is not merely a passive energy reservoir but an active endocrine organ [5]. It contains high concentrations of the cytochrome P450 enzyme—aromatase [5]. This enzyme catalyzes the conversion of androgens (androstenedione and testosterone) into estrogens (estrone and estradiol) [5]. Consequently, women with excess body weight experience continuous, extra-ovarian estrogen production, leading to a state of relative hyperestrogenism critical for tumor growth [2, 5].

Insulin Resistance and SHBG: Insulin resistance develops during the course of obesity and metabolic syndrome [5]. Elevated serum insulin concentrations directly inhibit hepatic synthesis of Sex Hormone-Binding Globulin (SHBG) [5]. The reduction in SHBG levels results in a dramatic increase in bioavailability—specifically the free, biologically active fraction of circulating estrogens that can freely stimulate ER- α receptors in the uterus [5].

Adipokine Dysregulation and Pro-inflammatory Profile: The adipose tissue of obese individuals synthesizes pathological amounts of pro-inflammatory cytokines (TNF- α , IL-6) and adipokines [5]. Elevated levels of leptin (which promotes angiogenesis and inhibits apoptosis in neoplastic cells) are observed alongside a concurrent reduction in adiponectin—a hormone with proven anti-inflammatory and anti-proliferative properties [5]. This chronic, low-grade systemic inflammation induces local oxidative stress in the myometrium, which predisposes to somatic mutations (such as the aforementioned *MED12* gene) and initiates the process of clonal fibroid proliferation [1, 5].

4.3. Physical Activity and Oxidative Stress

Regular physical exercise is recognized as one of the most potent non-pharmacological factors modulating a woman's hormonal and metabolic homeostasis, exerting a distinct protective effect against *leiomyomata uteri* [7].

Protective Mechanisms of Physical Activity: The beneficial impact of exercise primarily relies on reducing systemic concentrations of bioavailable estrogen and progesterone [7]. Physical activity stimulates an increase in hepatic Sex Hormone-Binding Globulin (SHBG) levels, resulting in the clearance of free hormones and limiting their mitogenic influence on the myometrium [7]. Furthermore, regular workouts (particularly aerobic and resistance training) directly reduce insulin resistance, thereby lowering circulating levels of insulin and free insulin-like growth factor 1 (IGF-1) [5, 7]. From an epidemiological standpoint, women who engage in moderate-to-vigorous physical activity (exceeding 3–4 hours per week) demonstrate up to a 30–40% lower risk of developing uterine fibroids compared to those leading a sedentary lifestyle [7].

Oxidative Stress and the Role of Cortisol: The development of uterine fibroids is closely linked to an imbalance between the generation of reactive oxygen species (ROS) and the efficiency of enzymatic antioxidant systems (such as superoxide dismutase and catalase) [7]. Chronic psychological and physical stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to hypercortisolemia. Excess cortisol induces generalized oxidative stress, which causes cellular DNA damage and promotes somatic mutations within the myometrium [1, 7]. Moreover, oxidative stress upregulates the local expression of prostanoid factors and inflammatory cytokines, which initiate the cascade of fibrosis and extracellular matrix (ECM) deposition [3, 7].

Stimulants and Environmental Toxins: Contemporary environmental gynecology places a strong emphasis on the analysis of exogenous substances that enter a woman's body through food, tobacco smoke, or transdermally, disrupting the endocrine system (known as EDCs—Endocrine Disrupting Chemicals) [6].

Xenoestrogenic Compounds: These are synthetic chemical substances commonly found in industrial applications and everyday consumer products [6]. They exhibit the capacity to bind to estrogen receptors (ER- α) and mimic the action of natural estradiol, often exerting a multifold stronger or continuous proliferative effect [6]. Among the most prominent xenoestrogens with a proven impact on fibroid growth are [6]:

1. **Bisphenol A (BPA):** Present in plastics, food packaging, and thermal receipts. Studies demonstrate that BPA directly stimulates the division of fibroid cells and induces the overexpression of genes responsible for their proliferation [6].

2. **Phthalates and Parabens:** Plasticizing agents and preservatives widely used in cosmetics. Elevated concentrations of these compounds in patient urine correlate with larger uterine volumes and the presence of multiple fibroid lesions [6].

3. **Organochlorine Pesticides and PCBs:** Agricultural and industrial toxins that accumulate in adipose tissue, possessing a potent endocrine-disrupting potential [6].

The Impact of Alcohol: Alcohol consumption, particularly beer, exhibits a linear relationship with an increased risk of fibroid development [6]. Alcohol impairs hepatic hormone metabolism, compromising estrogen clearance and leading to its accumulation in the bloodstream [6]. Furthermore, ethanol metabolism upregulates prolactin synthesis and stimulates the production of free radicals within the uterine tissue [6, 7].

The Nicotine Paradox: Tobacco smoking exhibits a specific, ostensibly protective effect in epidemiological studies (showing a slightly lower incidence of fibroids among smokers) [6]. This stems from the fact that compounds contained in tobacco smoke exert a potent anti-estrogenic effect by inhibiting aromatase and accelerating the metabolism of estradiol into inactive metabolites [6]. From a clinical standpoint, however, this effect carries no therapeutic significance; tobacco toxins drastically increase the risk of malignancies and cardiovascular diseases while exacerbating tissue hypoxia (oxygen deprivation) [6]. In patients with co-existing fibroids, this hypoxia can significantly intensify pelvic pain [6].

5. Modern Standards in the Management of Uterine Fibroids

5.1. Contemporary Pharmacotherapy

The contemporary approach to the pharmacotherapy of uterine fibroids has undergone a paradigm shift [9]. For years, medical treatments were utilized primarily for short-term preoperative optimization (to reduce tumor mass and mitigate anemia) [9]. Today, following the approval of innovative molecular compounds, pharmacotherapy is emerging as an independent, long-term therapeutic strategy [9]. This development allows many women to entirely avoid surgical intervention or delay it significantly, thereby preserving their reproductive potential [8, 9].

Next-Generation Oral GnRH Antagonists (Combination Therapy): These agents currently represent the most significant breakthrough in the conservative management of *leiomyomata uteri* [9]. The primary representative of this class is relugolix (administered as a combination product with estradiol and norethindrone acetate) [8], alongside linzagolix and elagolix [9].

Mechanism of Action: These drugs competitively and reversibly block gonadotropin-releasing hormone (GnRH) receptors in the anterior pituitary gland [9]. This action induces an immediate, dose-dependent suppression of LH and FSH secretion, subsequently halting ovarian production of estrogen and progesterone [9].

The Advantage of Combination Therapy (Add-back Therapy): Classical injectable GnRH agonists and antagonists previously used in clinical practice induced profound hypoestrogenism, causing severe vasomotor symptoms (hot flashes, depressive states) and an increased risk of bone mineral density loss, which restricted their use to a maximum of 3–6 months [9]. Modern oral formulations combine the GnRH antagonist with a minimal, protective dose of hormones (e.g., 1 mg estradiol / 0.5 mg norethindrone) [8]. This co-administration maintains serum estradiol levels within the "therapeutic window" (approximately 30–60 pg/ml)—a concentration low enough to prevent fibroid growth and reduce bleeding, yet optimal for protecting bone mineral density and eliminating menopausal symptoms [8, 9]. Clinical trials confirm that this therapy can be safely maintained long-term (exceeding 12–24 months), effectively controlling heavy menstrual bleeding in over 70–80% of patients [8].

Levonorgestrel-Releasing Intrauterine Systems (LNG-IUS): Intrauterine devices (such as those containing 52 mg of levonorgestrel) play an important role in symptomatic management. Although the LNG-IUS does not significantly reduce the total volume of the fibroid tumors themselves, it exhibits high efficacy in inducing local endometrial atrophy. This results in a drastic reduction in the volume and duration of menstrual bleeding, frequently leading to controlled amenorrhea. This method is primarily recommended for patients with intramural and subserosal fibroids (FIGO classes 4–7) where the uterine cavity is not distorted.

The Role of GnRH Analogs and Modified Indications for SPRMs:

- **GnRH Agonists (e.g., goserelin, triptorelin):** Administered as long-acting depot injections, these agents cause an initial surge in gonadotropins (the flare-up effect), followed by the downregulation and desensitization of pituitary receptors [9]. Currently, their clinical application is almost exclusively limited to short-term (2–3 months) preoperative preparation in patients with massive tumors to reduce vascularity and technically facilitate myomectomy [9].

- **Selective Progesterone Receptor Modulators (SPRMs, e.g., ulipristal acetate):** These agents directly block progesterone receptors (PR) within the fibroid tissue, demonstrating excellent efficacy in reducing tumor volume and rapidly controlling bleeding [2]. Due to rare but severe hepatotoxic complications (liver injury), their clinical application has been drastically restricted by the European Medicines Agency (EMA). Currently, ulipristal acetate is indicated exclusively as intermittent therapy for premenopausal women for whom surgical intervention is impossible or has failed.

5.2. Interventional Medicine and Minimally Invasive Techniques (Uterus-Preserving Methods)

The evolution of interventional techniques in gynecology has firmly established minimally invasive methods as the first-line option in the surgical management of uterine fibroids [10]. These procedures aim either at the enucleation of the lesions themselves (myomectomy) or their *in situ* destruction, while leaving the uterine corpus and cervix intact [10]. This approach drastically shortens patient recovery time and minimizes the risk of perioperative complications [10].

Hysteroscopy and Laparoscopy as the Gold Standard in Myomectomy

- **Transcervical Resection of Myoma (TCRM):** This is the method of choice for submucosal tumors (FIGO classes 0, 1, and selected type 2 cases). The procedure is performed transvaginally, eliminating the need for abdominal incisions. Utilizing a monopolar or bipolar resectoscope (or mechanical hysteroscopic morcelators), the tumor is removed under direct visualization from within the uterine cavity. This method features a negligible complication rate and restores normal uterine cavity architecture, which is critical for fertility.

- **Laparoscopy (including Robotic Laparoscopy):** This is the preferred surgical standard for subserosal and intramural fibroids (FIGO 3–7) whose diameter typically does not exceed 10–12 cm [10]. The use of advanced high-definition imaging towers and robotic platforms (e.g., da Vinci) allows for highly precise enucleation of the tumor from the myometrium, secure hemostasis (vessel sealing), and layered suturing of the uterine wall. To safely extract the enucleated tissue through small laparoscopic ports, morcellation (fragmentation) is performed within specialized endoscopic bags (contained morcellation), preventing the accidental dissemination of cells inside the peritoneal cavity.

Uterine Artery Embolization (UAE)

This is a highly effective interventional radiology procedure that serves as an alternative to conventional surgery [10]. Through the puncture of the femoral or radial artery, a radiologist guides a microcatheter into the vessels supplying the uterus [10]. Embolic material (e.g., polyvinyl alcohol microspheres) is then administered, mechanically occluding the lumen of the small vessels feeding the fibroids directly [10]. Because the neoplastic cells are hypervascular and highly sensitive to hypoxia, they undergo selective ischemic necrosis, causing the tumor volume to shrink by 40–60% over the following months [10]. This method allows for the simultaneous treatment of multiple lesions; however, due to a potential (though rare) adverse impact on ovarian reserve and endometrial perfusion, it requires caution in women planning a pregnancy [10].

Focused Ultrasound Thermal Ablation (HIFU / MRgFUS)

This is the most innovative, entirely non-invasive method for destroying fibroid tissue without disrupting the integrity of the skin [11].

Mechanism of Action: A high-energy ultrasound beam is precisely focused inside the tumor [11]. At the focal point of the wave, a rapid temperature spike occurs (reaching 60–85°C) along with acoustic cavitation, leading to thermal coagulative necrosis of the fibroid cells [11]. The entire procedure can be monitored in real time using magnetic resonance imaging (MRgFUS), which provides a precise thermal map of the tissue, or via ultrasound (HIFU / USgFUS) [11]. While this method features an immediate return to full activity for the patient, its availability remains limited, and the tumor must meet strict eligibility criteria (appropriate size, absence of hypervascularity, and favorable anatomical location) [11].

Transvaginal Radiofrequency Ablation (TVRFA)

This is a modern micro-invasive technique involving the ultrasound-guided insertion of a specialized needle-electrode through the vaginal fornix directly into the core of the fibroid. The emission of radiofrequency waves generates heat that destroys the tumor architecture from within. TVRFA serves as a valuable addition to the interventional armamentarium, offering minimal postoperative pain and high precision for patients presenting with intramural tumors.

5.3. Radical Management (Hysterectomy)

Despite the rapid development of contemporary pharmacotherapy and advanced organ-preserving techniques, radical management involving the surgical removal of the uterus continues to hold an important position in therapeutic algorithms [9, 10]. Hysterectomy represents the only definitive modality guaranteeing complete and permanent resolution of the condition, effectively eliminating the risk of recurrence (as *leiomyomata uteri* demonstrate a tendency to re-grow following myomectomy or thermal ablation procedures) [10].

However, current gynecological standards restrict the indications for radical treatment to strictly defined clinical scenarios. These include:

- **Failure of or Contraindications to Conservative Treatment:** Situations where heavy bleeding leads to life-threatening anemia, and next-generation pharmacotherapy (e.g., GnRH antagonists) or minimally invasive interventions have failed to yield satisfactory clinical results [8, 10].

- **Size and Anatomical Configuration of the Lesions:** Massive, multiple uterine fibroids that completely distort the reproductive organ and fill the abdominal cavity (reaching the level of the umbilicus or higher), preventing the safe enucleation of individual tumors.

- **Suspicion of Oncological Malignancy:** The clinical necessity to exclude uterine leiomyosarcoma. Although the malignant transformation of benign fibroids is exceedingly rare (occurring in less than 0.5% of cases), rapid and aggressive tumor growth—particularly in postmenopausal women—constitutes an absolute indication for radical surgical management.

- **Patient Age and Completion of Childbearing:** Hysterectomy is primarily considered in women who have consciously and definitively completed their family planning goals and accept the loss of reproductive potential in exchange for the permanent resolution of their symptoms.

Depending on the extent of the lesions and anatomical considerations, contemporary operative surgery distinguishes between:

- **Total Hysterectomy:** The removal of the uterine corpus along with the cervix.
- **Subtotal (Supracervical) Hysterectomy:** The removal of the uterine corpus alone with preservation of the cervix, which in selected cases allows for better preservation of pelvic floor architecture and sexual function.

6. Quality of Life (QoL) and Societal Implications of the Condition

6.1. Symptom Profile and Psychological Well-Being

Physical symptoms caused by uterine fibroids exhibit a direct, proven correlation with a decline in patients' mental health, frequently predisposing them to the development of anxiety and depressive disorders [14]. The psychosomatic dimension of this condition is primarily driven by two dominant symptoms: chronic pain and abnormal bleeding [14].

Chronic, heavy menstrual bleeding leads to the development of profound iron-deficiency anemia in the majority of symptomatic patients [14]. A drop in hemoglobin and ferritin levels triggers a spectrum of central nervous system symptoms: persistent fatigue, cognitive impairment, apathy, and reduced tolerance for psychophysical exertion. This condition drastically impairs daily functioning [14]. Consequently, supporting patients with iron supplementation during therapy is vital to achieve at least partial improvement in their overall clinical status. Furthermore, pain and persistent non-menstrual bleeding are very frequently observed, resulting in uninterrupted suffering and a deterioration of psychophysical capacity [14].

The unpredictability of bleeding episodes and the constant fear of hemorrhaging in public spaces generate perpetual psychological stress [14]. Affected women often intentionally withdraw from social, athletic, and cultural activities [14]. Lower abdominal pain, dysmenorrhea, and coital pain activate chronic stress pathways within the nervous system. Dyspareunia directly erodes intimate partnerships, inducing feelings of guilt, frustration, diminished self-esteem, and a perceived loss of femininity in women [14]. In advanced clinical scenarios, this psychological distress serves as the underlying foundation for full-blown depressive episodes [14]. For many years, such gynecological disorders have carried a profound societal stigma, particularly for women concurrently struggling with infertility.

6.2. Uterine Fibroids and Reproductive Plans

The presence of *leiomyomata uteri* in women of reproductive age represents one of the most formidable challenges in contemporary reproductive medicine [2]. These tumors can interfere with every stage of the reproductive process—ranging from fertilization and embryo implantation to the maintenance of pregnancy [2].

The impact of fibroids on fertility depends fundamentally on their FIGO classification. Submucosal lesions (Types 0, 1, and 2) and intramural lesions that distort the uterine cavity (Type 3) carry the highest clinical significance. These lesions can cause:

- **Mechanical Occlusion of the Fallopian Tube Ostia:** Preventing sperm migration and oocyte transport.

- **Disrupted Myometrial Contractility:** Impairing gamete transport within the uterus.

- **Local Inflammatory and Vascular Alterations in the Endometrium:** Such as endometrial thinning and compromised perfusion, which hinder proper embryo nidation (implantation).

Risk of Pregnancy Loss and Obstetric Complications

If conception occurs, the presence of fibroids significantly upgrades the risk of miscarriage (particularly during the first and second trimesters) due to the restricted space available for the expanding gestational sac and the induction of premature uterine contractions. In the third trimester, large tumors can lead to fetal

malpresentation (e.g., transverse or breech presentation), placental abruption, intrauterine growth restriction (IUGR), and preterm labor.

Psychological Burden

For young women, the realization that a benign uterine neoplasm stands in the way of motherhood—and that its surgical excision carries the risk of uterine scarring or, in severe cases, emergency hysterectomy—presents a profound emotional crisis. Consequently, modern medicine consistently strives to implement therapeutic protocols that are both highly effective and stringently organ-preserving [9, 10].

6.3. Societal Costs and Workplace Absenteeism

Uterine fibroids generate a massive economic burden on healthcare systems and state budgets, extending far beyond the direct costs of hospitalization, surgical procedures, or pharmaceutical reimbursement [13]. The most substantial component of the indirect costs associated with this condition is the loss of workplace productivity among women during their peak socioeconomic activity (between the ages of 25 and 50) [13].

The symptoms provoked by *leiomyomata uteri* manifest within the workplace environment through a dual pathway [13]:

- **Absenteeism:** Heavy, hemorrhagic menstrual periods coupled with acute lower abdominal pain frequently compel patients to take regular, short-term medical leave.
- **Presenteeism:** The phenomenon of attending work despite compromised health. Patients struggling with profound anemia, persistent fatigue, and somatic pain exhibit a drastic decline in efficiency and concentration, which directly translates into reduced work productivity.

International data indicate that the costs of lost workplace productivity due to uterine fibroids surpass the direct costs of surgical management [13]. This condition drastically restricts women's career mobility, prevents them from working overtime, and, in severe clinical scenarios—particularly when appropriate treatment is delayed for years—forces patients to entirely resign from full-time employment [13].

6.4. Holistic Patient Care

The contemporary medical model is shifting away from a narrow, purely surgical perception of uterine fibroids toward a holistic and individualized framework of care [14]. Because this disease impacts hormonal, metabolic, psychological, and social spheres, optimal therapeutic management necessitates the active involvement of an interdisciplinary team.

The Role of the Interdisciplinary Team

- **The Gynecologist:** Responsible for precise diagnostics, tumor classification according to the FIGO framework, and the optimal selection of modern pharmacotherapy (e.g., relugolix) or minimally invasive interventional techniques (such as laparoscopy or HIFU) [8, 10, 11].
- **The Clinical Dietitian:** Implements nutritional interventions targeting insulin resistance, the reduction of visceral adipose tissue (thereby decreasing peripheral estrogen aromatization), and the mitigation of systemic inflammation through an antioxidant-rich diet and the correction of vitamin D3 deficiencies [4, 5].
- **The Psychologist / Psychotherapist:** Provides crucial support during emotional crises associated with infertility, perioperative anxiety (including fear of hysterectomy), diminished sense of femininity, and altered sexual attractiveness [14].
- **The Urogynaecological Physiotherapist:** Aids in the management of chronic pelvic pain by normalizing pelvic floor muscle tone, which frequently exhibits a pathological increase secondary to the chronic pain stimuli generated by the tumors.

Outcome Objectification Using Questionnaires (UFS-QOL)

The modern standard of care mandates evaluating the efficacy of implemented treatments not only through sonographic measurement of tumor size but also via standardized research instruments [12]. The most widely utilized clinical tool is the **UFS-QOL (Uterine Fibroid Symptom and Health-Related Quality of Life)** questionnaire [12]. It allows clinicians to precisely assess symptom severity and its direct impact across six health-related domains: control, anxiety, physical activity, social awareness, body image, and sexual function [12].

7. Discussion

The findings synthesized in this review highlight a profound paradigm shift in the understanding and management of uterine fibroids (*leiomyomata uteri*). Once regarded purely as an isolated anatomical issue requiring standardized surgical extraction, contemporary evidence redefines uterine fibroids as a systemic, multifaceted condition intersecting molecular genetics, environmental influences, innovative clinical pharmacology, and psychosocial well-being. This discussion contextualizes these advancements within the broader clinical landscape and explores their direct implications for patient care and public health.

The Interplay of Genetics and Epigenetics in Pathogenesis

The realization that 70–80% of uterine fibroids harbor somatic mutations in the *MED12* gene, as robustly demonstrated by Mittal et al. [1], solidifies the monoclonal and genetic origin of these tumors. However, a critical insight arising from recent literature is that genetic mutations alone do not fully account for the clinical heterogeneity of the disease. The high prevalence of *MED12* mutations must be viewed in tandem with epigenetic dysregulations and hormonal hypersensitivity. As Ali and Al-Hendy [2] elucidated, estradiol and progesterone act in a highly coordinated, synergistic manner where estrogen fundamentally drives the upregulation of progesterone receptors, allowing progesterone to fuel luteal-phase proliferation.

Crucially, our analysis underscores that the extracellular matrix (ECM) is not merely a passive scaffolding byproduct but an active pathogenetic driver. The mechanical stress induced by excessive deposition of collagen and fibronectin, which constitutes over 50% of the total tumor mass [3], establishes a self-perpetuating mechanical signaling feedback loop. This biomechanical aspect explains why fibroids can continue to grow even during periods of relative systemic hormonal stability, presenting a significant challenge for purely hormone-targeted therapies.

Lifestyle Modification: The Untapped Preventive Frontier

One of the most compelling findings of this review is the substantial impact of modifiable lifestyle factors on fibroid risk and kinetics. The documentation that visceral adiposity, high red meat intake, and vitamin D3 deficiency directly stimulate tumor growth mechanisms [4, 5] opens a vital, yet historical underutilized, avenue for non-pharmacological intervention.

The biological plausibility of these factors is firmly rooted in endocrinology and immunology. Visceral fat functions as a highly active metabolic organ where heightened cytochrome P450 aromatase activity fuels extra-ovarian estrogen production [5]. Simultaneously, obesity-driven insulin resistance lowers Sex Hormone-Binding Globulin (SHBG) synthesis, resulting in an influx of free, biologically active circulating steroids. When combined with the anti-proliferative and pro-apoptotic transcription regulatory roles of calcitriol (vitamin D3) highlighted by Ciebiera et al. [4], it becomes evident that dietary and metabolic corrections can fundamentally alter the myometrial microenvironment. Given that regular physical activity (>3–4 hours/week) reduces fibroid risk by up to 40% [7], incorporating medical nutrition therapy and structured lifestyle counseling into standard gynecological practice represents a powerful, highly cost-effective public health strategy that has been historically overlooked in favor of purely reactive surgical approaches.

The Therapeutic Revolution: Balancing Efficacy, Invasiveness, and Fertility

The management of uterine fibroids is undergoing a profound evolution toward organ-preserving and personalized strategies. For decades, the reliance on radical options like hysterectomy created a significant clinical void for young women desiring to preserve their fertility or avoid the psychological trauma associated with uterine loss.

The introduction of next-generation oral GnRH antagonists, specifically relugolix combination therapy, represents a massive milestone in expanding the conservative therapeutic toolkit. By utilizing an "add-back" hormonal bridge, modern oral antagonists successfully navigate the narrow therapeutic window: suppressing heavy menstrual bleeding in up to 80% of patients while completely neutralizing the risks of profound hypoestrogenism, such as bone mineral density loss and severe vasomotor symptoms [8, 9]. This represents a vast improvement over historical injectable GnRH analogs, which were strictly limited to short-term pre-operative optimization due to their severe side-effect profiles.

Concurrently, the solidification of minimally invasive and non-invasive interventional procedures, such as uterine artery embolization (UAE) and magnetic resonance-guided focused ultrasound (MRgFUS/HIFU), offers robust mid-tier options [10, 11]. These modalities achieve substantial (40–60%) volume reduction and immediate symptom relief without disrupting abdominal wall integrity or demanding lengthy hospital stays. However, a critical nuance emerges when evaluating these techniques for patients with active procreative plans. While hysteroscopic resections (TCRM) remain the gold standard for preserving or restoring fertility in FIGO Type 0–2 submucosal fibroids, techniques like UAE and high-energy thermal ablation (HIFU) demand

cautious, highly individualized application. UAE carries an acknowledged, albeit small, risk of compromising ovarian reserve or endometrial perfusion, while thermal ablation requires strict topographical parameters to avoid uterine scarring that could complicate future pregnancies. Thus, the choice between advanced pharmacology, targeted intervention, and classical surgical enucleation (myomectomy) must strictly hinge upon a comprehensive, individualized mapping of the patient's exact FIGO subclassification alongside her reproductive and lifestyle goals.

Socioeconomic and Psychosocial Imperatives: The Interdisciplinary Solution

Beyond the physiological data, this review brings to the forefront the devastating, multi-dimensional burden that uterine fibroids impose on women and macroeconomics. The psychosomatic loop triggered by profound iron-deficiency anemia, severe dysmenorrhea, and dyspareunia routinely serves as a substrate for full-blown lenty and depressive episodes [14]. The constant, consuming *lek* of public hemorrhaging induces voluntary social, athletic, and cultural withdrawal, generating a profound societal stigma that isolates patients.

Furthermore, health economics data collected by Borah et al. [13] reveal that the indirect costs stemming from workplace productivity losses—namely absenteeism and presenteeism—frequently eclipse the direct costs of clinical and surgical treatment. This stark reality underscores that delaying appropriate, individualized care not only harms the patient's immediate well-being but imposes severe financial strain on corporate and state infrastructures.

To address a condition of this complexity, the traditional siloed approach of standard gynecology is structurally inadequate. The data overwhelmingly support the implementation of a comprehensive, interdisciplinary model of care. As outlined in Section 6.4, the integration of clinical dietitians to correct metabolic and nutritional pathways, urogynaecological physiotherapists to alleviate chronic pelvic floor muscle hypertension, and psychotherapists to guide patients through fertility crises and body image issues represents the gold standard of modern medicine. Crucially, the objective success of any therapeutic intervention must be measured using validated, multi-domain patient-reported outcome measures, such as the UFS-QOL questionnaire [12], ensuring that clinical success is defined by a comprehensive restoration of the patient's global quality of life rather than a simple metric of tumor mass reduction.

Limitations and Future Directions

While this narrative review compiles robust contemporary evidence, certain limitations must be acknowledged. First, narrative reviews are inherently vulnerable to selection bias compared to rigid systematic reviews, though we minimized this by cross-referencing findings across multiple electronic databases up to late 2024. Second, a significant gap remains in long-term data regarding the impact of next-generation GnRH antagonists on future pregnancy outcomes, as well as head-to-head randomized controlled trials directly comparing the long-term quality-of-life scores of patients undergoing MRgFUS versus robotic myomectomy.

Future clinical research should prioritize long-term prospective trials focusing heavily on fertility outcomes and recurrence rates post-pharmacotherapy. Additionally, further public health studies are required to establish structured, evidence-based lifestyle intervention guidelines that can be seamlessly implemented in primary care settings to actively prevent or slow fibroid progression before advanced clinical intervention becomes mandatory.

8. Conclusions

This narrative review represents a multifaceted analysis of the current state of medical knowledge regarding uterine fibroids (*leiomyomata uteri*). A critical appraisal of the recent literature unequivocally demonstrates that this condition is no longer viewed solely through the lens of an isolated gynecological pathology requiring radical surgical intervention. Contemporary medicine defines uterine fibroids as a complex, interdisciplinary challenge wherein molecular pathways, environmental factors, modern medical technologies, and the psychosocial well-being of patients are profoundly intertwined.

Based on the synthesized scientific evidence, the following definitive conclusions have been formulated:

1. **The etiopathogenesis of uterine fibroids is multifactorial.** Although genetic predispositions (particularly somatic mutations in the *MED12* gene) and the synergistic effects of estrogen and progesterone play a fundamental role, the initiation of clonal tumor proliferation and the pathological synthesis of the extracellular matrix (ECM) are heavily modulated by epigenetic mechanisms [1, 2, 3].

2. **Modifiable lifestyle factors constitute an essential component of prevention and adjunctive therapy.** Strong scientific evidence confirms that abdominal obesity (via peripheral aromatization), insulin resistance, a diet rich in red meat, chronic oxidative stress, and vitamin D3 deficiency directly stimulate lesion

progression. Conversely, regular physical activity and phytochemical substances (such as the polyphenol EGCG) demonstrate proven protective potential [4, 5, 7].

3. Contemporary gynecology is undergoing a paradigm shift toward organ-preserving modalities.

The introduction of innovative, next-generation pharmacotherapy—including oral GnRH antagonists (such as relugolix) in combination regimens—allows for safe, long-term disease management [8, 9]. Concurrently, the development of micro- and minimally invasive techniques, such as robotic laparoscopy, uterine artery embolization (UAE), and non-invasive high-intensity focused ultrasound thermal ablation (HIFU/MRgFUS), enables effective tumor destruction with minimal physical burden on the patient while preserving her reproductive potential [10, 11].

4. Uterine fibroids generate profound psychosocial and economic costs. Chronic pain, severe anemia resulting from prolonged bleeding, sexual dysfunction, and infertility drastically diminish patients' quality of life, serving as an underlying substrate for anxiety and depressive disorders [14]. Furthermore, high rates of workplace absenteeism and presenteeism render this disease a significant macroeconomic burden on society [13].

5. The optimal standard of patient care requires the implementation of a holistic model. Successful management of uterine fibroids should not rely solely on tumor reduction, but rather on striving for the comprehensive well-being of the patient. This requires close collaboration within an interdisciplinary team (gynecologist, clinical dietitian, psychologist, and urogynaecological physiotherapist) and the regular evaluation of treatment outcomes using standardized research tools, such as the UFS-QOL questionnaire [12, 14].

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