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UTERINE FIBROIDS: PATHOGENESIS, EPIDEMIOLOGY AND ITS CLINICAL MANIFESTATIONS ON HUMAN ENDOMETRIUM FUNCTIONING

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ABSTRACT

Uterine fibroids consist of smooth muscle cells and connective tissue. Growth is stimulated by estrogen. Fibroids arise during reproductive years, grow during pregnancy, and regress after menopause. Growth spurt can happen in premenopausal years—an ovulatory cycles with irregular relative estrogen excess. Prevalence estimates for uterine fibroids indicate that they affect 5.4% to 77% of women, depending on the method of diagnosis. A fibroid can be very small and difficult to feel, especially in an obese woman, or as large as a watermelon. Most gynecologists do not consider fibroids a problem until they are the size of a 12-week pregnancy or are causing significant symptoms, such as bleeding and painful menstruation. Hysterectomy has been the procedure of choice for large fibroid tumors. Approximately 300,000 hysterectomies are performed per year for fibroid tumors. Hysterectomy is not a benign procedure; in 1975, 1700 deaths occurred in the 787,000 hysterectomies performed.

Keywords: Uterine fibroids, hysterectomies, Pathogenesis, Epidemiology

INTRODUCTION

The term *fibroid* was first introduced in the 1860s by Rokitansky (1860) and Klob (1863). Uterine fibroid lesions were initially known as the "uterine stone." In the second

century AD, they were called scleromas. Uterine fibroids are heterogeneous in composition and size among women and within the same individual, and vary in number between individuals. The fibro-neurovascular is present on a fibroid pseudo capsule which is surrounded by a uterine fibroid, separating it from normal peripheral myometrium The ancient Greeks were also aware of the presence of fibroids, with Hippocrates (460-375 B.C.**)** referring to the tumors as 'uterine stones'. During women's reproductive life fibroids have a linear growth. According to evolving evidences this is not always the case and typically the life cycle of a fibroid may involve growth as well as regression. Indeed, Peddada *et al*. tracked the growth of 262 fibroids (range 1.0 to 13.0cms) in 72 premenopausal women by performing four MRI scans over a period of 12 months. . During women's reproductive life fibroids have a linear growth. According to evolving evidences this is not always the case and typically the life cycle of a fibroid may involve growth as well as regression. Indeed, Peddada *et al*. tracked the growth of 262 fibroids (range 1.0 to 13.0cms) in 72 premenopausal women by performing four MRI scans over a period of 12 month **[1-3]**.

Fibroids or uterine leiomyoma's, are often referred as benign tumors of the smooth muscle cells of the uterus. Most of the women suffer with fibroids. Few symptomatic changes can be evident like menorrhagia (30%), pelvic pain with or without dysmenorrhoea or pressure symptoms (34%), infertility (27%), and recurrent pregnancy loss (3%). This data is describing the relationship between the presence of fibroids and symptoms are based on uncontrolled studies that have assessed the effect of myomectomy on the presenting symptoms. According to the research one observed the study of 142 women which is undertaken in the USA suggested that the prevalence of fibroids in infertile women can be as high to 13%, but no direct causal relationship between fibroids and infertility has been established **[4]**.

The estrogen-dependent tumors within the myometrium are composed of high extracellular matrix (ECM) affecting 25%–30% of women worldwide. Typical leiomyoma symptoms, such as pain, menstrual disorders, and infertility tend to increase with age and tumor size, constituting the main cause of hysterectomy. Since no effective long-term medical treatment is available. However, the ablation of leiomyomata combined with magnetic resonance imaging–guided high-frequency ultrasound has been considered recently as an alternative medical intervention for this

pathology. Magnetic resonance-guided focused ultrasound surgery for leiomyoma-associated infertility. Since no effective long-term medical treatment is available. However, the ablation of leiomyomata combined with magnetic resonance imaging–guided high-frequency ultrasound has been considered recently as an alternative medical intervention for this pathology **[5-7]**.

Etiology

ULs are most often diagnosed in the peri menopausal years, but can become symptomatic much earlier in some women. The incidence of UL declines after menopause **[8]**. A study by Huyck *et al* looked at racial differences in UL severity in a study which included African American and Caucasian women who have a sister previously diagnosed with UL. Black women who participated in the study exhibited higher likelihood for some known UL risk factors, including earlier age at menarche and higher likelihood of being obese. However, black women participants also scored lower on other UL risk factors, including history of smoking and less consumption of red meat. Nevertheless, when other risk factors were controlled for, this study showed that African American women had a significantly younger age at diagnosis of UL, more severe pain associated with UL, and a higher UL rate compared with Caucasian women. It is not known what causes fibroids, but studies suggest genetics and prolonged exposure to estrogen may increase your risk of developing fibroids **[9]**.

Epidemiology

Although many studies on the epidemiology of UFs (uterine fibroids) have been published, reports of the incidence and prevalence of UFs vary widely depending on the method of diagnosis and the population studied; for example, estimates of the incidence of UFs range from 5.4% to 77% of women of reproductive age. Globally, the incident cases, prevalent cases, and the number of YLDs of uterine fibroids increased from 1990 to 2019 with the growth of 67.07%, 78.82% and 77.34%, respectively **[10]**. Many different risk factors have been associated with the development of UFs, including biological, demographic, and reproductive and lifestyle factors. The true incidence and prevalence of UFs global impact on women's health, and the role of putative risk factors, are therefore currently unknown. This study is the systematic review of the epidemiology of UFs. The objectives of this review are to comprehensively survey the epidemiological data on UFs to describe their incidence and prevalence, and to examine trends in the

epidemiology of UFs according to region **[11-13]**.

Risk Factors

There are several risk factors which are associated in the development of uterine fibroids. They are dependent on the Hormonal influence, Reproductive status, Disease status, Dietary factors, Clinical factors, Environmental toxins.

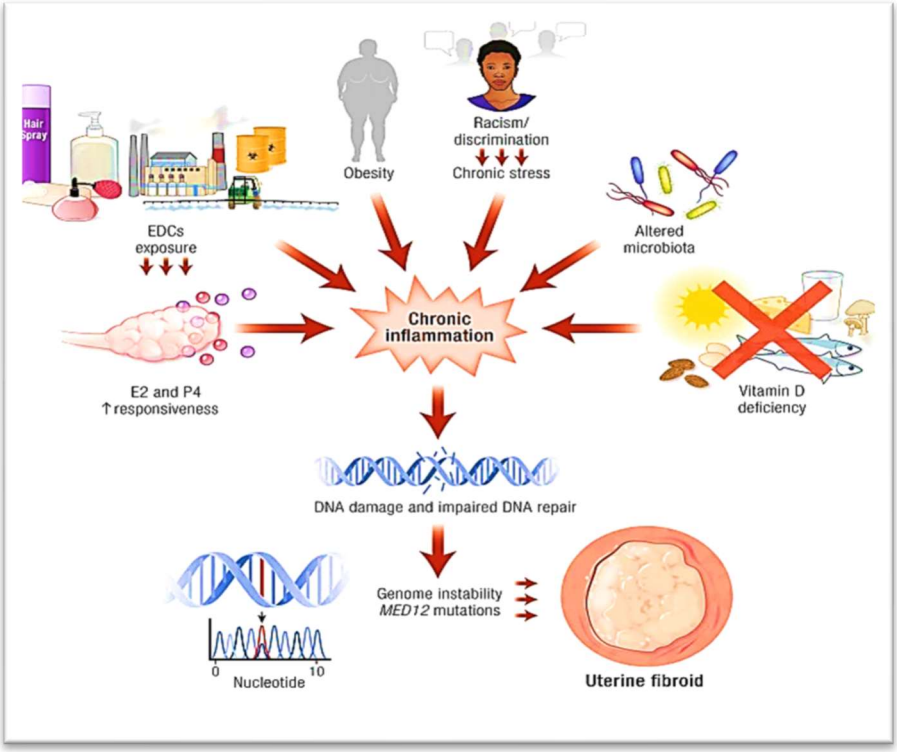
Physiological Factors

Several factors may affect a woman's risk for having uterine fibroids, including the following:

- Age (older women are at higher risk than younger women)
- African American race
- Obesity
- Family history of uterine fibroids
- High blood pressure
- No history of pregnancy
- Vitamin D deficiency
- Food additive consumption
- Use of soybean milk

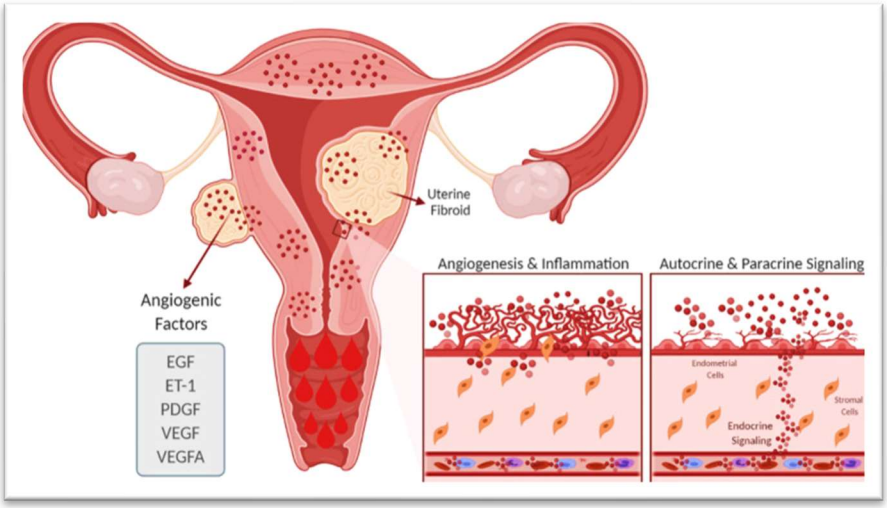
Disease status

Women with hypertension, defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or current use of antihypertensive medication, had an almost fivefold increased risk of UFs compared with those with normal blood pressure in a Japanese single-center, case–control study **[14]**.



Hormonal Influence on Uterine Fibroids

The development of fibriod is mainly due to high estrogen levels and if the progestron levels are low body cant stop the growth . Progesterone not only limits the effects of estrogen on fibroids, but it also can deter their growth and may limit their size. According to center of uterine fibroid the abundant evidence shows that estrogen promotes fibroid growth, which includes the clinical observations that fibroids grow in the presence of high levels of estrogen, such as during the reproductive years, or they regress in the presence of low levels of estrogen, such as following menopause or during gonadotropin releasing hormone (GnRH) agonist therapy **[15]**. Moreover, the risk of fibroids is greater in nulliparous women who might be subject to a higher frequency of an-ovulatory cycles and obese women with greater aromatization of androgens to estrone in the adipose tissue, the concept of unopposed estrogens, as an underlying cause of uterine fibroids, has been proposed in the literature **[16, 17]**.



Effect of uterine fibroids (UFs) on heavy menstrual bleeding. The presence of UFs causes alterations in the endometrial vascular architecture and function, contributing to increased and prolonged menstrual bleeding. UFs influence the production of angiogenic factors such as VEGF, VEGFA, ET-1, EGF, and PDGF, among others, which support increased angiogenesis. EGF, epidermal growth factor; ET-1, endothelin 1; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; VEGFA, vascular endothelia

Dietary factors

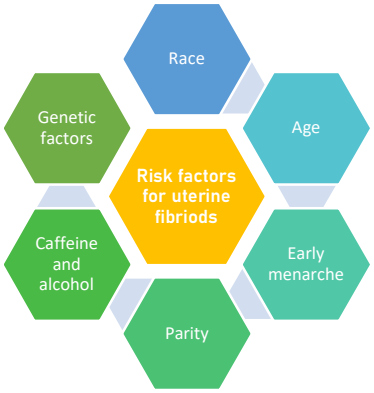
In a large case–control survey conducted at a hospital in China, exposure to food additives in processed, sweetened or preserved foods increased the risk of UFs more than threefold compared with no exposure. The same study found that women who consumed soybean milk had a 2.5-times greater risk of UFs than those who did not **[18]**.

Clinical and environmental influences

In this article Hypertension and fibroids have been linked through multiple epidemiological studies, and the fact that both are diseases of SMC proliferation raises the possibility of a shared pathogenesis **[19]**. Both are highly prevalent diseases that are associated with significant morbidity. so Many aligned between uterine fibroids (leiomyomas) and hypertension .Both diseases involve alterations of smooth muscle cells; with fibroids there are alterations both of the myometrium and vascular smooth muscle, and with hypertension only the vascular smooth muscle is altered. Moreover, hypertension and uterine fibroids both are more prevalent in people of African descent, making these diseases ones characterized by significantly health disparities **[20]**. The exciting possibility is that vitamin D deficiency may be associated with fibroid risk, because that outcome would also explain the increased risk of fibroids in women with darker skin. However, modification of risk with vitamin D supplementation would need to be demonstrated **[21]**. Statin use has been linked to decreased fibroid risk. One recent study suggested that the angiotensin-converting enzyme (ACE) pathway may be the link, where a large database study showed fibroid risk lessened with clinical ACE inhibitors **[22]**.

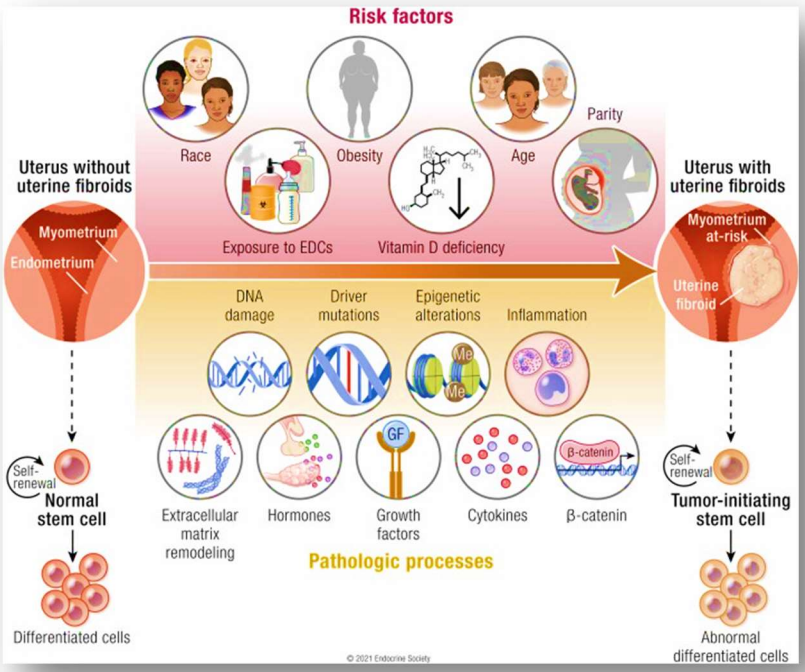
Environmental Factors

To prevent miscarriage in pregnant women between 1940s and 1970s Diethylstilbestrol (DES) was a pharmacological estrogen widely used The National Institute of Environmental Health Sciences Fibroid Study Group reported that women who were born in the era when DES was prescribed and who self-reported prenatal DES exposure had a greater incidence of uterine leiomyomas and had a tendency to develop larger fibroids **[23]**. Early-life exposure to environmental estrogens such as DES or genistein also led to increased tumor incidence and tumor size in Eker rats **[24]**.



Risk factors in developing fibroids

The greatest risk factor was age, which was found to increase the risk of UFs by up to approximately tenfold. In a retrospective, single-center study of the ultrasound records of women in Israel experiencing UF symptoms, those aged 41–50 or 51–60 years were 10 times more likely to have UFs than those aged 21–30 years **[25]**. Especially smoking women with low BMI were negatively associated with UF risk. In the Cancer and Steroid Hormone Study, smoking was associated with one third the risk of UFs in women with a BMI ≤22.2 kg/m^2 compared with women with similar BMI who had never smoked **[26]**.



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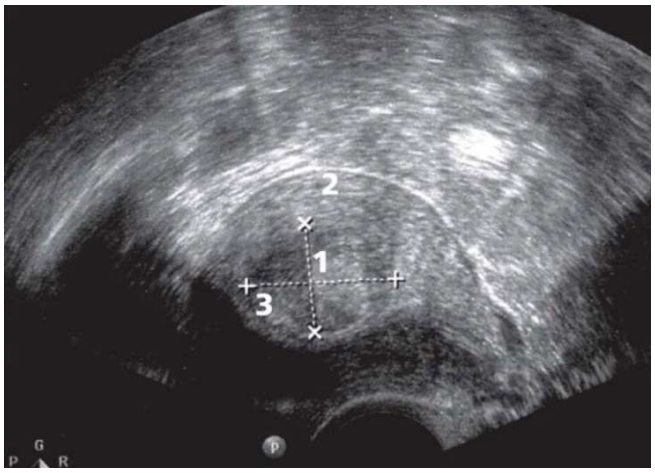
Types of Fibroids based on location

Complaints are often subjective and are perceived differently by different individuals. Some patients do not report any complaints.

a) Subserosal fibroids
b) Submucosal fibroids
c) Intramural fibroids
d) Pedunculated fibroids

Submucosal and intracavitary fibroids impair the endometrium or its function, impair the contractility of the uterus, and give rise to mainly menstrual disorders in the form of severe (hypermenorrhea) and prolonged bleeding (menorrhagia) which can even result in anemia. In an international study of 21 500 women, just under 60% of women with fibroids complained of hypermenorrhea, whereas the prevalence of hypermenorrhea in women without fibroids was 37.4%. Painful bleeding (dysmenorrhea) can also be associated with fibroids **[27]**.



Subserosal and pedunculated fibroids may become clinically manifest through pressure symptoms or a disturbing foreign-body sensation, with negative effects on sexual intercourse, micturition, or bowel movements (e.g., dyspareunia, pollakisuria, and constipation). The occurrence of the symptoms described correlates significantly with the size of the fibroids **[28]**

Factors that may lower the risk of fibroids:

- Pregnancy (the risk decreases with an increasing number of pregnancies)
- Long-term use of oral or injectable contraceptives

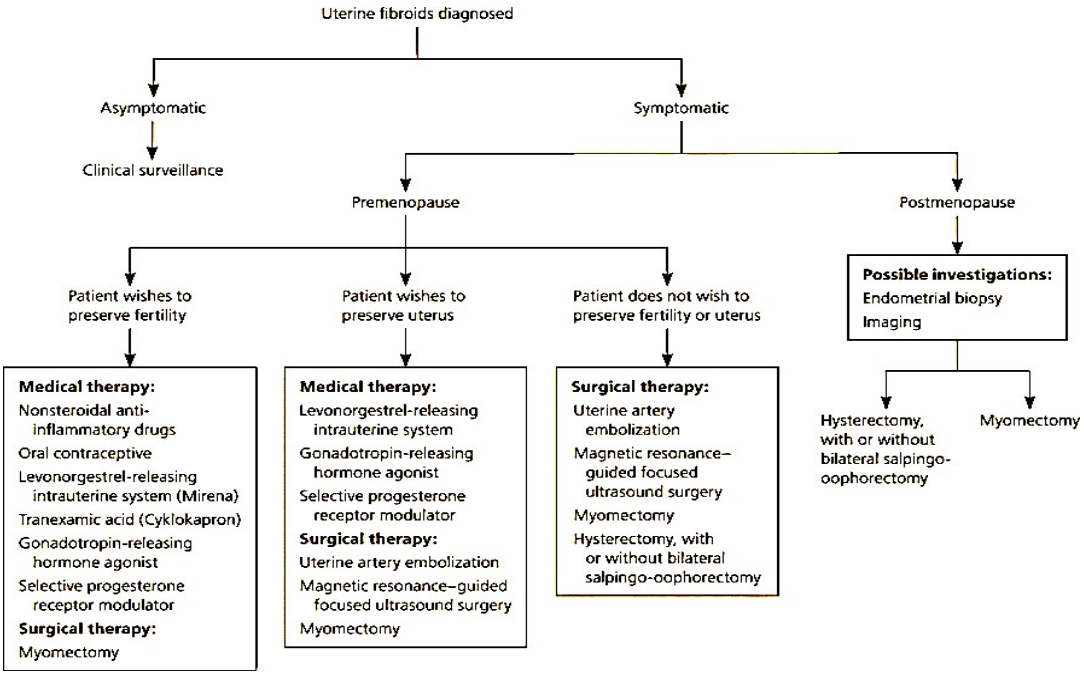
Reproductive status

The main two reproductive factors were found to increase the risk of UFs and three were found to exert a protective effect. According to the last birth increased the risk of developing UFs approximately two–threefold in women who last gave birth 5 or more years ago compared with those who gave birth more recently, in both black [the Black Women's Health Study (100% black

women)] and white populations. Three–five times higher risk of symptomatic UFs were mainly seen in premenopausal women than postmenopausal women in two registry studies. Furthermore, in an Italian single-center case–control study, premenopausal women showed a tenfold increase in UF risk compared with postmenopausal women **[29]**.

Diagnosis

Based on the patient presenting symptoms fibroids are evaluated. Abnormal menstrual bleeding, bulk symptoms, pelvic pain, or findings suggestive of anemia. Fibroids are sometimes found in asymptomatic women during routine pelvic examination or incidentally during imaging. Transvaginal ultrasonography is about 90% to 99% sensitive for detecting uterine fibroids, but it may miss subserosal or small fibroids. There are no reliable means to differentiate benign from malignant tumors without pathologic evaluation. Some predictors of malignancy on magnetic resonance imaging include age older than 45 years (odds ratio [OR] = 20), intratumoral hemorrhage (OR = 21), endometrial thickening (OR = 11), T2-weighted signal heterogeneity (OR = 10), menopausal status (OR = 9.7), and non-myometrial origin (OR = 4.9) **[30]**. Any imaging technique cannot diagnose Leiomyosarcoma (incidence 0.2%) and cannot be distinguished with certainty from a benign fibroid. Risk factors for leiomyosarcoma include radiation of the pelvis, increasing age, and use of tamoxifen, which has implications for surgical management of fibroids **[31]**.



Treatment

First line treatment for premenopausal women who have menstrual disorders without having fibroids, oral progesterones and progesterone-releasing intrauterine pessaries (IUP) are successfully used. But in women with fibroids these therapeutic options are of only limited efficacy. Neither progesterone nor mifepristone (a progesterone receptor antagonist) leads to reduction in fibroid volume. However, mifepristone did reduce fibroid-related hypermenorrhea **[32, 33]**. Despite the existence of large randomized studies, it has not yet been possible to evaluate herbal preparations targeted specifically at fibroid symptom relief **[34]**. Although a direct comparison of letrozole (an aromatase inhibitor) and gonadotropin-releasing hormone analogs (GnRH analogs) showed fibroid volume reduction by 46% after letrozole treatment, no effect on symptoms was seen, and the lack of blinding must be seen as a further limitation in the studies. Unwanted effects included dizziness and hot flushes, and also, after long-term ingestion, loss of bone density. Consequently GnRH analogs and selective progesterone receptor modulators (SPRMs) are the two drug classes which are basically available to treat uterine fibroids. The primary indication for drug therapy is pretreatment before surgery. There are no studies showing improved pregnancy or birth rates.

Although pretreatment with GnRH analogs leads to a reduction in fibroid size and in symptoms, neither improved resectability nor reduced operative time has been demonstrated. Suppression of ovarian steroid hormone production, and the strong vasomotor symptoms triggered which are the main disadvantage of treatment with GnRH analogs as a consequence; and also, with prolonged hypoestrogenemia, the associated loss of bone density. For this reason, the use of GnRH analogs is usually limited to 3 to 6 months. Since February 2012, the SPRM ulipristal acetate has been licensed for pretreatment before scheduled surgery. The main advantage of ulipristal acetate over GnRH analogs (leuprorelin acetate) is the lower incidence of unwanted effects. Particularly worth noting is its rapid effect on disordered menstruation (bleeding ceased within a week in over 90% of cases) compared with leuprorelin acetate. The direct action of ulipristal acetate on the endometrium leads to eversible benign histological changes (progesterone receptor modulator–associated endometrial changes) **[35, 36]**

Owing to fact the fibroid shrinkage reverses after treatment stops, GnRH analogs

are not suitable for long-term treatment of fibroids and within a short time the fibroids have returned to their original size In the PEARL-III study (open label—all enrolled patients received ulipristal acetate, there was no control group), the mean volume reduction of the three largest fibroids after 3 months was 59.8% (range, 21.0–72.2%). The main unwanted effects were hot flushes, which were reported less frequently the longer the drug continued to be taken **[37]**.

Pharmacological treatment

Non-steroidal Anti-inflammatory Agents (NSAID'S)

The non-hormonal alternatives used for the treatment of UF are non-steroid anti-inflammatory drugs (NSAIDS) and antifibrinolytics according to this article they are commonly prescribed especially in the cases with no identified organic pathology **[38]**. These agents significantly reduce blood loss (mean reduction = 124 mL per cycle; 95% CI, 62 to 186 mL) and improve pain relief **[39]**.

Combination (Oral Contraceptives)

Combination oral contraceptives (COCs) were considered a risk factor for fibroid growth, in the past **[40]**. But now in short terms COCs can be used to improve heavy menstrual bleeding associated with fibroids, primarily through their suppressive effects on endometrial proliferation **[41]**, but overall they have no effect on decreasing uterine fibroid volume or uterine size.**[40]**.

Antiprogesterons

A Cochrane systematic review demonstrated that mifepristone reduced UF-associated bleeding and improved fibroid-specific quality of life, without reducing fibroid volume **[42]** Long-term use, however, is still controversial, due to the potential of inducing endometrial pathology **[43]**. The guidelines usually specify that there is insufficient evidence of benefits from use of progestins and therefore they cannot be advocated as a medical therapy for uterine myomas **[44]**.

Non-hormonal antifibrinolytic agents

One small nonrandomized study reported a higher rate of fibroid necrosis in patients who received tranexamic acid compared with untreated patients with intralesional thrombi in one-half of the 22 cases involving fibroid necrosis **[45, 46]**. Tranexamic acid (Cyklokapron) is an oral nonhormonal antifibrinolytic agent that significantly reduces menstrual blood loss compared with placebo **[47]**.

Selective estrogen receptor modulators

These molecules have agonist-antagonist activity on estrogen receptors (ER),

with different actions across various estrogen-sensitive tissues. The main agents in this class are tamoxifen, frequently used in the treatment of breast cancer, and raloxifen, used as an antiresorptive drug in the treatment of osteoporosis. They have sparked interest in the treatment of leiomyoma due to their anti-estrogen potential. Tamoxifen has an agonist action on endometrial ERs and carries the risk of leading to endometrial pathology. Also, there are reports of significant leiomyoma growth in women with fibroids who used the drug for breast cancer treatment **[48].** There is no high quality evidence regarding the use of SERMS for treating fibroids. But on the other hand Raloxifen, has a more favorable profile, and a randomized clinical trial including 70 women with fibroids has shown volume reductions of 40% for up to 1 year of follow-up with the use of 60 mg daily. The study, however, only enrolled women who were postmenopausal, and it is not known whether this efficacy is maintained in premenopausal women **[49]**.

Other Agents

Other, less-studied options for the treatment of uterine fibroids include aromatase inhibitors and estrogen receptor antagonists. Aromatase inhibitors (e.g., letrozole [Femara], anastrozole arimidex], fadrozole [not available in the United States]) block the synthesis of estrogen **[50]**. Limited data have shown that they help reduce fibroid size as well as decrease menstrual bleeding, with adverse effects including hot flashes, vaginal dryness, and musculoskeletal pain **[51]**. Tamoxifen did not reduce fibroid size or uterine volume, but did reduce menstrual blood loss by 40% to 50% and decrease pelvic pain compared with the control group. Based on its adverse effects (e.g., hot flashes, dizziness, endometrial thickening), the authors concluded that its risks outweigh its marginal benefits for fibroid treatment **[52]**.

Non-Pharmcological Treatment

Vitamins

Vitamin D is a common name for a group of fat-soluble steroid compounds that present pleiotropic effects on the human body with receptor found in various tissues **[53]**. Vitamin D supplementation is usually recommended in oral or injectable forms **[54]**. Dietary sources of vitamin D include fatty fish like tuna, mackerel, and salmon, beef liver, egg yolks, and foods fortified with vitamin D such as dairy products, orange juice, and breakfast cereals **[53]**. Vitamins C and E, as antioxidants, protect cell membranes and the DNA from oxidative stress, and vitamin A is essential for cell differentiation and proliferation control and may help reduce fibroid growth**[55]**. A 2020 study by Wise *et*

al. found no association of UF incidence with dietary Vitamin A intake (i.e., salad greens, carrots, spinach, sweet potatoes, eggs, cheese, and cereal products) **[56]**

These results were generated within a particular racial group of women and as such might be worth exploring in the remaining population. Previously, in 2011, Wise *et al*. observed an inverse correlation between dietary intake of Vitamin A and the risk of UFs. They noted that it was predominantly conditioned by preformed Vitamin A derived from animal sources (i.e., liver and milk), but not by provitamin A from fruit and vegetable sources **[57]**.

Retinoids, as derivatives of Vitamin A, have structural or functional similarity to vitamin A **[58]**. Retinoids can be natural or synthetic **[59]**. The proven effects of retinoids include reduction in inflammation, regulation of cell growth and proliferation, and inhibition of carcinogenesis. Studies confirm that retinoids inhibit the growth of primary cultures of human uterine myomas **[60,61].**

Food sources of Vitamin E include canola oil, olive oil, almonds and peanuts, meat, dairy, leafy greens, and fortified cereals. It is also available in oral supplements. Little data is available on Vitamin E and its effects on UFs. Wise *et al*. found no associated risks with consumption of diet-derived Vitamin E **[62].** Martin *et al*. highlighted a positive, dose-dependent link between vitamin E and the incidence of UFs; the findings were, however, not statistically significant **.** Vitamin E is a potent antioxidant that acts by scavenging lipid hydroperoxyl radicals and so can protect cells from the effects of free radicals **[63]**.

Herbal treatment

The need to seek new medical treatments remains a reality, and a safer, cost-effective approach is highly warranted. So new treatment options or drugs must be found so that treatment can be provided. In recent years, Chinese herbal medicine, as a representative of complementary and alternative medicine, has attracted extensive attention in the treatment of UFs **[64,65].** GZFL [guizhi Fuling Capsule] is a Chinese herbal formula widely used in gynecological diseases in China. GZFL is exclusively produced by Jiangsu Kangyuan Meiyu Biopharmaceutical Co., Ltd. It consists of five herbs Cinnamomum cassia (L.) J.Presl, Lauraceae; Paeonia × suffruticosa Andrews, Paeoniaceae; Poria cocos(Schw.)Wolf, Polyporaceae; Paeonia lactiflora Pall., Paeoniaceae; and *Prunus persica* (L.) Batsch or *Prunus davidiana* (CarriŠre) Franch., Rosaceae **[66]**.

A randomized controlled trial reported on the effect of green tea extract [45% epigallocatechin gallate (EGCG)] in women with symptomatic UF showed a significant reduction in the fibroid volume as compared to the placebo group after taking 800 mg of green tea extract for the duration of 4 months. The severity of symptoms associated with fibroid, average blood loss and HRQL were also significantly improved with the use of green tea extract as compared to placebo, with no adverse effects identified **[67]**.

The ability of green tea to exert anti-UF activity is mainly attributed by epigallocatechin gallate (EGCG), one of the main active constituents in green tea, which constitutes more than 40% of the total polyphenol of green tea catechin and is present at about 142 mg in a 200 ml of green tea **[68]**. Numerous studies have identified the antiproliferative and apoptosis induction effect of EGCG on uterine fibroid cells. Although the exact mechanisms and pathways involved are unclear, a combination of mechanisms has been proposed in respective to this.

Modern pharmacological experiments show that GZFL can inhibit the proliferation, migration, and invasion of UFs, and increase the levels of CD3+, CD4+/CD8+. In addition, GZFL can induce the apoptosis of UFs and inhibit cell proliferation by down-regulating the expression of Wnt/β-Catenin signaling pathway-related proteins and mRNAs. **[69]**.

Ayurvedic treament

Vata, Kapha dominating Tridoshas are involved in the pathogenesis of the Granthi Roga hence Vata-Kaphahara medications are required, Dushyas are Rakta, Mamsa, and Meda hence the medications should possess Raktashodhaka (blood purifier), Lekhana (scrapping or dissolving) properties. Srotodushti is type of Sanga, Vimargagamana, Atipravritti so by Aamapachana and Vatanulomana drugs this problem can be controlled, and to combat Agnimandhya, medicines having Deepana (stomachic), Pachana (digestive) properties are required; with this hypothesis, Vata-Kaphahara (which alleviates vitiated Vata and Kapha Doshas), Raktashodhana (purification of blood), Lekhana (bio-scraping) and Shothahara (anti-inflammatory) Ayurvedic medicines, easily available in the market such as Shigru guggulu, kanchanara gugglulu.**[70]**.

Surgical interventions

Hysterectomy

Hysterectomy provides a definitive cure for women with symptomatic fibroids who do not wish to preserve fertility, resulting in complete resolution of symptoms and improved quality of life. Hysterectomy by the

least invasive approach possible is the most effective treatment for symptomatic uterine fibroids **[71]**.

Myomectomy

Hysteroscopic myomectomy is the preferred surgical procedure for women with submucosal fibroids who wish to preserve their uterus or fertility. It is optimal for submucosal fibroids less than 3 cm when more than 50% of the tumor is intracavitary **[72]**. Laparoscopy is associated with less postoperative pain at 48 hours, less risk of postoperative fever (OR = 0.44; 95% CI, 0.26 to 0.77), and shorter hospitalization (mean of 67 fewer hours; 95% CI, 55 to 79 hours) compared with open myomectomy **[73]**. In estimated 15% to 33% of fibroids recur after myomectomy, and approximately 10% of women who undergo this procedure will have a hysterectomy within five to 10 years **[74]**. Laparoscopic and hysteroscopic myomectomies are minimally invasive options but can be used only with fibroids in specified locations and sizes. **[75].** Surgical alternatives to hysterectomy in the management of leiomyomas (2000) uterine artery embolization (UAE) are an alternative for treating a wider range locations and size of fibroids. However, post procedure pain and fever, termed post embolization syndrome, are common. **[76]**.

Myolysis

Myolysis is a minimally invasive procedure targeting the destruction of fibroids via a focused energy delivery system such as heat, laser, or more recently, magnetic resonance–guided focused ultrasound surgery (MRgFUS). A study of 359 women treated with MRgFUS showed improved scores on the Uterine Fibroid Symptoms Quality of Life questionnaire at three months that persisted for up to 24 months ($P <$ .001).**[77].** According to research of Quinn SD, Vedelago J in a five-year follow-up study of 162 women, the re-operative rate was 59% **[78]**. Overall, this less-invasive procedure is well tolerated, although risks include localized pain and heavy bleeding. Spontaneous conception has occurred in patients after MRgFUS, but further studies are needed to examine its effect on future fertility **[77]**.

Uterine Artery Embolization

Uterine artery embolization is an option for women who wish to preserve their uterus or avoid surgery because of medical comorbidities or personal preference.**[79]**. It is an interventional radiologic procedure in which occluding agents are injected into one or both of the uterine arteries, limiting blood supply to the uterus and fibroids. Compared with hysterectomy and myomectomy, uterine artery embolization has a significantly

decreased length of hospitalization (mean of three fewer days), decreased time to normal activities (mean of 14 days), and a decreased likelihood of blood transfusion (OR = 0.07; 95% CI, 0.01 to 0.52) **[80]**. Contraindications include pregnancy, active uterine or adnexal infections, allergy to intravenous contrast media, and renal insufficiency. The most common complication is postembolization syndrome, which is characterized by mild fever and pain, and vaginal expulsion of fibroids. **[81]**.

CONCLUSION

In this article we have focused on the detailed etiology, incidence, symptoms and various treatments for treating uterine fibroids like pharmacological, herbal, interventional and surgical treatments. Conventional medicine has little else to offer other than a "watch and wait" attitude to women who suffer from small fibroids. If fibroids are approached holistically when initially observed, however, much of the disability and invasive surgical procedures can be avoided.

REFERENCES

[1] Al-Hendy Myers ER, Stewart. Uterine fibroids: burden and unmet medical need - *Semin Reprod Med. Plos One.* 2019; 14 (4): e0215646.

[2] Tinelli A, Malvas A, Hurst BS, *et al*. Surgical management of neurovascular bundle in uterine fibroid pseudocapsule. *JSLS.*2012;16(1):119 -129

[3] Peddada SD, Laughlin SK, Miner K, Guyon J-P, Haneke K, Vahdat HL, Semelka RC, Kowalik A, Armao D, Davis B Baird DD. Growth of uterine leiomyomata among premenopausal black and white women. *Proc Natl Acad Sci.* 2008;105(50):19887–19892.

[4] Anne Lethaby, Cochrane Menstrual Disorders and Subfertility Group, Auckland, New Zealand;

[5] Buttram Jr., V.C. Uterine leiomyomata-aetiology, symptomatology and management. *Prog Clin Biol Res.* 1986; 225: 275-296

[6] S, Aplin J. The endometrium. Informa Healthcare, ISBN: 0415273439, 2002

[7] Bouwsma E.V.; Gorny K.R.; Hesley G.K.; Jensen J.R; Peterson L.G.; Stewart E.A. Magnetic resonance-guided focused ultrasound surgery for leiomyoma-associated infertility. *Fertil Steril.* 2011; 96: e9-e12

[8] Walker CL, Stewart EA. Uterine fibroids: the elephant in the

room. *Science.* 2005;308(5728):1589–1592

[9] Huyck KL, Panhuysen CI, Cuenco KT, *et al*. The impact of race as a risk factor for symptom severity and age at diagnosis of uterine leiomyomata among affected sisters. *Am J Obstet Gynecol.* 2008;198(2):168.e1–168.e9

[10] Cramer SF, Patel A. The frequency of uterine leiomyomas. *Am J Clin Pathol* 1990; 94: 435– 8.

[11] Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. *Environ Health Perspect* 2003; 111: 1037– 54.

[12] Parazzini F. Risk factors for clinically diagnosed uterine fibroids in women around menopause. *Maturitas* 2006; 55: 174 – 9.

[13] Sparic R, Mirkovic L, Malvasi A, Tinelli A. Epidemiology of uterine myomas: a review. *Int J Fertil Steril* 2016; 9: 424– 35.

[14] Takeda T, Sakata M, Isobe A, Miyake A, Nishimoto F, Ota Y, *et al*. Relationship between metabolic syndrome and uterine leiomyomas: a case-control study. *Gynecol Obstet Invest* 2008; 66: 14– 17.

[15] Center for Uterine Fibroids [Internet] *What are fibroids?* Boston: Brigham and Women's Hospital; 2011. 2006 Sept 19 [cited 2011 Mar 13]

[16] Romieu I, Walker AM, Jick S. Determinants of uterine fibroids. *Post Marketing Surveill.* 1991;5:11939

[17] Ross RK, Pike MC, Vessey MP, Bull D, Yeates D, Casagrande JT. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *Br Med J (Clin Res Ed)* 1986;293(6543):359–62.

[18] Shen Y, Xu Q, Xu J, Ren ML, Cai YL. Environmental exposure and risk of uterine leiomyoma: an epidemiologic survey. *Eur Rev Med Pharmacol Sci* 2013; 17: 3249– 56

[19] Stewart EA, Borah BJ. Uterine fibroids and hypertension: steps toward understanding the link. *J Clin Endocrinol Metab* 106: e1039– e1041, 2021.

[20] Stewart EA Clinical practice. Uterine fibroids. *N Engl J Med.* 2015; 372(17):1646-1655.

[21] Wise LA. Study of Environment Lifestyle and Fibroids (SELF): advancing the field of fibroid

epidemiology. *J Womens Health (Larchmt)* 24: 862–864, 2015.

[22] Gupta JK, Sinha A, Lumsden MA, *et al*. Uterine artery embolization for symptomatic uterine fibroids. *Cochrane Database Syst Rev.* 2014(12):CD005073.

[23] Fischer NM, Nieuwenhuis TO, Singh B, Yenokyan G, Segars JH. Angiotensin-converting enzyme inhibitors reduce uterine fibroid incidence in hypertensive women. *J Clin Endocrinol Metab* 106: e650–e659, 2021.

[24] Baird DD, Kesner JS, Dunson DB. Luteinizing hormone in premenopausal women may stimulate uterine leiomyomata development. *J Soc Gynecol Investig* 13: 130–135, 2006.

[25] Cook JD, Davis BJ, Cai SL, Barrett JC, Conti CJ, Walker CL. Interaction between genetic susceptibility and early-life environmental exposure determines tumor-suppressor-gene penetrance. *Proc Natl Acad Sci USA* 102: 8644–8649, 2005.

[26] Lurie S, Piper I, Woliovitch I, Glezerman M. Age-related prevalence of sonographicaly confirmed uterine myomas. *J Obstet ynaecol* 2005; 25: 42– 4.

[27] Samadi AR, Lee NC, Dana FW, Boring JR, Parris EB. Risk factors for self-reported uterine fibroids: a case-control study. *Am J Public Health* 1996; 86: 858– 62.

[28] Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. *BMC WomensHealth.* 2012; 12.

[29] David M, Krätschell R. Uterusmyome: Korrelation von Befundkenntnisstand und Beschwerden. *Frauenarzt.* 2013;54: 119–123

[30] Stewart EA. Uterine fibroids. *Lancet.* 2001; 357:293–298.

[31] Wright JD, Tergas AI, Burke WM, *et al*. Uterine pathology in women undergoing minimally invasive hysterectomy using morcellation. *JAMA.* 2014; 312(12):1253-1255.

[32] Sangkomkamhang US, Lumbiganon P, Laopaiboon M, Mol BW. Progestogens or progestogen-

releasing intrauterine systems for uterine fibroids. *Cochrane Database Syst Rev.* 2013 Feb 28; CD008994.

[33] Tristan M, Orozco LJ, Steed A, Ramírez-Morera A, Stone P. Mifepristone for uterine fibroids. *Cochrane Database Syst Rev.* 2012; 8 CD007687

[34] Liu JP, Yang H, Xia Y, Cardini F. Herbal preparations for uterine fibroids. *Cochrane Database Syst Rev.* 2013; 4 CD005292

[35] Donnez J, Vázquez F, Tomaszewski J, *et al*. Long-term treatment of uterine fibroids with ulipristal acetate. *Fertil Steril.* 2014; 101:1565–1573. e1-18.

[36] Donnez J, Tatarchuk TF, Bouchard P, *et al*. PEARL I Study Group: Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med.* 2012; 366:409–420

[37] Donnez J, Tomaszewski J, Vázquez F, *et al*. PEARL II Study Group. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med.* 2012; 366:421–432.

[38] Ylikorkala O, Pekonen F. Naproxen reduces idiopathic but not fibromyoma-induced menorrhagia. *Obstet Gynecol.* 1986;68:10–2.

[39] Ethaby A, Duckitt K, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2013;1:CD000400.

[40] Qin J, Yang T, Kong F, Zhou Q. Oral contraceptive use and uterine leiomyoma risk: a meta-analysis based on cohort and case-control studies. Arch Gynecol Obstet. 2013; 288:139–148.

[41] Marret H, Fritel X, Ouldamer L, Bendifallah S, Brun JL, De Jesus I, *et al*. Therapeutic management of uterine fibroid tumors: updated French guidelines. Eur J Obstet Gynecol Reprod Biol. 2012; 165:156–164

[42] Tristan M, Orozco LJ, Steed A, Ramírez-Morera A, Stone P. Mifepristone for uterine fibroids. *Cochrane Database Syst Rev.* 2012;8:CD007687.

[43] Eisinger SH, Bonfiglio T, Fiscella K, Meldrum S, Guzick DS. Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. *J Minim Invasive Gynecol.* 2005;12: 227–33.

[44] Lefebvre G, Vilos G, Allaire C, Jeffrey J. The management of uterine leiomyomas. *J Obstet Gynaecol Can.* 2003;**25**:396–405.

[45] Lukes AS, Moore KA, Muse KN, *et al*. Tranexamic acid treatment for heavy menstrual bleeding. *Obstet Gynecol.* 2010;116(4):865-875.

[46] Aarts JW, Nieboer TE, Johnson N, *et al*. Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst Rev.* 2015(8):CD003677

[47] Ip PP, Lam KW, Cheung CL, *et al*. Tranexamic acid-associated necrosis and intralesional thrombosis of uterine leiomyomas. *Am J Surg Pathol.* 2007;31(8):1215-1224.

[48] Le Bouëdec G, de Latour M, Dauplat J. Expansive uterine myoma during tamoxifen therapy. 11 cases. *Presse Med.* 1995;24:1694–6.

[49] Palomba S, Orio F, Jr, Morelli M, Russo T, Pellicano M, Zupi E, *et al*. Raloxifene administration in premenopausal women with uterine leiomyomas: A pilot study. *J Clin Endocrinol Metab.* 2002;87:3603–8.

[50] Hilário SG, Bozzini N, Borsari R, *et al*. Action of aromatase inhibitor for treatment of uterine leiomyoma in perimenopausal patients. *Fertil Steril.* 2009;91(1):240-243.

[51] Gurates B, Parmaksiz C, Kilic G, *et al*. Treatment of symptomatic uterine leiomyoma with letrozole. *Reprod Biomed Online.* 2008;17(4):569-574.

[52] Sadan O, Ginath S, Sofer D, *et al*. The role of tamoxifen in the treatment of symptomatic uterine leiomyomata—a pilot study. *Eur J Obstet Gynecol Reprod Biol.* 2001;96(2):183-186.

[53] Holick, M.F. Vitamin D: A millenium perspective. *J. Cell Biochem.* **2003**, *88*, 296–307

[54] Pludowski, P.; Holick, M.F.; Grant, W.B.; Konstantynowicz, J.; Mascarenhas, M.R.; Haq, A.; Povoroznyuk, V.; Balatska, N.; Barbosa, A.P.; Karonova, T.; *et al*. Vitamin D supplementation guidelines. *J. Steroid Biochem. Mol. Biol.* **2018**, *175*, 125–135.

[55] Martin, C.L.; Huber, L.R.B.; Thompson, M.E.; Racine, E.F. Serum Micronutrient Concentrations and Risk of Uterine Fibroids. *J. Women's Health* **2011**, *20*, 915–922.

[56] Wise, L.A.; Wesselink, A.K.; Bethea, T.N.; Brasky, T.M.; Wegienka, G.; Harmon, Q.; Block, T.; Baird, D.D. Intake of Lycopene and other Carotenoids and Incidence of Uterine Leiomyomata: A Prospective Ultrasound Study. *J. Acad. Nutr. Diet.* **2021**, *121*, 92–104.

[57] Wise, L.A.; Radin, R.G.; Palmer, J.R.; Kumanyika, S.K.; Boggs, D.A.; Rosenberg, L. Intake of fruit, vegetables, and carotenoids in relation to risk of uterine leiomyomata. *Am. J. Clin. Nutr.* **2011**, *94*, 1620–1631.

[58] Broaddus, R.R.; Xie, S.; Hsu, C.-J.; Wang, J.; Zhang, S.; Zou, C. The chemopreventive agents 4-HPR and DFMO inhibit growth and induce apoptosis in uterine leiomyomas. *Am. J. Obstet. Gynecol.* **2004**, *190*, 686–692.

[59] Zaitseva, M.; Vollenhoven, B.J.; Rogers, P.A. Retinoids regulate genes involved in retinoic acid synthesis and transport in human myometrial and fibroid smooth muscle cells. *Hum. Reprod.* **2008**, *23*, 1076–1086.

[60] Lattuada, D.; Vigano, P.; Mangioni, S.; Sassone, J.; Di Francesco, S.; Vignali, M.; Di Blasio, A.M. Accumulation of Retinoid X Receptor-α in Uterine Leiomyomas Is Associated with a Delayed Ligand-Dependent Proteasome-Mediated Degradation and an Alteration of Its Transcriptional Activity. *Mol. Endocrinol.* **2007**, *21*, 602–612

[61] Ben-Sasson, H.; Ben-Meir, A.; Shushan, A.; Karra, L.; Rojansky, N.; Klein, B.Y.; Levitzki, R.; Ben-Bassat, H. All-trans-retinoic acid mediates changes in PI3K and retinoic acid signaling proteins of leiomyomas. *Fertil. Steril.* **2011**, *95*, 2080–2086

[62] Wise, L.A.; Radin, R.G.; Palmer, J.R.; Kumanyika, S.K.; Boggs, D.A.; Rosenberg, L. Intake of fruit, vegetables, and carotenoids in relation to risk of uterine leiomyomata. *Am. J. Clin. Nutr.* **2011**, *94*, 1620–1631

[63] Martin, C.L.; Huber, L.R.B.; Thompson, M.E.; Racine, E.F. Serum Micronutrient Concentrations and Risk of Uterine Fibroids. *J. Women's Health* **2011**, *20*, 915–922.

[64] Management of Symptomatic Uterine Leiomyomas ACOG Practice Bulletin, Number 228.

Obstet Gynecol. 2021;137(6):e100–e115.

[65] Jacoby VL, Jacoby A, Learman LA, Schembri M, Gregorich SE, Jackson R, Kuppermann M. Use of medical, surgical and complementary treatments among women with fibroids. Eur J Obstet Gynecol Reprod Biol. 2014;182:220–225.

[66] Rozenberg, S., Praet, J., Pazzaglia, E., Gilles, C., Manigart, Y., and Vandromme, J. (2017). The Use of Selective Progestin Receptor Modulators (SPRMs) and More Specifically Ulipristal Acetate in the Practice of Gynaecology. *Aust. N. Z. J. Obstet. Gynaecol.* 57, 393–399.

[67] Yen, H. R., Chen, Y. Y., Huang, T. P., Chang, T. T., Tsao, J. Y., Chen, B. C., *et al*. (2015). Prescription Patterns of Chinese Herbal Products for Patients with Uterine Fibroid in Taiwan: A Nationwide Population-Based Study. *J. Ethnopharmacol.* 171, 223–230. doi:10.1016/j.jep.2015.05.038

[68] Pan XH, Shao MF, Wang LY, Li Q, Zhu WP. Guizhi Fuling Capsules inhibit the proliferation, migration and invasion of uterine fibroids by mediating down-regulation of ICAM-1 and HE4 expression in T lymphocytes through MAPK signaling pathway. Chin J Hosp Pharm. 2021;41(22):2305–2310.

[69] Himsagara Chandra Murthy P., editor. 2nd ed. Varanasi: Chowkhambha Sanskrit Series Office; 2007. Sharangadhara, Sarangadhara Samhita, Madhyama Khanda, Vataka Kalpana Adhyaya, 7/95-100. 190.

[70] Aarts JW, Nieboer TE, Johnson N, *et al*. Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst Rev.* 2015(8):CD003677.

[71] Camanni M, Bonino L, Delpiano EM, *et al*. Hysteroscopic management of large symptomatic submucous uterine myomas. *J Minim Invasive Gynecol.* 2010;17(1):59-65

[72] Templeman C, Marshall SF, Clarke CA, Henderson KD, Largent J, Neuhausen S, *et al*. Risk factors for surgically removed fibroids in a large cohort of teachers. Fertil Steril 2009; 92: 1436– 4

[73] Martin, C.L.; Huber, L.R.B.; Thompson, M.E.; Racine, E.F.

Serum Micronutrient Concentrations and Risk of Uterine Fibroids. J. Women's Health 2011, 20, 915–922.

[74] Bhave Chittawar P, Franik S, *et al*. Minimally invasive surgical techniques versus open myomectomy for uterine fibroids. *Cochrane Database Syst Rev.* 2014(10):CD004638.

[75] Singh SS, Belland L. Contemporary management of uterine fibroids: focus on emerging medical treatments [published correction appears in *Curr Med Res Opin*. 2016;32(4):797]. *Curr Med Res Opin.* 2015;31(1):1-12.

[76] Surgical alternatives to hysterectomy in the management of leiomyomas (2000)

[77] J.B. Spies, A. Spector, A.R. Roth, C. M. Baker, L. Mauro, K. Murphy-Skrynarz Complications after uterine artery embolization for leiomyomas Obstet Gynecol, 100 (2002), pp. 873-880

[78] Stewart EA, Gostout B, Rabinovici J, *et al*. Sustained relief of leiomyoma symptoms by using focused ultrasound surgery. *Obstet Gynecol.* 2007;110(2 pt 1):279-287.

[79] Quinn SD, Vedelago J, Gedroyc W, *et al*. Safety and five-year re-intervention following magnetic resonance-guided focused ultrasound (MRgFUS) for uterine fibroids. *Eur J Obstet Gynecol Reprod Biol.* 2014;182:247-251

[80] Vilos GA, Allaire C, Laberge PY, *et al*. The management of uterine leiomyomas. *J Obstet Gynaecol Can.* 2015;37(2):157

[81] Gupta JK, Sinha A, Lumsden MA, *et al*. Uterine artery embolization for symptomatic uterine fibroids. *Cochrane Database Syst Rev.* 2014(12):CD005073.

[82] Goodwin SC, Spies JB. Uterine fibroid embolization. *N Engl J Med.* 2009;361(7):690-697.