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Current Understanding of Pathogenesis, Histopathology, Diagnosis, and Treatment Options of Uterine Fibroids-Review

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Abstract

Uterine fibroids are the most common benign monoclonal tumors of the uterus..They are associated with a significant morbidity rate and affect women mainly during their reproductive age. These tumors are usually asymptomatic however, they may present as heavy or prolonged menstrual bleeding, abnormal uterine bleeding, consequent anaemia, pelvic pain, infertility, and/or recurrent abortions. Despite many factors playing a role in the development and incidence of these common tumors namely; modifications in growth factor expression, abnormalities in the vascular system, and tissue reaction to injury and even genetics, a clear understanding of the pathogenesis of uterine fibroids is yet to be achieved. However, there has been significant progress made towards understanding their origin witnessed in recent years which has provided more options for the treatment of uterine fibroids including medical, surgical, and radiological interventions. This article briefly reviews the current knowledge of pathology, histology, and diagnosis of uterine fibroids while highlighting their treatment options

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1. Introduction

Uterine fibroids (UFs) (also called leiomyoma or myomas) are the ubiquitous non-cancerous neoplasms in women of child-bearing age arising from myometrial smooth muscle cells (Islam, Protic, Giannubilo, et al., 2013). They affect up to 80% of women in some regions. Furthermore, UF's may impair normal activity and decrease the quality of the patient's life (Ciebiera et al., 2017). UFs typically

present as round well-delineated masses. In most instances, they are found in the corpus, they can also be located in the cervix, uterine ligaments, but rarely in the ovary or fallopian tube. The uterus could carry multiple UFs with varying sizes, ranging from negligible millimeters to 20 cm or even more (Williams, 2017). However, the size of the fibroids is not directly correlated with the presence or the severity of clinical symptoms. It has been found that UFs rarely occur before menarche and frequently regress in size after menopause (Flake, Andersen, & Dixon, 2003; Wise & Laughlin-Tommaso, 2016).

1. Pathogenesis: The Origin and Growth of Myomas

Theories of Initiation

Whereas the main factor/factors behind the initiation of fibroids is/are still unknown (Nivethithai, Nikhat, & Rajesh,, 2010), several theories on the origin of uterine fibroids have been developed based on experimental studies done on the risk factors and causes of UFs (Figure 1). The first theory proposes that fibroids may result from rising estrogen and progesterone levels, which lead to a high mitotic rate and, as a result, stimulate the development of myomas (Reis, Bloise, & Ortiga-Carvalho, 2016). This may explain why fibroids grow during the reproductive years when the levels of estrogen are elevated, conversely they regress after menopause or during gonadotropin releasing hormone (GnRH) agonist therapy when estrogen levels are depressed. Moreover, fibroids have higher concentrations of estrogen, contain more estrogen receptors, and they can transform estradiol to estrone, which is a less active estrogen, in a slow manner compared to the normal myometrium (Nivethithai et al., 2010; Parker, 2007). Progesterone also plays a role in fibroid development through facilitating the growth of UFs. Additionally, the concentrations of progesterone receptors in myomas are elevated in comparison to that of the normal myometrium (Nivethithai et al., 2010). On the other hand, estrogen, progesterone, and growth factors, which increase the effect of estrogen and play a crucial role in myoma development, can stimulate UF growth, but only after the tumor development has already been initiated (Nivethithai et al., 2010).

An alternative theory suggests that the pathogenesis of uterine fibroids might be due to an immune response, the body's response to uterine injury in a manner similar to the response that leads to keloid formation (hypertrophic scars) after surgery (Stewart & Nowak, 1996). Contractions of the myometrium during menstruation may cause ischemic injury in myometrial smooth muscle cells which might be the sources of uterine fibroid progenitor cells (Pascual Botia, Camarasa, Raga Baixauli, & Sanchez, 2017). These cells that are positive for the apoptotic markers p53 and p21 are present only in the follicular phase of menstruation, whereas cells positive for the proliferative marker Ki-67 are mainly found in the luteal phase (Islam, Protic, Stortoni, et al., 2013). Many of the damaged cells are destroyed during the follicular phase. However, the cells that survive the destruction obtain mechanisms that protect them from oxidative stress and apoptosis. In doing so, they become uterine fibroid progenitor cells. Moreover, inflammations derived from environmental agents or infections have also been suggested as mechanisms for the initiation of UF development. Yet, there is no evidence of an elevated prevalence in women with sexually transmitted diseases, multiple sexual

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partners, first intercourse at a younger age, and preceding intrauterine device use.

In addition, Herpes simplex virus I or II, chlamydia, Epstein-Barr virus, or cytomegalovirus were not detected in leiomyomas (Laughlin, Schroeder, & Baird, 2010; Moore et al., 2015).

2. Risk factors

Risk factors, whether constant or variable, are linked to the evolution of fibroids. These include ethnicity, age, obesity, uterine infection, hormonal fluctuations, and lifestyle namely; diet, caffeine, and alcohol abuse, stress, smoking, and others (Table-1). There is an increasing need for further studies in order to better understand the factors that affect fibroid growth and development, considering the contradictions in epidemiological data currently.

The most important risk factors are:

2.1. Ethnicity

Ethnicity is considered one of the most important risk factors for leiomyoma development. Many studies support the effect of ethnicity on UFs. African American women are at a higher risk of developing UFs than white women. According to a study done by Pan et al., in uterine fibroids versus normal myometrium, 1,470 genes have been recognized to be differentially expressed regardless of race. 268 of these genes were either highly demonstrated (177 genes) or negligibly demonstrated (91 genes) in leiomyoma acquired from African American in comparison with white women ($p < 0.01$). In addition, the concentration of 34 protein spots was 1.5-fold in leiomyoma of African Americans compared with whites (Donnez & Dolmans, 2016; Pan, Luo, & Chegini, 2007). On the other hand, Al-Hendy et al. examined the ethnic distinctions in leiomyoma and its impact on the function of estrogen receptors (ERs) instead of looking at the expression level. They concluded that the ERα PP genotype is a genetic risk factor for uterine fibroid development in surgically treated women and the increased appearance of this tumor among African women may be due to the high prevalence of this genotype in Afro-Americans compared to others (Al-Hendy & Salama, 2006). Based on an American study, the prevalence of uterine myomas was 60% by age 35 among Afro-Americans and raised to >80% by age 50, while Caucasians manifested a rate of 40% by age 35 and increased to 70% by age 50 (Baird & Dunson, 2003), and this may be due to the variations in gene expression in myomas between those 2 groups (Davis et al., 2013).

2.2. Age

The risk of myoma development rises with age mainly during the reproductive years. Fibroids do not appear before puberty and their incidence decreases with menopause (Parker, 2007; Perrine Susan, 2005; Sparic et al., 2016). Uterine fibroids have been identified in 20-25 percent of reproductive-aged women, and in 30-40 percent of women over the age of 40 (Duhan, 2011). Women with an early menarche and late menopause have a higher risk for uterine fibroid development because of longer exposure to gonadal steroids (Flake et al., 2003; Khan, Shehmar, & Gupta, 2014; Williams, 2017).

2.3. Genetic factors

Genetic factors are significant in the development of myomas. Heritage may be the reason behind the

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growth of multiple UFs in the same uterus and it makes some women more susceptible to UFs than others (Sparic et al., 2016). Leiomyomas are associated with 40-50% karyotypically noticeable chromosomal abnormalities. The development of leiomyomas is related to the disruptions in HMGIC and HMGIY genes. Genes like RAD51L1 act as translocation partners to HMGIC and this causes dysregulation of gene structure, contributing to the resultant pathogenesis of uterine fibroids (Medikare et al., 2011). Genes involved in urogenital development, such as WNT4, WT1, SALL1, MED12, ESR1, GREB1, FOXO1, DMRT1, and CD44 (uterine stem cell marker antigen), are attributed to another important subgroup (Välimäki et al., 2018).

2.4. Parity

Pregnancy can be considered as a protective factor against the development of uterine fibroids, meaning that there is an inverse relationship between parity and risk of fibroids (Sparic et al., 2016; Wise & Laughlin-Tommaso, 2016). This could be due to the decreased time of exposure to unopposed estrogen (estrogen therapy alone without progesterone) during pregnancy compared with nulliparity which characterized by long-term unopposed estrogen exposure (Vessey, 1986). Nonethelss, the mechanism is still unclear (Donnez & Dolmans, 2016). Based on a study that was done to evaluate the effects of pregnancy on fibroids within a comprehensive prospective study that used vaginal ultrasound to determine the percentage of tumors which are decreased in size after pregnancy, the study found that 36% of fibroids were difficult to be detected, while the remaining fibroids had a median diameter reduction of 0.5 cm (Laughlin et al., 2010). As for breastfeeding, the studies revealed that, despite its hypoestrogenic effect, breastfeeding is not associated with fibroids growth (Samadi et al., 1996; Wise et al., 2004a).

2.5. Caffeine, Tobacco and Alcohol

Alcohol and caffeine addiction may influence endogenous levels of hormones through changing ovarian function or remodelling hormone metabolism (Wise et al., 2004b). Smoking may lead to low levels of serum and urinary estrogen as attested in some studies (Chiaffarino et al., 2016; Khalid et al., 2017; Parazzini et al., 1996; Windham et al., 2005). Alcohol consumption results in high levels of endogenous estradiol (E2) and estrone (Frydenberg et al., 2015; Nagata et al., 2009). Caffeine, on the other hand, is associated with elevated levels of early follicular phase E2, it may also enhances synthesis of sex steroid (Lucero, Harlow, Barbieri, Sluss, & Cramer, 2001; Tinelli et al., 2021).

2.6. Endogenous hormones

Myomas can be considered as estrogen and progesterone-dependent tumors and this has been demonstrated in both clinical and experimental studies (Levy, 2020), yet the mechanism is not well understood (Borahay et al., 2017). Estrogen is believed to assist in the growth of UFs (Reis et al., 2016). Besides, progesterone may also be a significant factor in the development of myomas because it works in tandem with estrogen to enhance leiomyomas (Omar, Yang, Laknaur, & Al-Hendy, 2016). In addition, the risk of UFs has a mutual relationship with increased levels of luteinizing hormone (LH) (Sparic et al., 2016).

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2.7. Exogenous hormone use

Multiple studies have shown that using combined oral contraceptives has no effect on the occurrence of UFs (Parker, 2007; Wise, Palmer, Harlow, Spigelman, et al., 2004). However, there is an increased incidence of myoma enlargement that has been seen in postmenopausal women taking hormone replacement therapy, whether estrogen alone or combined therapy (Moro et al., 2019). Exogenous hormones in food are other factors that could also contribute to myoma development. They can be presented in the form of phytoestrogens, as well as those of manufactured origin (Wise, Palmer, Ruiz-Narvaez, Reich, & Rosenberg, 2013).

2.8. Other factors

Lifestyle factors, such as diet, exercise, and anxiety, have a possible impact on uterine fibroid initiation and growth (Baird, Dunson, Hill, Cousins, & Schectman, 2007; Boynton-Jarrett, Rich-Edwards, Jun, Hibert, & Wright, 2011; Brasky et al., 2020; He, Zeng, Dong, et al., 2013). Based on some epidemiological studies, obesity and diabetes mellitus are directly related to the increased risk of leiomyoma development (Lethaby & Vollenhoven, 2015; Sommer et al., 2015). The common factor for this affiliation is insulin resistance, which is thought to be behind the development of myomas in obese women along with raised IGF-I and androgen levels (Sparic et al., 2016). On the other hand, no relationship between serum insulin levels and the presence of leiomyomas has been determined (Wise & Laughlin-Tommaso, 2016). Consequently, the development of myomas is believed to be inhibited by systemic vascular impairment in diabetic women (Sparic et al., 2016). Hypertension has been regarded as predisposing factor for leiomyoma development (Jacoby, Fujimoto, Giudice, Kuppermann, & Washington, 2010) especially chronic Hypertension that requires prolonged treatment (Sparic et al., 2016; E. A. Stewart, Cookson, Gandolfo, & Schulze-Rath, 2017). Infection and uterine injury are thought to be possible causes for myoma development. This because changes in different growth factors may occur as a result of uterine damage, leading to the appearance of myoma (Laughlin, Schroeder, et al., 2010).

2.9. Vitamin D

Many current epidemiological studies have proposed a reverse relationship between serum levels of vitamin D and the prevalence of myomas in both black and white women (Paffoni et al., 2013; Sabry et al., 2013). Black women are more prone to have vitamin D deficiency due to the high levels of melanin in their skin — the percentage is 80% in dark-skinned women compared with 20% in white women (Paffoni et al., 2013). Consequently, many studies have shown an important inverse connection between serum vitamin D levels and the severity of fibroids in African-American women; in other words, the lower the level of vitamin D, the greater the fibroid severity (Pascual Botia et al., 2017; Sabry et al., 2013). Vitamin D therapy has been shown to hinder myometrial cell proliferation in vivo and to lower the size of UFs in Eker rats model because of its anti-proliferative effect in myomas in vivo due to the ability of vitamin D to modulate COMT expression and protein action (Borahay, Al Hendy, Kilic, & Boehning, 2015; Pascual Botia et al., 2017). Furthermore, Vitamin D3 inhibits proliferation and causes apoptosis in human myometrial cells cultures

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because of its ability to downregulate proliferating cell nuclear antigen (PCNA), CDk1, and BCL-2 and restrain COMT expression and action (Sharan et al., 2011). Additionally, vitamin D suppresses the activity of TGF-B3 which plays a role in fibrosis formation in human myometrial cells (Halder, Goodwin, & Al-Hendy, 2011; Halder, Osteen, & Al-Hendy, 2013).

3. Histopathology of uterine fibroids

The exact cellular and molecular changes that might be responsible for the formation and growth of uterine myomas are not completely understood. Nevertheless, current studies have shown that smooth muscle cells and fibroblasts, which are the main cell types presented in myomas, are all acquired from a parental cell with multipotent stem cell characteristics (Holdsworth-Carson, Zaitseva, Vollenhoven, & Rogers, 2014). One study revealed that around 3 % of human myometrial cells have properties of stem cells; these cells were positive for CD34 marker and negative for CD45, CD106, vascular endothelial growth factor receptor 1 (VEGF R1), and antigen- associated factor VII markers (Pascual Botia et al., 2017). Stem cells derived from leiomyomas carry mediator complex subunit 12 (MED12) modifications which means that at least one genetic mutation might allow the transformation of myometrial stem cells into myoma progenitor cells (Mas, Cervello, Gil-Sanchis, & Simón, 2014; Ono et al., 2012). Tumors acquired from myoma progenitor stem cells have much elevated proliferation rates than those that do not obtain these cells. Additionally, these cells do not have sufficient estrogen and progesterone receptors (PRs) but when stimulated with these hormones, they have the capacity to cause tumors. They need mature myometrial cells in order to be able to proliferate (Ono et al., 2012).

Compared to myometrium, uterine leiomyoma is characterized by an abnormal accumulation of extracellular matrix (ECM) components such as collagens, laminins, fibronectin and proteoglycans (Herndon et al., 2016; Malik, Segars, & Catherino, 2012). Collagen fibrils that present in uterine fibroids are short and untidy when compared to those in normal myometrium (Leppert et al., 2004). Moreover, type I/III collagen ratio is modified. Additionally, many investigators revealed that Type V collagen, which is found in fibrotic tissue, was a prominent element of fibroids (Iwahashi & Muragaki, 2011; Jayes et al., 2019). Researchers have also revealed that myomas and myometrium contain different ratios of glycosaminoglycans, chondroitin sulfate, and dermatan sulfate, in which there is 78% in myometrium and 95% in fibroids. Decorin, which is the main glycosaminoglycan that correlates with fibroid size, is present in UFs in a high molecular weight form. Also, its distribution patterns with collagen were completely different in fibroids, in which its ratio to Type I collagen was raised in fibroids. These changes affect the ECM coordination of myoma and, as a result, affect its stiffness (Leppert, Jayes, & Segars, 2014).

Fibrosis found in UFs is formed by the proliferation and perseverance of cells due to their resistance to apoptosis, the synthesis of collagen by cells, mainly myofibroblasts, and the arrangement of collagen fibrils that are extremely cross-linked and disordered, in addition to the discharge of other matrix components including proteoglycans. Furthermore,

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the augmentation and function of ECM is controlled by growth factors (Islam, Ciavattini, Petraglia, Castellucci, & Ciarmela, 2018), cytokines (Wang et al., 2015), and steroid hormones (Islam et al., 2018; Pascual Botia et al., 2017). ECM glues and isolates growth factors to advance their stability at the same time to limit their activity. By breaking down ECM components, Matrix Metalloproteinases (MMPs) and other proteolytic enzymes liberate growth factors and activate a variety of cell signaling pathways.

Myofibroblasts play a crucial role in fibrosis development. In a current study, , they found cells that were positive for α-smooth muscle actin (α-SMA) and negative for desmin. They also found a high concentration of collagen in myoma tissue, indicating myofibroblast existence and their function in ECM accumulation (Islam et al., 2018). In chronic inflammation associated with injury due to menstruation, ovulation, and implantation which may lead to physiological injuries in the uterus, myofibroblasts generate ECM to encourage subsequent repair mechanisms and tissue homeostasis (Islam et al., 2018; Wynn & Wynn, 2007). Nevertheless, during chronic inflammation, myofibroblasts constantly and inordinately form ECM leading to pathological fibrosis. Growth factors such as TGF-βs and activin-A are important factors that can lead to myofibroblast differentiation during the mechanism of fibrosis (Islam et al., 2018; Joseph, Malik, Nurudeen, & Catherino, 2010). The accumulation of ECM is a demanding event in creating myoma rigidity, and the stiffness could be behind the pelvic pain, abnormal bleeding, and pressure. Consequently, preventing more accumulation of ECM and fibrosis formation could be an option for treating leiomyomas. In addition, mechanical tension acting via focal adhesion kinase (FAK) stimulates the mitogen-activated protein kinase (MAPK) pathway, resulting in upregulation of collagen type I and other ECM proteins that are involved in the restructuring and remodelling of the ECM (Thorne et al., 2015).

2. Types of Uterine Fibroids

Expansion and position are key factors in determining whether a fibroid is symptomatic or asymptomatic (Nivethithai et al., 2010). UFs can take different positions as follows:

- **Intramural fibroids** are the most common type which located within the myometrium and they are usually symptomatic.
- **Subserosal fibroids** are placed beneath the perimetrium and can grow to be quite large. They may also grow out in a plexiform way to become pedunculated fibroids that can be literally separated from the uterus to become a parasitic leiomyoma.
- **Submucosal fibroids** are located in the muscle underneath the endometrium and deform the uterine cavity; even a small tumor in this position can be symptomatic. A pedunculated lesion inside the cavity is named as intracavitary fibroid and can be permeated into the cervix.
- **Cervical fibroids** are positioned in the cervical wall.

It is unusual to find fibroids in the supporting structures of the uterus like the round ligament and the broad ligament, although they contain smooth muscle tissue in their structure (Nivethithai et al., 2010).

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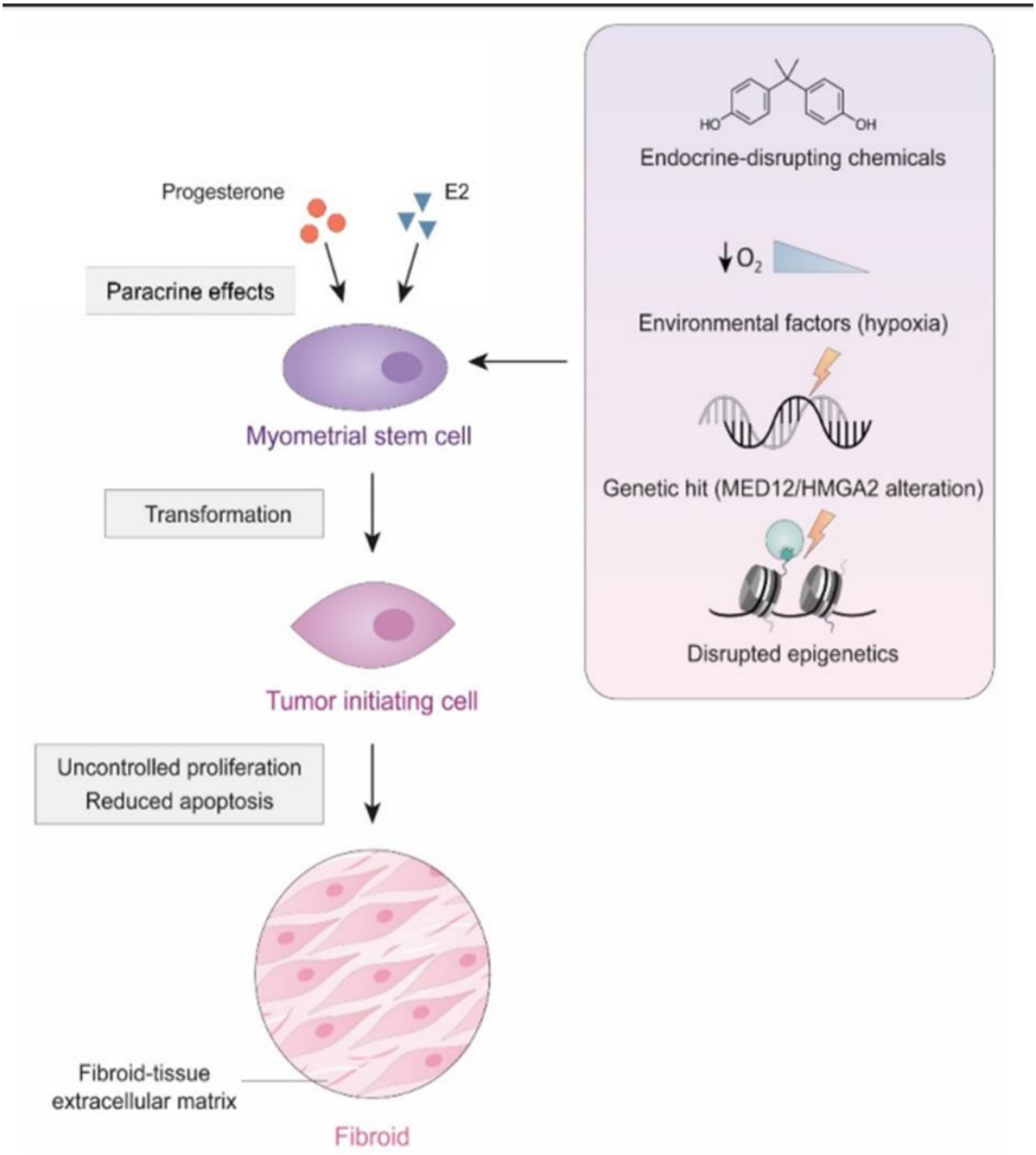

Figure 1. Uterine fibroid's cellular origin. Specific genetic and environmental changes can cause myometrial stem cells to transform into tumor initiating cells, which may eventually give rise to an UF tumor due to uncontrolled proliferation and reduced apoptosis (Machado-Lopez, Simón, & Mas, 2021).

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Table 2: Risk factors associated with Uterine Fibroids

Factor	Risk	Reference
African-American ethnicity	Increased	Pan, Luo, & Chegini, 2007 Doonez & Dolmans, 2016
Age		
Before Puberty	No effect	Parker, 2007
Reproductive age	Increased	Duhan,2011
Menopause	Decreased	Sparic et al., 2016
Early menarche/late menopause	Increased	Flake et al., 2003
Heritage	Increased	Sparic et al., 2016
Parity		
Nulliparity	Increased	Wise et al., 2016
Multiparity	Decreased	Sparic et al., 2016
Endogenous hormones		
Estrogen	Increased	Borahay et al., 2017
Progesterone	Increased	Omar et al., 2016
Exogenous hormones		
Combined oral contraceptives	No effect	Parker, 2007
Hormone Replacement Therapy	Increased	Moro et al., 2019
Vitamin D deficiency	Increased	Paffoni et al., 2013
Lifestyle factors		
Dietary factors		
Plant-based diet	Decreased	Wise et al., 2016
Red meat-based diet	Increased	Brasky et al., 2020
Physical activity	Decreased	Baird et al., 2007
Anxiety	Increased	Boynton et al., 2011
Alcohol consumption	Increased	Nagata et al., 2009
Caffein intake	No effect	Tinelli et al., 2021
Smoking	Decreased	Parazziniet al., 1996
	No effect	Chiaffarino et al., 2016
	Increased	Dragomir et al., 2010
Obesity	Increased	Sommer et al., 2015

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3. Symptoms

A large number of myomas are asymptomatic, yet 30–40% of cases show a range of symptoms based on the position and size of the myomas as mentioned before. UFs can end up causing bulky menstrual bleeding with consequent anaemia which could be life threatening (Ritchie & Nelson, 2017). Large fibroids can also cause pressure symptoms as well, which may lead to bowel and bladder disorder such as urgency, increased daytime urination and urinary incontinence. In addition, dysmenorrhea and pelvic pain are symptoms of UFs that may affect and impair daily activities. Infertility and recurrent abortions can also be the results of fibroids, mainly submucous and intramural fibroids that deform the uterine cavity (Yan et al., 2014). In fact, Fibroids can reduce fertility through many possible mechanisms including:

- Anatomical deformation of the uterine cavity with changes in endometrial function.
- Functional modifications such as raised uterine constriction and a reduction in blood supply to the endometrium and myometrium (Donnez & Dolmans, 2016).
- Changes in the municipal hormone environment as well as paracrine molecular remodelling that could weaken the transport of gametes and lower blastocyst implantation (Donnez & Dolmans, 2016; Sinclair, Mastroyannis, & Taylor, 2011).

Furthermore, fibroids can impact obstetric outcomes as UFs are remarkably correlated with preterm labour (<37 weeks), breech presentation, first cesarean section, and low birth weight infants (Lam, Best, & Kumar, 2014).

4. Diagnosis

- **Pelvic examination:** The size and shape of the tumour can be revealed by manual pelvic evaluation and when myomas are suspected and the patient shows symptoms such as heavy menstrual bleeding, hemoglobin evaluation should be asked.
- **Ultrasonography:** transabdominal and transvaginal ultrasonography have been used regularly due to their extensive availability and quite low cost. Transvaginal ultrasounds are more sensitive for the detection of small myomas (Khan et al., 2014).
- **Saline infusion sonohysterography:** a procedure done to evaluate the uterus and the shape of the uterine cavity. It is a less invasive, commercial, and acceptable diagnostic procedure (Seshadri, El-Toukhy, Douiri, Jayaprakasan, & Khalaf, 2015).
- **Hysteroscopy:** this modality could be needed to differentiate between intracavitary fibroids and large endometrial polyps. It is commonly performed in outpatients and does not need any anesthesia. If the patient has irregular vaginal bleeding or risk factors for endometrial hyperplasia, hysteroscopy may also be coupled with endometrial biopsy (Donnez &Dolmans, 2016; Vitner, Filmer, Goldstein, Khatib, & Weiner, 2013).

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- **Magnetic Resonance Imaging (MRI):** This procedure can give information about the count, dimensions, vascularization of UFs, their association with the endometrial cavity and serosal exterior, as well as their borders with normal myometrium (Donnez & Dolmans, 2016; Lumsden, Hamoodi, Gupta, & Hickey, 2015).

5. Treatment

Present management strategies include mainly surgical interferences, yet the choice of treatment is directed by the patient's age and desire to conserve fertility or bypass surgery (Lumsden et al., 2015) . Medical treatments are useful in the following situations (Khan et al., 2014):

- as a separate treatment for temporary relief of symptoms. It is mainly given to perimenopausal women with symptomatic myomas or to patients who cannot have surgical interventions because of medical issues.

- as a pre-operative addition to decrease the size of UFs, to control bleeding, and to better hemoglobin levels in order to make the surgery easier and with less complications. Most usable medications are:

Antifibrinolytics agents (tranexamic acid)

Tranexamic acid has indeed been correlated with up to a 50 % reduction in bleeding in women with menorrhagia (Laughlin & Stewart, 2011). It is only used during menstrual cycle; that's why major side effects are rare. However, increased necrosis in myomas has been detected in tranexamic acid users (Khan et al., 2014).

Combined estrogen-progestin oral contraceptives (COCs)

Combined hormonal contraceptives decrease the blood loss associated with myomas. However, based on a large prospective study, the use of combined estrogen-progestin oral contraceptives before the age of 17 years has a significant correlation with the incidence of UFs (Marshall et al., 1998).

GnRH Analogs (GnRHa)

They are used prior to surgery to minimize the size of myoma and to facilitate surgery. They shrink fibroids to a degree that is directly related to the percentage of cells which are estrogen receptor positive (Khan et al., 2014). Currently, two types of analogs are used: Superagonists (GnRHSA) work by prolonging GnRH activation, resulting in desensitization and reduction in gonadotropin secretion; The antagonists (GnRHAT) instead rival GnRH for cell membrane receptors, leading to inhibition of the signal transduction and gonadotropin secretion (Farris, Bastianelli, Rosato, Brosens, & Benagiano, 2019). GnRH analogs cannot be given for long durations because of their side effects such as osteoporosis and hot flushes.

Selective Estrogen Receptor Modulators (SERMs)

They are mainly used in the treatment and avoidance of estrogen receptor-positive carcinoma of the breast. They act through inducing changes in estrogen receptors resulting in distinctive expression of specific estrogen-regulated genes in various tissues including fibroids as they get influenced by estrogen

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(Khan et al., 2014). Common examples are tamoxifen and raloxifene. Raloxifene has been shown to intensify the shrinkage of myomas in postmenopausal women (Palomba et al., 2005) although the findings are still inconclusive (Premkumar et al., 2007).

Selective Progesterone Receptor Modulators (SPRMs)

Selective progesterone receptor modulators provide a viable alternative in the medical management of UFs since these agents reduce blood loss and shrink fibroids. Furthermore, they reduce pain and improve the quality of the patient's life. The main SPRMs that have been the topic of current research studies regarding fibroid management are: mifepristone, ulipristal acetate, telapristone, and asoprisnil (Khan et al., 2014). Ulipristal acetate has recently been proved as a short-term pre-operative medication (3 months) and as an alternative for surgical intervention for long-term intermittent use (12 months) (Donnez et al., 2018).

Vitamin D

Vitamin D has shown anti-fibrotic properties by inhibiting growth of the tumor and inducing apoptosis in cultured human leiomyoma cells as it inhibits the expression and activity of proliferating cell nuclear antigen (PCNA), cyclin-dependent kinase 1 (CDK1), and B-cell lymphoma 2 (BCL-2), as well as catechol-O-methyl transferase (COMT) in leiomyoma cells (Sharan et al., 2011).

Surgical treatments

Fibroids are one of the most recurrent indications for pre-menopausal women to undergo surgery and they represent a significant public health cost. The main surgical management strategies are:

Myomectomy

Myomectomy is the removal of fibroids but preserving the uterus. It is effective in resolving the bulk of symptoms and can be accomplished laparoscopically as well as hysteroscopically, where large fibroids are usually resected by open myomectomy while submucous fibroids less than 5 cm in diameter can be removed by the hysteroscopical procedure. However, there is insufficient evidence on the ability of myomectomy to improve fertility or pregnancy outcomes (Khan et al., 2014). Moreover, myomectomy, especially the hysteroscopic one, has been associated with major complications such as hemorrhage (2.4%), uterine perforation (1.5%), cervical laceration (1%–11%), in addition to intrauterine adhesions and infertility as delayed complications with the possibility of recurrence within 5 years (Farris et al., 2019).

Hysterectomy

Hysterectomy is the second most recurrent surgery in reproductive women after caesarean section. It is the removal of fibroids along with the uterus (Khan et al., 2014; Taran, Brown, & Stewart, 2010). Hysterectomy is the final procedure and provides a remarkable outcome as well as a permanent cessation of menses with no risk of myomas recurrence. It can be performed through the abdominal, vaginal, as well as laparoscopic (total or laparoscopic-assisted vaginal) routes. Each one of them has its own advantages and disadvantages.

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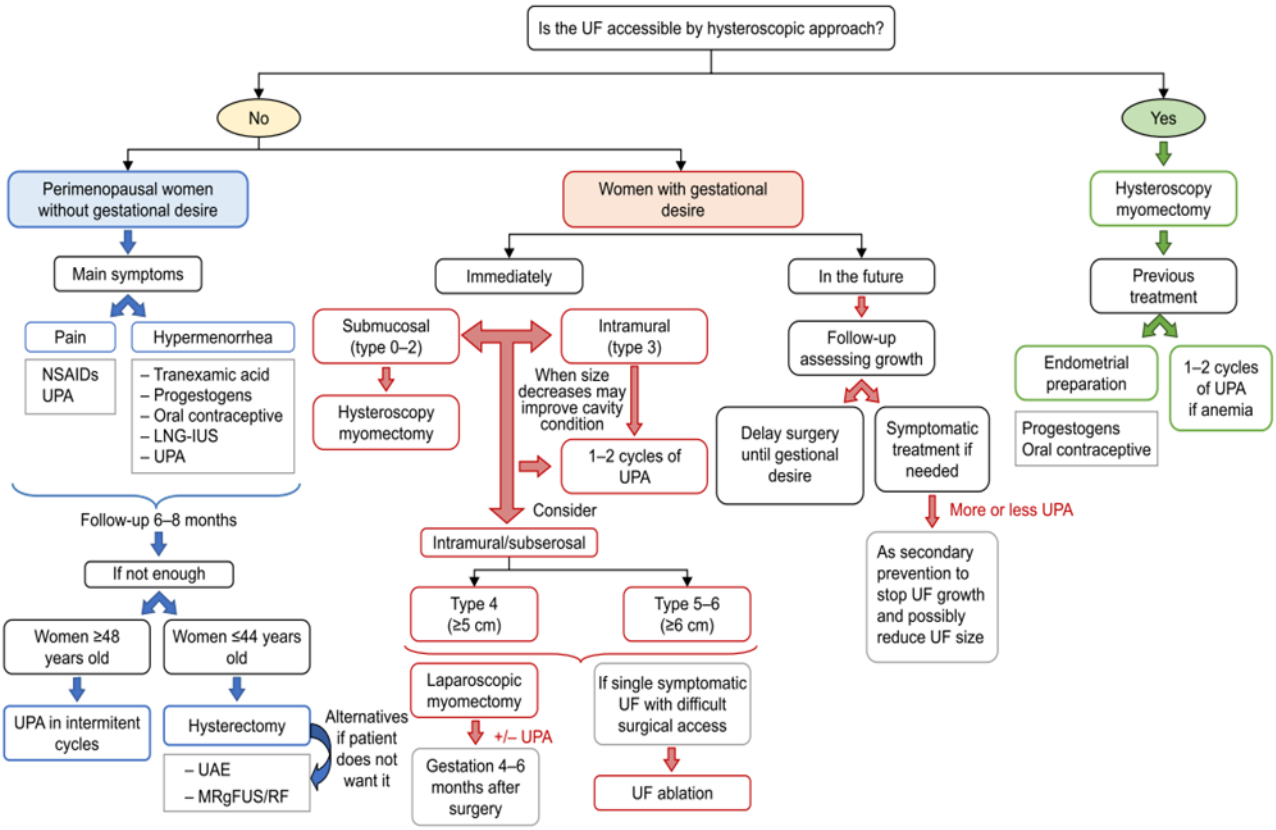

Figure 2. A medical algorithm for managing UFs based on the patient's profile. Abbreviations: LNG-IUS, levonorgestrel intrauterine system; MRgFUS, magnetic resonance-guided focused ultrasound surgery; NSAID, nonsteroidal anti-inflammatory drug; RF, radiofrequency ablation; UAE, uterine artery embolization; UF, uterine fibroid; UPA, ulipristal acetate (Mas et al., 2017).

Uterine artery embolization (UAE)

It is a radiological treatment based on blocking the blood supply to the uterus, leading to ischaemic deterioration of fibroids even though the myometrium acquires a new blood source from collateral circulation. It provides the same success rates as surgery but with shorter hospitalization and earlier restarting of normal activities (Gupta, Sinha, Lumsden, & Hickey, 2014). Despite its raised effectiveness for treating symptoms such as reduction in bleeding and tumor size, there is high risk of reoperation compared with surgery (Donnez & Dolmans, 2016; Gupta et al., 2014) as well as the additional risk of fibroid expulsion (5%) (Bulman, Ascher, & Spies, 2012).

With the advancement of noninvasive surgical techniques, particularly the introduction of ulipristal acetate as a medically effective treatment, some obstetric and gynecological societies, such as the Spanish Society of Gynecology and Obstetrics (Figure 2), have updated protocols for the management of UFs based on the choices and clinical situation of the patients, reserving surgical

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techniques and invasive therapies for only the most severe symptomatic cases.

6. Conclusion

Despite their benign origin, fibroids cause remarkable morbidity in close to 40% of women throughout their fertile life and even in postmenopausal life. Although noticeable progress has been achieved on leiomyoma-related research in the last few years contributing to a better understanding of the pathogenesis and risk factors as well as their management strategies, there is still need for a deeper understanding of the mechanisms underlying their formation, stimulation, and expansion. The development of uterine fibroids may be initiated by non-hormonal factors yet hormonal stimulation is a necessary factor for their growth. Histologically, UFs show an extensive ECM component diversity including collagens, laminins, fibronectin, proteoglycans, and integrins, also MMPs and TIMPs. Additionally, current research has proven that the various cell types presented in myomas all arise from a parental cell that has properties of multipotent stem cells. Most of UFs are asymptomatic, otherwise symptomatic UFs can cause serious symptoms such as excessive bleeding, pelvic pain, anaemia among others which might have a negative influence on women's life thus affecting their sexual, social, and work life. For this reason, symptomatic myomas require quick management through surgical and/or medical treatment based on the presence and severity of the symptoms, the age of the patient, fertility, and the patient's wish to preserve the uterus.

Conflicts of interest

There are no relevant conflicts of interest to disclose.

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