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REVIEW

The etiopathogenesis of uterine leiomyomas: A review

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Abstract

Background. The most frequent female reproductive system tumors are uterine leiomyoma (UL). They are benign monoclonal tumors of uterine smooth muscle. They affect reproductive-age women with a lifetime prevalence of 30–70%. UL is a disease with complex etiology determined by many genetic and environmental factors. Despite the frequency of UL, there is no long-term, cost-effective or fertility-preserving therapy option for it.

Aim. To summarize the available literature data on the etiopathogenesis of uterine fibroids as well as the risk factors for the development of this disease.

Materials and methods. The PubMed, Scopus, and Web of science literature databases were searched for relevant articles using such keywords as uterine fibroids, UL, association, genetic and hormonal factors, gene, etiology in various combinations.

Results. Genetic disorders and hormonal and growth factors all have a part in the etiology of UL, and studies have resulted to the use of hormone therapy for fibroids, with varying results. Recent findings on the etiopathogenesis of UL, as well as the introduction of relevant genetically modified mouse models of UL, have rekindled interest in the disease. In this review, the basic features of fibroids are discussed, as well as the primary contributors to UL etiopathogenesis, including as genetic, hormonal, and growth causes. Besides the risk factors that contribute to the development of UL.

Conclusion. Many questions about the causes and mechanisms of development factors that predispose remain unanswered, necessitating the continuation of these studies in order to obtain new information. Prospective studies are needed to better understand the biology and epidemiological associations, both to better understand modifiable risk factors and to shed light on the etiopathogenesis of this disease.

Keywords: uterine fibroids, leiomyomas, etiopathogenesis, genetic, hormonal, risk factors

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ОБЗОР

Этиопатогенез миомы матки (обзор)

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Аннотация

Обоснование. Наиболее частой опухолью женской репродуктивной системы является лейомиома матки (UL). Это доброкачественная моноклональная опухоль гладкой мышечной ткани матки. Она поражает женщин репродуктивного возраста и встречается в течение всей жизни у 30-70%. UL это заболевание со сложной этиологией, в которую вовлечены многие генетические и средовые факторы. Несмотря на значительную распространенность UL, для нее в полной мере не разработаны долгосрочные, экономически эффективные варианты терапии и сохранения фертильности.

Цель. Обобщить имеющиеся в литературе данные об этиопатогенезе миомы матки, а также о факторах риска развития этого заболевания.

Материалы и методы. В базах данных литературы PubMed, Scopus и Web of Science был проведен поиск соответствующих статей с использованием таких ключевых слов, как «миома матки», «UL», «ассоциация», «генетические и гормональные факторы», «ген», «этиология» в различных комбинациях.

Результаты. Генетические нарушения, гормональные факторы и факторы роста играют определенную роль в этиологии UL, при этом результаты исследований использования гормональной терапии при миоме различаются. Исследования этиопатогенеза UL, связанные с использованием генетически модифицированных мышиных моделей заболевания, являются достаточно интересными. В этом обзоре обсуждаются основные факторы этиопатогенеза миомы матки, и в том числе генетические, гормональные и факторы роста. Рассматриваются факторы риска, которые способствуют развитию UL.

Заключение. Многие вопросы о причинах и механизмах развития миомы матки, ее факторах риска остаются без ответа, что обуславливает необходимость продолжения этих исследований с целью получения новой информации. Проведение дальнейших работ в этой области позволит лучше понять причины и факторы риска развития заболевания.

Ключевые слова: миома матки, лейомиома, этиопатогенез, генетические, гормональные факторы риска

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Introduction

The most frequent female reproductive system tumors are uterine fibroids (also known as leiomyomas or myomas) [1, 2]. They are benign monoclonal tumors of uterine smooth muscle that arise from the myometrium [3, 4]. They are made up of vast volumes of extracellular matrix containing collagen, fibronectin, and proteoglycans. Uterine fibroids affect more than 70% of women by the time they reach menopause. They effect 20–40% of reproductive-age women [4] (they often regress after menopause) [5], with a lifetime prevalence of 30–70% [5, 6].

While many women with uterine fibroids stay without noticing their symptoms, around a quarter of them have symptoms, such as, heavy or prolonged menstrual bleeding, pelvic pressure/pain, abdominal pain, pregnancy complications, dysmenorrhea,

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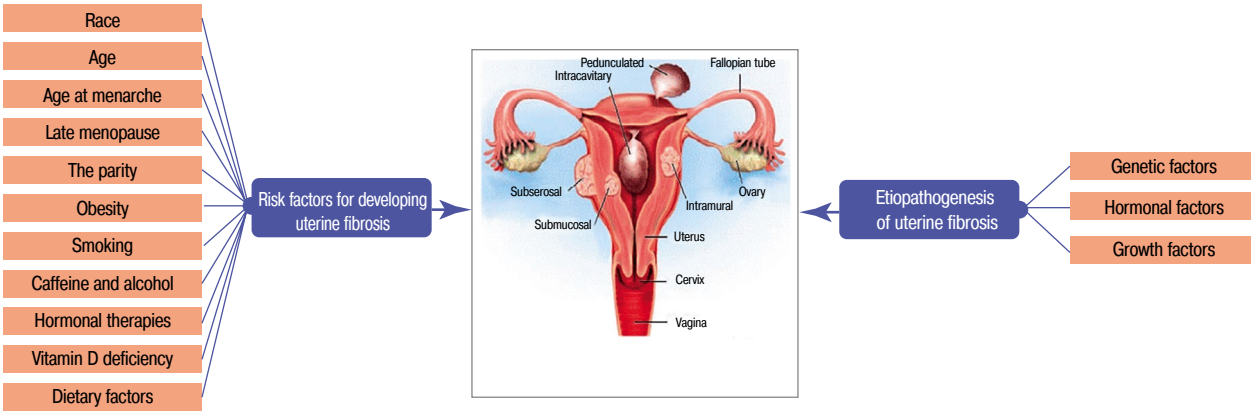
Fig. 1. Etiopathogenesis and risk factors for the development of ULs.

Рис. 1. Этиопатогенез и факторы риска развития UL.



menorrhagia, anemia, urine incontinence, preterm labor, and infertility are all possible outcomes [7] and possible reproductive disruption, as well as other indications of fibroids' bulk effect on health-related quality of life. Complications occur in 10–40% of pregnancies with uterine leiomyoma (UL) present, and miscarriage is up to two times higher in women with symptomatic UL [8]. The symptoms are exacerbated by the position of UL within the uterus. According to their location, ULs are characterized as subserosal, intramural, submucosal, or pedunculated [3]. In a meta-analysis of many research on fibroids and infertility, submucosal fibroids were found to have a significant impact on all fertility outcomes and subserosal fibroids are thought to have a minor effect on fertility [9].

Uterine fibroids are a leading source of gynecologic morbidity, one of the leading causes of gynecological hospitalizations, and the most common reason for hysterectomy in the United States [10]. Fibroids account for 29% of gynecologic hospitalizations in women aged 15–54 years. Fibroids also account for 40–60% of all hysterectomies performed, and 30% of hysterectomies conducted among young women 18–44 years of age [11]. ULs have a significant economic impact: the annual cost of treating this disorder in the United States is estimated to be around $34 billion, which is more than the combined cost of treating breast and colon cancers [12].

Inpatient admissions for UL in U.S. hospitals increased by more than 20% between 1993 and 2003, and UL remains the most common diagnosis among gynecologic inpatient hospitalizations in women 15–54 years of age [11]. The percentage of hysterectomies owing to UL fell from 31.4–26.9% between 1997 and 2005 [10]. Alternative surgeries such as myomectomy, uterine artery embolization have all increased during the same time period [10, 11], thermo-ablative therapies, magnetic resonance-guided focused ultrasounds, and symptomatic medical therapies (i.e., progesterone receptor modulators, tranexamic acid, gonadotropin-releasing hormone agonists, and primarily both the oral contraceptive and the levonorgestrel intrauterine device) [1]. Treatments for uterine myomas are mostly guided by the need to protect female fertility and the myoma's unique characteristics.

ULs are associated with a high rate of morbidity and can jeopardize everyday activities, relationships, and work performance [13]. The overall quality of life of women with ULs is severely harmed, and it deteriorates as the quantity and severity of symptoms grow. Medical intervention is frequently required for lesions that cause these symptoms [14]. Health-care costs and indirect costs associated with myoma, such as the cost of sanitary goods, complementary and alternative therapies, and lost monetary revenue owing to disability and time away from work, are substantial social and economic issues. Furthermore, fibroids-related infertility and pregnancy complications could be added to the overall expenditures and morbidity [10].

Etiopathogenesis of ULs

Despite their widespread occurrence, little is known about the causes of ULs. Many studies have been conducted on the etiopathogenesis of uterine fibroids (fig. 1), but they were not enough, and there are currently more questions than answers [1]. Several biological and genetic causes and mechanisms for the initiation and progression of ULs have been investigated [15–20]. But more studies are still needed to clarify and understand the mechanisms of growth and development of these tumors.

Genetic factors

The relevance of chromosomal alterations in the etiopathogenesis of uterine fibromatosis has recently been demonstrated [21]. Thus, common chromosomal abnormalities with other types of tumors, such as renal, pulmonary, or leiomyosarcoma, produce roughly 40% of uterine fibroma [22].

Several investigations have discovered evidence of a genetic predisposition to UL values ranging from 8–70% [23], including familial aggregation studies, which revealed that the prevalence of leiomyomas was greater among first-degree related women than among unrelated women [21, 24]. Heritability estimates of UL from twin studies range from 26–69% in European populations [4, 25]. Twin studies found greater concordance percentages between monozygotic twins than between dizygotic twins [2], as well as genetic linkage studies in families with UL-related syndromes [10].

The important sites in tumor growth are recognized to be genetic abnormalities, and a large quantity of evidence has lately gathered in this sector. Multiple gene changes in UL cells distinguish them from normal ute1rine muscle cells. A probable functional involvement of promoter deoxyribonucleic acid methylation-mediated gene silencing in the etiology of those tumors has been hypothesized, as in many other cases [26].

Translocations between chromosomes 12 and 14, translocations between chromosomes 6 and 10, and deletions of chromosomes 3 and 7 are among the mutations that cause uterine fibromatosis [22].

According to new study, most fibroids are caused by one of four alterations: *MED12* mutations, FH inactivation, COL4A6-COL4A5 deletions, or *HMGA2* overexpression [21].

FH is a tumor suppressor enzyme from the Krebs cycle. HLRCC (hereditary leiomyomatosis and renal cell carcinoma) is an autosomal-dominant condition caused by a germline mutation in the FH gene, which is located on chromosome 1q42.2. A somatic change in the wild-type copy of the *FH* allele (the so-called "second hit") causes loss of FH activity and, as a result, fumarate buildup in target tissues (skin, uterus, and kidney) in these patients [27]. HLRCC patients acquire ULs at a younger age, and they are generally many (up to 20) and larger in size (from 1.5 to 10 cm). Even in reproductive age, these women are symptomatic and at high risk for hysterectomy [10].

The two discrete genetic events in UL tumorigenesis in one research of *HMGA2* and *MED12* mutations in fibroids, suggesting the hypothesis that various genetic abnormalities in fibroids truly reflect separate pathophysiology [28]. *HMGA2* mutations are strongly associated with large fibroid tumors, whereas *MED12* mutations are associated with smaller tumors. Because they may play a role in stem cell function [29].

As a result, both types of mutations define distinct tumor entities that can be distinguished based on clinical and histological characteristics such as size and stromal content, gene expression patterns, and metabolome, and may even differ in terms of cellular growth capacity in vitro. Furthermore, they only very infrequently coexist among the tumors of individual patients [30]. One of the most often seen cytogenetic anomalies is the *HMGA2* found in translocations 12:14, which destroys a putative regulatory region generally 5' of the high-mobility group AT-hook 2 (*HMGA2*) gene [31].

HMGA2 mutations are found in about 7.5% of fibroid tumors but not in the normal myometrium, and *HMGA2* overexpression is caused by chromosome 12q1415 rearrangements, which are the most common cytogenetic anomaly, occurring in about 20% of uterine fibroma but not in the normal myometrium [29].

The *HMGA2* gene produces proteins that act on cellular deoxyribonucleic acid to promote embryo-type proliferation. This gene is expressed not only in leiomyomatous cells, but also in other organs such as the lung and liver [22]. *HMGA2* expression reduces senescence in mouse neural stem cells by downregulating p16INK4a, a stem cell self-renewal suppressor. In fibroid cells, *HMGA2* has been found to downregulate p14Arf, another negative regulator of self-renewal. Finally, uterine fibroids have low levels of Let-7, a protein that suppresses *HMGA2*. These findings have led us to believe that when the Let7-*HMGA2*-p14Arf pathway is disrupted, it can result in greater self-renewal and reduced senescence in fibroid stem cells [29].

Specific *MED12* mutations were discovered in 70% of fibroids in the biggest investigation of *MED12* mutations in fibroids, however other studies have shown prevalence ranging from 48–92% [32]. *MED12* mutations have been found in fibroid stem cells but not in myometrial stem cells, confirming our hypothesis that a genetic hit might explain the change of a myometrial stem cell to a fibroid stem cell [29]. *MED12* mutations are common in codon 44 of exon 2 [33] and less common in exon 1 [34] in UL, generally in the absence of any other recurrent mutations. This study suggests that *MED12* mutations alone may be enough to trigger tumor growth. A hotspot for minor deletions in *MED12* has also been discovered in UL, which might be caused by non-canonical deoxyribonucleic acid structures seen in this hotspot [33]. Because *MED12* modulates Wnt signaling by attaching to β-catenin, it's likely that fibroid stem cells lacking *MED12* or having abnormalities in *MED12* might lead to uncontrolled Wnt/β-catenin pathway-stimulated tumor growth [3]. Furthermore, *MED12* loss, which may occur in somatic stem cells, causes transforming growth factor β (TGF-β) signaling to be negatively regulated, resulting in enhanced cancer cell proliferation. This data implies that *MED12* loss may activate the Wnt/β-catenin and TGF-β pathways, promoting stem cell renewal, proliferation, and fibrosis in uterine fibroids [3].

Other less common genetic abnormalities are reported in double-negative (no *MED12* mutations or *HMGA2* rearrangements) fibroids [35], which also have a larger frequency of histological variations. Nonetheless, it has been established that solitary fibroids may be recognized in these circumstances as well based on the particular mutations they carry [30].

Six genome-wide association studies of UL have been reported, and certain common single nucleotide polymorphisms have been linked to leiomyoma risk at 1p36.12 (CDC42/WNT4) [7, 36–38], 1q24.3(DNM3) [36], 2p25.1(GREB1) [7, 37, 38], 2p23.2(BABAM2) [7], 3p24.1(NEK10) [37], 3q26.2(TERC/LRRC34) [7, 38], 3q2915,4q12(SCFD2/LNX1/PDGFRA) [7, 37, 38], 4q13.3(SULT1B1/SULT1E1) [7, 37, 38], 4q22.3(PDLIM5) [7], 5p15.33(TERT) [7, 37, 38], 5q35.2(ZNF346) [7, 38], 6p21.31(GRM4/HMGA1) [7], 6q25.2(SYNE1/ESR1) [7, 36–38], 9p24.33(KANK1/DMRT1/ANKRD15/LOC105375949) [7, 36–38], 10p11.22(ZEB1/ARHGAP12) [7], 10q24.33(OBFC1) [7, 36–38], 11p15.5(SCGB1C1/BET1L/SIRT3/RIC8A) [7, 36–38], 11p14.1(FSHB) [7], 11p13(WT1/PDHX/CD44) [7, 36–38], 11q22.3(ATM/C11orf65/KDELC2)[7,37,38],12q13.11(SLC38A2/LOC100288798) [7, 38], 12q15(PTPRR) [7], 12q24.31(PITPNM2) [7], 13q14.11(LINC0/FOXO1) [7, 37, 38], 16q12.1(HEATR3/SALL1) [36, 38], 17p13.1(TP53) [7, 36–38], 20p12.3(MCM8) [7, 37], 20q13.13(LOC105372640) [36], 22q13.1(TNRC6B/CYTH4) [7, 36–38], Xq13.1(TEX11/*MED12*) [7, 38], and Xq26.2(RAP2C) [7, 38]. Furthermore, UL is haven genetic alterations of some driver genes, including *MED12* mutations, biallelic inactivation of FH, and *HMGA2* rearrangements. However, only a percentage of the UL genetic variants could be explained. It has been discovered three risk loci for ULs on 10q24.33, 11p15.5, and 22q13.1 in a prior study including 1,607 Japanese patients [39].

Hormonal Factors

Uterine fibroids are heavily reliant on estrogen and progesterone for development [22, 40], ovarian activity is required for fibroid growth, and most fibroids diminish after menopause. Hormone and hormone receptor concentrations in uterine tissue differ between UL and healthy myometrial tissue [40].

Estradiol, aromatase, progesterone receptor (PR), and estrogen receptor (ER) concentrations are all increased in ULs. Increased ER-α and PR expression is independent of tumor size, can be diverse within a single patient's tumors, and is constant throughout all menstrual cycle phases. As a result, unlike the usual myometrial response to estrogen and progesterone, ULs appear to be hypersensitive to sex steroid hormones [40]. UL tissue displays an increase in estrogen-regulated genes in the luteal phase, but normal myometrium has a restricted sensitivity to estrogen and becomes dormant in the luteal phase. UL also increases in response to progesterone, which has a suppressive impact on the myometrium [41], in addition to the loss of estrogen's temporal/cyclical control. When this shift in response to sex steroid hormones happens in UL is unknown. Women with and without UL had equal amounts of estrogen and progesterone in their blood. African American women, on the other hand, had 18% greater estradiol levels than Caucasians, with no difference in progesterone levels.

Progesterone appears to play a critical role in uterine fibroid growth, whereas estrogen appears to play a more permissive function in uterine fibroids, mostly through upregulating PRs in uterine fibroids [3, 42].

Estrogen has been linked to the pathophysiology of UL because of its strong influence on the expression of genes involved in cell

proliferation and apoptosis [12]. Estrogen levels in UL patients may be high due to two factors. The first is estrogen in the circulation, and the second is estrogen generated in fibroid tissue by aromatase conversion of androgens. The latter appears to be especially critical for the development of UL, since aromatase expression was not detected in healthy myometrium. Furthermore, even in the absence of estrogen from other sources, this source of estrogen is sufficient to keep fibroid tissue growing [12].

Progesterone's involvement in fibroid development is multifaceted, encompassing proliferative and antiapoptotic actions, as well as stimulatory effects on extracellular matrix proteins [42]. Increased expression of both PR isoforms (PR-A and PR-B) in fibroid tissue compared to adjacent normal myometrium, increased mitotic activity and proliferation marker (Ki-67) expression, and upregulation of epidermal growth factor in fibroid tissue during the luteal phase or after progestogen treatment are all evidence supporting progesterone's critical role in the pathophysiology of uterine fibroids.

The rapid growth of the fibroma after the age of 30, particularly during premenopause, was linked to age-related changes in the hormonal constellation (fluctuations) – the change of the estroprogestative balance, which implies an increasing luteinizing hormone (LH) level during perimenopause, leading to an increase in the volume of the uterine fibroma [22].

The researchers anticipated that perimenopausal elevations in LH would boost fibroid growth because LH shares a receptor with human chorionic gonadotropin, which stimulates uterine growth during early pregnancy. As predicted, rising LH levels resulted in a considerable rise in fibroid development [11]. The impact, however, was shown to be more significantly linked to tumor beginning than to tumor growth [43].

Growth factors

Growth factors are proteins that control a variety of cellular functions such as survival, proliferation, migration, and differentiation. Scientists frequently use the terms "growth factor" and "cytokine" interchangeably [44]. For years, scientists have recognized that certain growth factors play a role in UL cell proliferation and tumor formation in UL biology. Epidermal growth factor, fibroblast growth factor, insulin-like growth factor, platelet derived growth factor, TGF, and vascular endothelial growth factor (VEGF) [24] are the different types of growth factors [45].

TGF signaling activation has been considered as a key contribution to UL pathogenesis, owing to smooth muscle cell proliferation and extracellular matrix deposition, which may serve as a reservoir of pro-fibrotic growth factors and a stabilizer of their signaling duration [46]. TGF-β1, TGF-β2, and TGF-β3 are three different TGF-β isoforms found in the myometrium. TGF-β1 and 2 are expressed in the myometrium and UL tissue at equal levels, however TGF-β3 is overexpressed in UL [22]. TGF- expression in the uterus is interestingly sensitive to sex steroid hormones and functions downstream of ambient estrogen signaling, which is a major risk factor for the development of UL. TGF-β3 expression levels vary during the menstrual cycle, maximum during the secretory phase, indicating regulation by progesterone and estrogen [22].

Because of its function in angiogenesis, which is critical for tumor development and cell proliferation, vascular endothelial growth factor-A has been extensively researched. Estrogen and progesterone impact vascular endothelial growth factor expression, which is stronger in UL than in myometrium [10]. Endothelium, smooth muscle cells, and fibroblasts are all affected by fibroblast growth factor, which is primarily expressed in the extracellular matrix [10].

Insulin-like growth factor-1 is also greater in leiomyoma tissue and may be controlled by estrogen and autocrine control. Insulin-like growth factor-1 increases leiomyocyte proliferation, however high levels in the blood are not linked to tumor incidence. Growth factor alterations caused by myometrial damage promote cellular proliferation, reduce apoptosis, and boost extracellular matrix production [10].

Risk factors for the development of uterine fibroids

There are numerous epidemiological studies examining some of the main risk factors for ULs, including race (e.g. African-American), age at menarche, parity, premenopausal state, hypertension, positive family history of ULs, nulliparity, time since last birth, and various food additives, including soy [10, 11, 47]. Obesity and a lack of vitamin D are also important factors [48].

Race

Race is a significant risk factor for the development of leiomyoma [1]. According to a US study, African-American women's uterine fibroids were 60% by age 35, rising to >80% by age 50, while Caucasian women's rates were 40% by age 35, rising to 70% by age 50 [34]. These growth rates may be influenced by differences in gene expression in uterine fibroids between these two groups [49]. Nonetheless, it is known that African-American women are more likely to develop uterine fibroids, especially at a younger age [10]. A similar trend has been observed among African-American women living in Europe, with more severe symptoms and surgery required at a younger age. Furthermore, for African-American women, recurrence rates after surgery (myomectomy) might be as high as 59% after 4–5 years [50].

It's unclear why black women are diagnosed with UL more frequently and earlier. The discrepancy does not appear to be due to differences in symptom kinds and severity, health-care utilization, or the presence of putative risk factors. Adjusting for many known or suspected risk factors did not significantly reduce the three-fold difference in risk between black and white women in both the Nurses' Health Study (NHS II) and the ULs. The fact that black women have more UL, larger tumors, and more uterine weight than white women shows that the racial disparity is due to a hereditary foundation. Vitamin D insufficiency, reproductive tract infections, psychosocial stressors, and other environmental factors, which have yet to be found or clarified, cannot be ruled out as plausible explanations [10].

Age

Fibroids are more likely to develop as people get older. Fibroids that have been pathologically diagnosed increase in frequency with age, peaking at 50 years. Myomas do not appear before puberty and become less common after menopause [10, 11]. Early-pregnancy screening of pregnant women provided the data on young women (19–35 years old) [11]. Fibroids appear to appear earlier in black women than in white women, according to studies on pregnant women. African-American women have a 60% uterine fibroids incidence by age 35, rising to >80% by age 50, whereas Caucasian women have a 40% uterine fibroids incidence by age 35, rising to almost 70% by age 50 [11]. The risk of ULs hospitalization rises with age, peaking at 62.7 per 10.000 among women aged 45–49 years old, then falling to 31.8 per 10.000 among women aged 50–54 years old [10]. As women get older, the incidence and quantity of fibroids increases dramatically, mirroring the natural history of fibroids, which is that they grow over time and are so predicted to be detected in higher numbers as they get older [10].

Age at menarche

On average, women who start menstruating early or have a late menopause experience more ovulatory cycles throughout their lives. Due to the extended period of exposure to estradiol and progesterone, which are lowered after menopause [10], menarche at a young age increases the chance of developing fibroids [1, 22].

Because myometrial mitotic activity is highest during the luteal phase of the menstrual cycle, a longer history of cycling is likely to increase the risk of UL. Most studies have found that the incidence of UL rises as menarche occurs earlier in life [10].

Early menarche is also linked to other hormonally induced diseases such endometrial cancer and breast cancer [43]. The molecular processes are unknown, and they may or may not be similar across hormonally induced conditions [22]. Associations of candidate genes for menarche with UL are shown [51].

Late menopause

No researchs have looked into the link between late menopause and the risk of UL. The NIEHS Fibroid Growth Study studied UL growth rates in women nearing menopause and discovered that white women's growth rates decreased with premenopausal age, but not black women's [10]. The UL growth rate every 6 months for women 45 years and older was 2% for white women and 15% for black women.

Fibroids in the uterus are most commonly detected throughout the reproductive years and disappear following menopause. Although tumors can continue to grow after menopause, no incidence of uterine fibroid has been recorded before puberty. Estrogen is thought to be the primary source of ULs based on this profile [52]. The significant incidence of the condition in the last years before menopause, when anovulatory cycles are more common and progesterone levels may drop, suggests that estradiol plays a larger role in fibroid pathogenesis than progesterone. However, a more thorough examination of clinical and translational evidence has revealed that progesterone action is required for full development and proliferation of leiomyoma cells, as well as estrogen, but especially to increase tissue sensitivity to progesterone by increasing PR availability [53]. Women have a decreased chance of developing UL after menopause [10], and pathologic examinations of hysterectomy tissues revealed a reduction in both the size and number of UL in postmenopausal women compared to premenopausal women. Physical evidence of UL was found in the same proportion of premenopausal and postmenopausal women [10].

The link between UL and menstrual cycle patterns is a little more hazy. In the NHS II, irregular menstrual cycles and longer menstrual cycle duration were linked to a lower risk of UL, whereas prior studies revealed no such link [10].

The parity and the pregnancy

Having a child has been linked to a lower risk of UL in many studies [11], with risk reductions ranging from 20–50% when comparing parous to nulliparous women, and risk appears to decrease with a larger number of children in most, but not all studies [11]. This apparent contradiction might be explained by myometrium differentiation during pregnancy [54], which makes the tissue less vulnerable to growth stimuli and genetic alterations that cause disease pathogenesis.

Although pregnancy has been shown to have a direct protective impact, nothing is known about the process. Parturition ischemia has also been hypothesized as a mechanism [43].

Pregnancy can have a profound influence on fibroid growth because to the large increases and decreases in estrogen and progesterone levels that are linked with very early pregnancy and the postpartum period. Almost 36% of fibroids present in the first trimester of pregnancy are not detected on an ultrasound scan conducted 3–6 months after delivery, and those that are detected have a median diameter reduction of 0.5 cm. Fibroids that were not removed shrank with time. Based on nonpregnant women's statistics, the degree of removal and shrinking was substantially higher than expected [11].

Breastfeeding, which reduces ovulation and ovarian hormone production, had no effect on UL elimination during pregnancy. These findings are in line with epidemiologic research that suggest breastfeeding has little, if any, protective impact on UL after parity adjustment [11].

Incomplete pregnancies or spontaneous abortions appear to be unrelated to risk. Women who are infertile are more likely to develop UL, especially those who are infertile at a young age (under 25 years). Multiparity is linked to a lower incidence of UL even when infertility is taken into account [10].

In three of the eight studies, older age at first term delivery was linked to a decreased risk of UL. In addition, the adverse relationships seen with later age at first birth and shorter time since last birth are consistent with a nonhormonal explanation of UL removal during pregnancy [10]. Although the link is not linear in all research, the longer the interval since the last birth, the higher the risk of UL. In the ULs, birth age in the reproductive years (25–29 years) was shown to be the most protective against UL [10].

In experimental data from the Eker rat, direct protective effects for parity were discovered. Although little is known about the cause, there are a few ideas, including changed endocrine profiles after a first or second pregnancy, especially if it began late in life. Similarly, ER levels in myometrial tissue may be reduced during pregnancy [43]. Childbearing, on the other hand, may inhibit UL growth through nonhormonal pathways. For example, postpartum changes in collagen content and smooth muscle cell cytoplasm might destroy or diminish the size of UL, and ischemia during parturition and uterine remodeling could selectively eradicate UL owing to vascularity differences compared to myometrium [43].

Obesity

Obesity is one of the most prominent illness predisposing factors [11]. The waist-to-hip ratio and body mass index are crucial indices for determining female obesity [55]. Obesity is a well-known high-risk factor for chronic illnesses. Obesity raises the likelihood of endometrial polyps and symptomatic uterine fibroids in women's reproductive systems [56]. Obesity and overweight in women has become more common in recent years.

Estrogen operates on the uterus to promote tumor growth and even create pathological alterations in the endometrium, which is one of the key contributors in the onset and progression of UL [57]. Obesity contributes to tumor growth by disrupting blood lipid balance and activating inflammatory signaling pathways. At the same time, cytokines released by obese women's surrounding adipose tissue can cause the body to increase estrogen secretion and reduce sex hormone-binding globulin production in the liver, resulting in an increase of free estrogen in the surrounding blood and an increase in UL incidence through various pathophysiological changes [54].

It is thought that a rise in body mass index and waist-to-hip ratio is linked to the start of UL [43], and that maintaining a healthy weight can help avoid UL [22]. The incidence of irregular vaginal bleeding, multiple tumors, tumor degeneration, and lesion diameter 40 mm was higher in the obesity body type group than in the normal body type group, according to waist-to-hip ratio. The findings suggest that, independent of the type of obesity, an increase in peripheral adipose tissue is associated with an increased risk of UL [22, 58].

Insulin resistance and hyperinsulinemia may be exacerbated by central obesity. By stimulating myometrial smooth muscle cell proliferation and raising circulating levels of ovarian hormones, hyperinsulinemia may directly or indirectly promote the formation of fibroids. Metabolic syndrome includes central obesity, insulin resistance, high blood pressure, and hyperlipidemia, all of which are linked to an increased risk of fibroids formation [59].

Smoking

The results of epidemiological research looking at the link between cigarette smoking and the development of uterine fibroids are mixed. Some research have shown that smoking has a protective effect. In contrast, following studies have found an elevated incidence of myoma, while others have found no link [11].

Early research revealed a negative relationship between UL and smoking, with risk reductions ranging from 20–50% among current or ever smokers compared to never smokers [10]. Nicotine inhibits the aromatase, which is responsible for converting androgens to estrone and moving E2 metabolism to 2 hydroxylation pathways, lowering estrogen bioavailability [22]. Smoking, on the other hand, may have estrogen-like effects on the uterus, which may stimulate cell proliferation [60].

The caffeine and alcohol consumption

Several studies have linked drinking alcohol and taking more than 500 mg of caffeine per day to an increased risk of developing uterine fibroids [1, 10, 43]. Alcohol may increase total estrogen levels and bioavailable estrogens, which might explain the findings [10, 11].

Caffeine consumption raises early follicular phase estradiol levels and inhibits phosphodiesterase, perhaps enhancing sex steroid synthesis. Despite this biological evidence, caffeine use has not been demonstrated to be a risk factor for fibroids in women of all ages, while younger women who consume a lot of coffee or caffeine have a higher risk of fibroids [11, 43]. Caffeine and coffee use are linked to higher levels of early follicular phase estradiol, which might boost sex steroid production [10].

Hormonal therapies

Oral contraceptive (OC) usage has been linked to a lower, similar, and higher risk of developing ULs, respectively, as compared to never users [10, 61]. Prolonged ovarian suppression may reduce the development of uterine fibroids while also minimizing the volatility and hormonal changes associated with different reproductive time intervals. Thus, even if oral contraceptives do not diminish tumor growth, they may reduce symptomatology and bleeding in women with uterine fibroma without any contraindications [22].

The results for the state of usage (present versus prior use) and the length of use are also mixed. Although there is no link between risk and time since most recent OC use, two studies found a higher risk (20–29%) among women who started using OCs before the age of 17 compared to never users. Because the beginning of OCs at a young age may be a sign of early sexual activity and infection with sexually transmitted diseases [10].

According to a case-control research, cases were more likely than controls to take OCs containing progestins with estrogenic characteristics. The BWHS, on the other hand, discovered no link between UL and estrogenic and progestational potency, progesterone type, or estrogen formulation (monophasic vs. biphasic/triphasic) [10]. In addition, women who had taken the injectable contraceptive depot medroxy progesterone acetate were less than half as likely as those who had never used it to develop ULs [61].

Vitamin D deficiency

Vitamin D is a class of steroid chemicals with significant effects on the musculoskeletal, neurological, and immunological systems, as well as the genital tract. Vitamin D's fundamental role is to maintain calcium-phosphate equilibrium as well as the healthy structure and function of the skeleton. Vitamin D, which is commonly found in vitamins, also meets the criteria for classification as a hormone [62, 63].

Vitamin D is thought to control cell proliferation and differentiation, as well as prevent angiogenesis and promote apoptosis [63]. Vitamin D operates through a specific type of receptor known as the vitamin D receptor. It is a mediator of this vitamin's pleiotropic effect. Steroid transcriptional processes regulate vitamin D's metabolic functions [62]. This vitamin can suppress cell proliferation, differentiation, and apoptosis by modulating the expression of numerous genes in a tissue-specific way. These mechanisms, such as those seen in UL [25], can help to prevent neoplastic transformation and tumor progression.

Hypovitaminosis D has been linked to the development of UL in recent studies. Furthermore, some researchers suggest that adequate vitamin D blood levels are linked to a lower incidence of ULs. Vitamin D has been shown in studies to be a potential single or combination treatment [64].

The Study of Environment, Lifestyle, and Fibroids (SELF) was conducted to determine the role of hypovitaminosis D and other variables in the development of fibroids. The majority of this field's study focuses on Afro-American women, who have a higher risk of UL. In comparison to white women, vitamin D insufficiency in Afro-American women results in lower blood vitamin D levels and lower expression of the vitamin D receptor in the surrounding myometrium due to greater melanin concentrations [64].

In comparison to normal myometrium, ULs are hormonally controlled, and over-expression of PR and estrogen ER is one essential element in the genesis and proliferation of fibroma. In leiomyoma cells, vitamin D3 displayed inhibitory effects on the production of ER and PR in a dose-dependent manner [52].

Recent research has also discovered a link between the prevalence of ULs and vitamin D metabolism genetic polymorphisms. UL risk was positively linked with two single nucleotide polymorphisms near the gene 7-dehydrocholesterol reductase and rs6058017 in Agouti-signaling protein in a large cohort of African-American women [62].

There are numerous theories on how vitamin D can be used to prevent or cure UL [25]. Despite the growing body of knowledge on ULs, little is known about the role of vitamin D in their pathogenesis.

Dietary factors

Diet may influence the risk of uterine fibroids. Indeed, several food components, particularly estrogen impacts, appear to alter endogenous hormone metabolism. As a result, differences in the occurrence of myomas might be explained in part by the dietary patterns of various countries. When looking at the effects of consuming soybeans [43], it was discovered that it has antiestrogenic effects when endogenous estrogen levels are high (premenopausal women), suggesting that soy consumption might lower fibroid risk. As indicators of soy ingestion, urinary isoflavones and lignans were examined. The study found no link with isoflavone. In a cross-sectional research in Japan, where soy intake is higher than in the United States, soy intake was not linked to fibroids (based on dietary frequency data) [43]. In TULEP, lignans were shown to be inversely associated to fibroid prevalence. Other research, on the other hand, have shown the opposite [61, 65].

A plant-based diet is thought to lower the incidence of UL by lowering endogenous hormone bioavailability. The BWHS discovered that eating more fruits and vegetables was linked to a lower incidence of UL [43, 61]. Lignans, which may be found in fruits and vegetables, were linked to a decreased risk of UL in the TULEP, which matched findings from the Italian case-control study and the BWHS [43].

The BWHS was the first epidemiologic study to show that dairy intake lowers the incidence of UL. Both high-fat and low-fat dairy had similar results. Dietary calcium, phosphorus, and the calcium-to-phosphorus ratio (a bioavailable calcium measure) were all found to be inversely related to risk [66].

The data on fish consumption and myoma risk, which the Chinese study and others do not recognize, but which the Italian case-control study reports as an inverse link. Fish intake was positively related with fibroid risk in a cohort research done in the Great Lakes region of the United States of America, with an incidence rate ratio of 1.2 for each ten-year increase of fish consumption. They did, however, discover a beneficial link with dark-meat fish, which are a good source of long-chain omega-3 PULAs [10].

However, the processes behind this link may not be limited to marine fatty acids: according to a research done in the Great Lakes region, these disparities might be due to the presence of varying levels of environmental contaminants in various nations' seafood. Polychlorinated Biphenyls, for example, have been associated to myoma prevalence in animals and have a wide range of levels in fish. Increased consumption of red meat and ham has been positively linked with UL in some studies [65].

Conclusion

Uterine fibroids are a common source of reproductive health issues and usage of medical services. Learning about primary and secondary preventive routes requires understanding the etiology of UL start and development. Although better understanding of tumor beginnings may lead to primary preventive efforts, identifying risk factors for tumor development and symptoms may reduce the negative consequences and public health burden of these malignancies.

In principle, studies attempting to explain behavioral, social, and physiological variables that underpin disparities in UL development and growth across women of various ethnic backgrounds might provide positive results.

Finally, many questions about the causes and mechanisms of development factors that predispose remain unanswered, necessitating the continuation of these studies in order to obtain new information. Prospective studies are needed to better understand the biology and epidemiological associations, both to better understand modifiable risk factors and to shed light on the etiopathogenesis of this disease. These research' findings may assist patients and health-care professionals with information that can help them better manage their UL.

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