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HORMONAL AND METABOLIC FACTORS IN THE DEVELOPMENT OF UTERINE FIBROIDS

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Abstract

Uterine fibroids, also known as uterine leiomyomas, are benign monoclonal tumors arising from the smooth muscle cells of the myometrium. They are among the most common gynecological tumors in women of reproductive age and represent a major cause of abnormal uterine bleeding, pelvic pain, infertility, pregnancy complications, anemia, and reduced quality of life. Although fibroids are histologically benign, their biological behavior is strongly influenced by hormonal and metabolic factors. Estrogen and progesterone are central regulators of fibroid growth, while obesity, insulin resistance, chronic low-grade inflammation, dyslipidemia, vitamin D deficiency, and altered extracellular matrix metabolism may contribute to fibroid initiation, progression, and symptom severity.

Modern studies increasingly describe uterine fibroids as hormonally responsive and metabolically active tumors rather than simple “overgrowths” of uterine muscle. Fibroid cells respond to ovarian steroids through estrogen and progesterone receptors, and their growth is supported by local growth factors, angiogenesis, extracellular matrix accumulation, and altered cellular signaling. Recent evidence also suggests that metabolic disorders, especially obesity and insulin resistance, may increase fibroid risk

or prevalence. A 2025 meta-analysis reported that obesity may increase the risk/prevalence of uterine fibroids, while insulin resistance and body mass index may be independently associated with fibroid presence in non-diabetic women.

Keywords: uterine fibroids, leiomyoma, estrogen, progesterone, obesity, insulin resistance, metabolic syndrome, inflammation, extracellular matrix, reproductive health.

Introduction

Uterine fibroids are one of the most important benign diseases of the female reproductive system. They may remain asymptomatic for years, but in many women they cause heavy menstrual bleeding, prolonged menstruation, pelvic pressure, pain, infertility, recurrent pregnancy loss, urinary frequency, constipation, and anemia. The American College of Obstetricians and Gynecologists describes symptomatic uterine leiomyomas as a major clinical problem requiring individualized medical, procedural, and surgical management.

The epidemiological burden of uterine fibroids is high. A comprehensive review reported that fibroids are particularly common by midlife, with ultrasound-screening studies showing cumulative prevalence approaching 70% among White women and exceeding 80% among Black women by age 50 in the United States. Global burden studies also show that fibroid incidence and prevalence increase during reproductive age, with higher rates commonly observed after age 35–40 and a substantial burden among women aged 40–54 years.

The development of fibroids is multifactorial. Genetic mutations, especially in MED12 and other molecular pathways, are involved in tumor initiation, but hormonal and metabolic factors strongly influence growth and clinical expression. Fibroids rarely appear before puberty, often enlarge during reproductive years, may grow during pregnancy, and typically regress after menopause, all of which demonstrates their dependence on the reproductive hormonal environment. Estrogen and progesterone do

not simply "feed" fibroids in a linear way; they regulate a network of growth factors, extracellular matrix production, angiogenic signaling, and cellular proliferation.

Metabolic factors are also increasingly recognized. Obesity, insulin resistance, hyperinsulinemia, chronic inflammation, and adipose-derived estrogen production may create an internal environment favorable to fibroid growth. This connection is clinically important because metabolic risk factors are potentially modifiable. Therefore, understanding the hormonal and metabolic mechanisms of fibroid development can improve prevention, early detection, counseling, and individualized treatment.

Materials and Methods

This article was prepared as a narrative scientific review. Current gynecological, endocrinological, metabolic, and reproductive medicine sources were analyzed. Priority was given to peer-reviewed reviews, epidemiological studies, meta-analyses, and clinical guidance from authoritative organizations such as ACOG. The review focused on the following domains: hormonal regulation of fibroid growth, estrogen and progesterone receptor activity, metabolic syndrome, obesity, insulin resistance, inflammation, extracellular matrix remodeling, clinical manifestations, and treatment implications.

The analysis used a clinical-biological approach. First, the hormonal basis of fibroid development was described. Second, metabolic contributors were analyzed. Third, the interaction between hormonal and metabolic pathways was discussed. Finally, clinical significance, prevention, and limitations of current knowledge were evaluated.

Results

Hormonal dependence of uterine fibroids

The reviewed evidence confirms that uterine fibroids are highly hormone-responsive tumors. Their occurrence during reproductive age, tendency to change during pregnancy, and regression after menopause show the central role of ovarian steroids. Estrogen promotes myometrial and fibroid cell proliferation, stimulates growth factor expression, and may increase progesterone receptor expression. Progesterone, once

considered less important than estrogen, is now recognized as a major driver of fibroid growth and extracellular matrix accumulation.

Recent physiological reviews emphasize that fibroid growth is associated with states of increased progesterone production, including ovulatory cycles and early pregnancy. This is clinically important because it explains why progesterone signaling is a major therapeutic target and why medications that modulate progesterone receptors can reduce bleeding or fibroid volume in some settings.

Estrogen and fibroid biology

Estrogen acts mainly through estrogen receptors in fibroid and myometrial cells. It supports cell proliferation, increases local growth factor activity, and may enhance tissue sensitivity to progesterone. Fibroids often contain increased expression of steroid hormone receptors compared with adjacent normal myometrium, making them more responsive to ovarian hormones.

Estrogen also interacts with local aromatase activity. Some fibroid tissues may produce estrogen locally through aromatase-mediated conversion of androgens to estrogens, creating a local hormonal microenvironment that supports tumor growth even when systemic hormone levels are not markedly abnormal. This helps explain why circulating hormone levels alone do not always predict fibroid size or symptoms.

Progesterone as a growth-promoting hormone

Progesterone has a complex but central role in fibroid pathophysiology. It promotes cell survival, decreases apoptosis, enhances extracellular matrix deposition, and stimulates growth factors such as transforming growth factor-beta. Fibroids are not only cellular tumors; they are also rich in extracellular matrix, which contributes to their firmness, enlargement, and mechanical effects on the uterus.

This progesterone-driven matrix accumulation is important because fibroid symptoms are not determined only by cell number. A fibroid may become clinically significant because of its size, location, vascularity, and matrix density. Submucosal fibroids may

cause heavy menstrual bleeding even when small, whereas large intramural or subserosal fibroids may cause pressure symptoms.

Obesity and adipose-derived hormonal effects

Obesity is one of the most important metabolic factors associated with fibroids. Adipose tissue is not passive fat storage; it is an endocrine organ. It produces adipokines, inflammatory cytokines, and contributes to peripheral estrogen production through aromatase activity. In women with increased adiposity, higher peripheral estrogen availability may support fibroid growth, especially when combined with insulin resistance and chronic inflammation.

A 2025 analysis found that obesity may increase uterine fibroid risk or prevalence, and BMI was independently and positively associated with fibroid presence in non-diabetic women. This does not mean that obesity is the only cause of fibroids, but it supports the idea that body composition and metabolic health can influence fibroid biology.

Insulin resistance and hyperinsulinemia

Insulin resistance may contribute to fibroid development through several mechanisms. When tissues become less responsive to insulin, the pancreas produces more insulin to maintain normal glucose levels. Hyperinsulinemia can increase insulin-like growth factor signaling, promote cellular proliferation, reduce apoptosis, and interact with ovarian steroid pathways.

Recent evidence suggests that insulin resistance and BMI may be independently associated with uterine fibroids in non-diabetic women. This finding is clinically meaningful because it suggests that fibroid risk is not only connected to reproductive hormones but also to systemic metabolic regulation.

Chronic inflammation and oxidative stress

Metabolic dysfunction is often accompanied by chronic low-grade inflammation. Adipose tissue can release inflammatory mediators such as interleukins and tumor necrosis factor-alpha, which may influence uterine tissue remodeling, angiogenesis,

and extracellular matrix production. Oxidative stress may also damage cellular signaling and promote abnormal proliferation.

Inflammation may help connect obesity, insulin resistance, and fibroid growth. In this model, fibroids develop in a local uterine environment influenced by systemic metabolic status, vascular changes, immune signaling, and hormone sensitivity.

Vitamin D and fibroid risk

Vitamin D deficiency has been investigated as a possible factor in fibroid development. Vitamin D has anti-proliferative, anti-inflammatory, and anti-fibrotic effects in several tissues. Some studies suggest that low vitamin D levels may be associated with increased fibroid risk or growth, although evidence is still developing and not all findings are uniform.

The biological plausibility is strong because fibroids are characterized by excessive proliferation and extracellular matrix accumulation. Vitamin D may theoretically reduce these processes, but more randomized clinical trials are needed before it can be considered a standard preventive or therapeutic intervention.

Discussion

The development of uterine fibroids cannot be explained by a single factor. A more accurate model is that fibroids arise from genetically altered myometrial cells and then grow under the influence of hormonal, metabolic, inflammatory, and extracellular matrix-related factors. Estrogen and progesterone create a permissive reproductive environment, while metabolic dysfunction may intensify growth signaling and tissue remodeling.

Why hormones matter

The reproductive pattern of fibroids clearly shows hormonal dependence. They are uncommon before menarche, grow during reproductive years, and usually shrink after menopause. However, it is not enough to say that “estrogen causes fibroids.” Estrogen and progesterone act through receptors, growth factors, local tissue enzymes, vascular

signals, and extracellular matrix pathways. Their effects depend on cell sensitivity and local uterine microenvironment.

Progesterone is especially important because it supports fibroid cell survival and matrix accumulation. This explains why progesterone receptor modulators and gonadotropin-releasing hormone analogues or antagonists can reduce symptoms in selected patients. However, medication effects may be temporary, and fibroids may regrow after therapy stops.

Why metabolic factors matter

Metabolic health influences the hormonal environment. Obesity increases peripheral estrogen production and inflammatory signaling. Insulin resistance increases growth-promoting pathways. Dyslipidemia and chronic inflammation may contribute to endothelial dysfunction and abnormal tissue remodeling. Together, these factors may create an environment that supports fibroid growth.

This relationship has practical importance. Lifestyle modification cannot guarantee fibroid prevention, especially because genetics, age, race, reproductive history, and molecular factors are also involved. However, weight management, physical activity, improved insulin sensitivity, and correction of metabolic risk factors may reduce overall gynecological and cardiovascular risk and may be beneficial as part of holistic care.

Clinical significance

Hormonal and metabolic factors influence not only fibroid growth but also symptom severity. Heavy menstrual bleeding can lead to iron-deficiency anemia, fatigue, reduced work capacity, and poor quality of life. Large fibroids can cause pelvic pressure, urinary symptoms, constipation, and reproductive difficulties. Fibroids can also complicate pregnancy depending on size and location.

ACOG emphasizes that management of symptomatic uterine leiomyomas should be individualized, considering symptom burden, fibroid size and location, patient age, reproductive goals, medical comorbidities, and preference for uterine preservation.

This individualized approach is especially important in women with metabolic disorders, because obesity, hypertension, diabetes, or thrombotic risk may affect treatment choice.

Modern treatment implications

Understanding hormonal mechanisms has led to medical therapies that suppress ovarian hormone production or modulate hormone receptors. These include gonadotropin-releasing hormone agonists and antagonists, selective progesterone receptor modulators in some regions, hormonal intrauterine systems for bleeding control, and other symptom-directed approaches. Procedural options include myomectomy, uterine artery embolization, radiofrequency ablation, focused ultrasound, and hysterectomy when appropriate.

Metabolic factors also influence treatment outcomes. Obesity may increase surgical complexity, anesthesia risk, wound complications, and recurrence risk. Insulin resistance and chronic inflammation may worsen general reproductive health. Therefore, metabolic assessment should be part of fibroid care, especially in women with obesity, polycystic ovary syndrome, diabetes risk, or hypertension.

Limitations and unresolved questions

Despite major progress, several questions remain unresolved. It is still unclear why some women with obesity or insulin resistance develop fibroids while others do not. The role of vitamin D supplementation, diet, microbiome, environmental endocrine disruptors, and genetic-metabolic interactions requires more research. There is also a need for better biomarkers predicting fibroid growth, symptom progression, and treatment response.

Another limitation is that many women with fibroids remain undiagnosed until symptoms become severe. Because fibroids are common, symptoms such as heavy bleeding are sometimes normalized, delaying care. Public education and early gynecological evaluation are important, particularly for women with anemia, infertility, recurrent pregnancy loss, or pelvic pressure symptoms.

Conclusion

Uterine fibroids are common benign tumors whose development and growth are strongly influenced by hormonal and metabolic factors. Estrogen and progesterone regulate fibroid cell proliferation, survival, growth factor activity, angiogenesis, and extracellular matrix accumulation. Progesterone is particularly important in sustaining fibroid growth and matrix deposition.

Metabolic factors such as obesity, insulin resistance, hyperinsulinemia, chronic inflammation, dyslipidemia, and possibly vitamin D deficiency may contribute to fibroid risk and progression. Recent evidence supports an association between obesity, insulin resistance, BMI, and fibroid presence, suggesting that metabolic health should be considered in fibroid prevention and management.

Clinically, fibroid care should be individualized. A woman's symptoms, reproductive goals, hormonal status, metabolic profile, anemia risk, fibroid location, and treatment preference should all guide management. The most effective approach is not only to treat the fibroid mass but also to understand the hormonal and metabolic environment in which it develops.

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