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Uterine leiomyomas (Uterine fibroids)

Suhair Hassan Alkutbi[1], Eman S. Nassir[1], Aseel I. Ibrahim[1]

[1]Clinical and laboratory science department, college of pharmacy, university of Baghdad, Iraq

Abstract

Uterine fibroids are neoplasms of the uterus with both smooth muscle and fibroblast constituents, additionally to an amount of fibrous extracellular matrix. Fibroids are completely different in their pathophysiology, size, site and their clinical symptoms. In spite of the fact that uterine leiomyomas represent a significant public health concern, the causes and pathogenesis of these lesions not very well understood. Fibroids are usually associated with race; seen in black women more than in white one with more-severe forms of the disease. Symptomatic fibroids interfere with physical and social activities, affecting relationships, employment and making women feel worn out and sad or depressed. About one- third to half of all hysterectomies are fibroids . Treatments are surgical and interventional. The progesterone receptor modulators, such as ulipristal acetate, are used as a medical therapy. There is a new suggestion that the genetic subgroups lead to fibroid formation, aid in the understanding of the clinical heterogeneity of this disease and lead to individualized treatments. This article will summarize the important information published in recent years about this disease.

Keyword: uterus, ovarian follicle, leiomyomas

1. Introduction

Uterine fibroids (i.e. leiomyomas or myomas) are the mainly frequent type of benign uterine tumors .They are monoclonal tumors of uterine smooth muscle (i.e., the myometrium).This type of tumor composed of huge amounts of extracellular matrix (ECM) containing collagen, fibronectin and proteoglycans [1 ,2]. Uterine leiomyomas first described in 1793 by Matthew Baillie at St George's Hospital in London. The "fibroid" term was introduced later by Rokitansky (1860) and Klob (1863) at the same time as the famous German Pathologist Virchow, confirmed that those tumors a raised from the uterine smooth muscle.so, the term "myoma" became current in clinical use [3].The greater part of women with uterine fibroids are commonly asymptomatic. Only

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20% and 50% Of women with uterine fibroid experiencing symptoms. These symptoms include menstrual cycle irregularities such as menorrhagia and pain with dysmenorrhea, . infertility and spontaneous abortion also may be resulted from uterine fibroid [4]. Leiomyomas badly affect up to 60 % of reproductive aged women and 80 %of women during their lifetime [5]. Even though the fact that uterine

leiomyomas represent the most common gynecologic tumor in women and form a important public health problem, the causes and pathogenesis of these lesions remain weakly understood [6]. The primary indication for hysterectomy in women of reproductive age is uterine leiomyomas and reason for more than 200,000 hysterectomies a year in the USA [7]

2. Classification

According to the International Federation of Gynecology and Obstetrics (FIGO) uterine fibroid location classified into the following types [8]:

- Submucosal myomas (FIGO type 0, 1, 2) – These leiomyomas raised from myometrial cells just below the endometrium (lining of the uterine cavity). These neoplasms project into the uterine cavity
- Intramural myomas (FIGO type 3, 4, 5) – These leiomyomas are located within the uterine wall. They may enlarge to the uterine cavity or serosal surface. Some fibroids may be transmural and bulge from the serosal to the mucosal surface.
- Subserosal myomas (FIGO type 6, 7) – These leiomyomas raised from the myometrium at the serosal surface of the uterus and may be intraligamentary (i.e., extending between the folds of the broad ligament).
- Cervical myomas (FIGO type 8) – These leiomyomas are located in the cervix rather than the uterine corpus

3. Histology

Histologically, the uterine leiomyoma is characterized by [Figure 1]:

1. Cellular arrangement: Bundles of spindle cells similar to those present in the myometrial wall are mainly composed the tumor. These cells appear elongated with acidophilic cytoplasm and central, pale elongated nucleus, sometimes with an

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aggregation of chromatin. cells form rotating fascicles interlaced at right angles. This arrangement obviously recognized the leiomyoma from the surrounding myometrium .More regular pattern of muscle fibers is seen in the myometrium [9].

2. Extracellular matrix: a large amount of extracellular matrix (ECM) deposit in leiomyomas than normal myometrium. The ECM is not only too much, but also there is an alterations in its composition [10]. Both structure and orientation of collagen fibrils is altered compared with normal myometrium. Collagens are loosely packed and arranged in a nonparallel, disordered manner [11].

in addition, a great number of tumors exhibit an obvious boundary with the myometrium, that will form a ring of compressed myometrial cells called *pseudocapsule*. This pseudocapsule is look like a continuous layer between the fibroid and myometrium .Thick collagen fibers and blood vessels are seen in this pseudocapsules [Figure 2] [9].

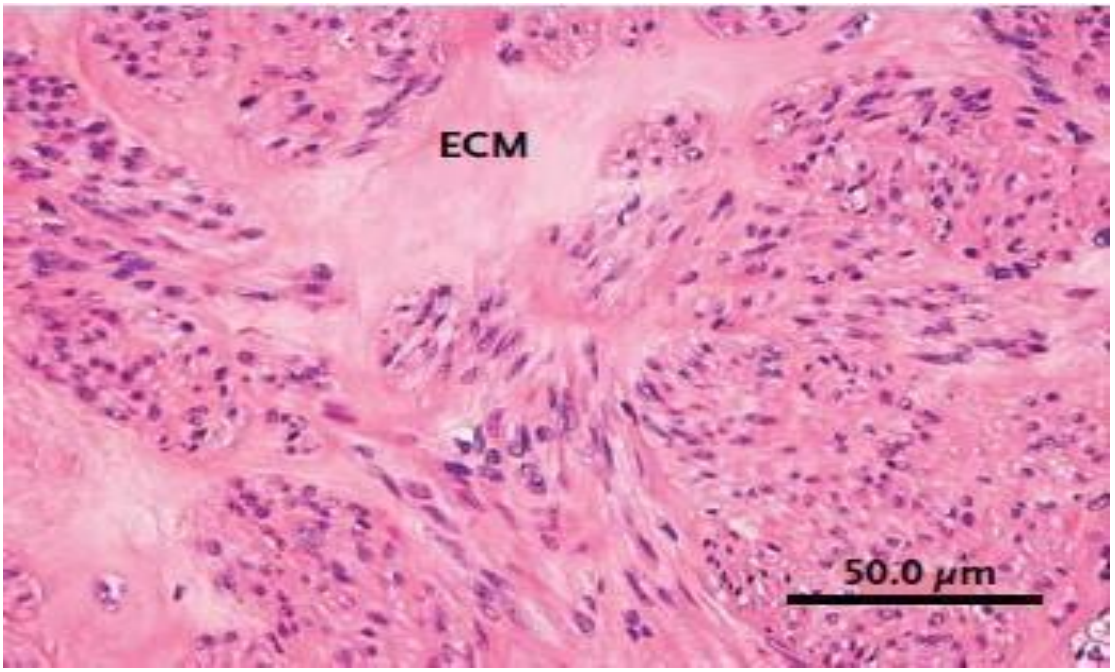

Figure 1: *A typical uterine leiomyoma:* spindle-shaped smooth muscle cells arranged in disoriented fascicles, separated by substantial ECM, stain H&E.[9]

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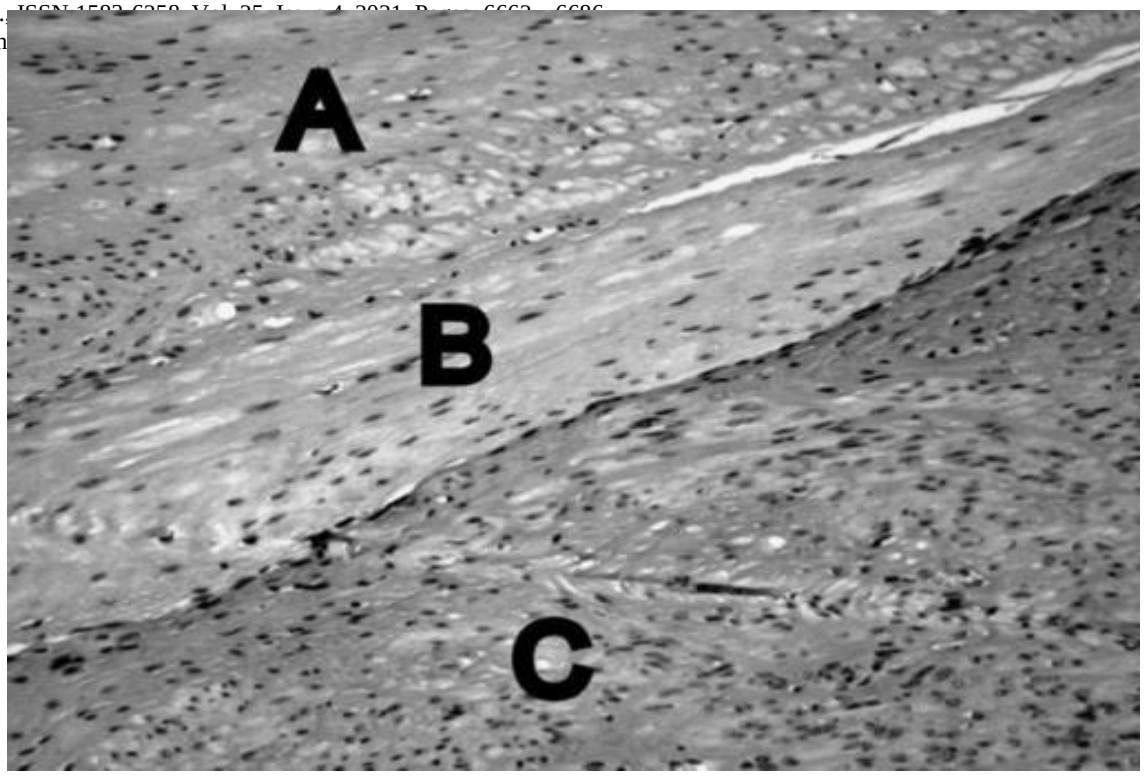

Figure 2: *Pseudocapsule of uterine leiomyoma:* A=myometrium, B=pseudocapsule, C=leiomyoma, Histological microphotograph stained by H&E at10x [(9)].

4. Gross Findings

Leiomyomas occur normally in the uterine fundus .They are usually intramural, and to a less extent submucosal or subserosal, and rarely they are found in lower uterine part or cervix. Subserosal leiomyoma may go through torsion with secondary necrosis of the pedicles, losing its connection to uterus and on some occasion becoming attached to the adjacent pelvic structure creating a new vascular peduncle (parasitic leiomyoma) [(12)]. Single or multiple fibroid can be seen (leiomyomatosis). Only one large fibroid may occupy the whole uterine fundic region [figure 3] and demolish the endometrial cavity, other than numerous fibroids of variable size can develop in a single uterus [figure 4]. The size of these lesion is variable and they can reach large sizes. The figure (4) show uterus at the time of abdominal myomectomy contained multiple fibroids of **≥10 cm** in size. The tumors are typically round, well-circumscribed (they are not invasive, either within the uterine wall or bulging into the lumen), nonencapsulated myometrial masses (which can be enucleated) with white, whorled, bulging, solid sectioned surfaces [(12)]. The cut surface of enlarged and distorted uterine body (viewed in figure.5) show multiple nodules, well-circumscribed, hard, white-grayish with a whorled appearance shaped through the intersecting bundles of brown muscle fibers and white fibrous tissue .

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Many degenerative changes are common including ulceration (mostly in the submucosal leiomyoma), edema, cyst formation and, less frequently, calcification or ossification. Red degeneration is feature of pregnant women present with central hemorrhage of fibroid [figure 6] [(12)].

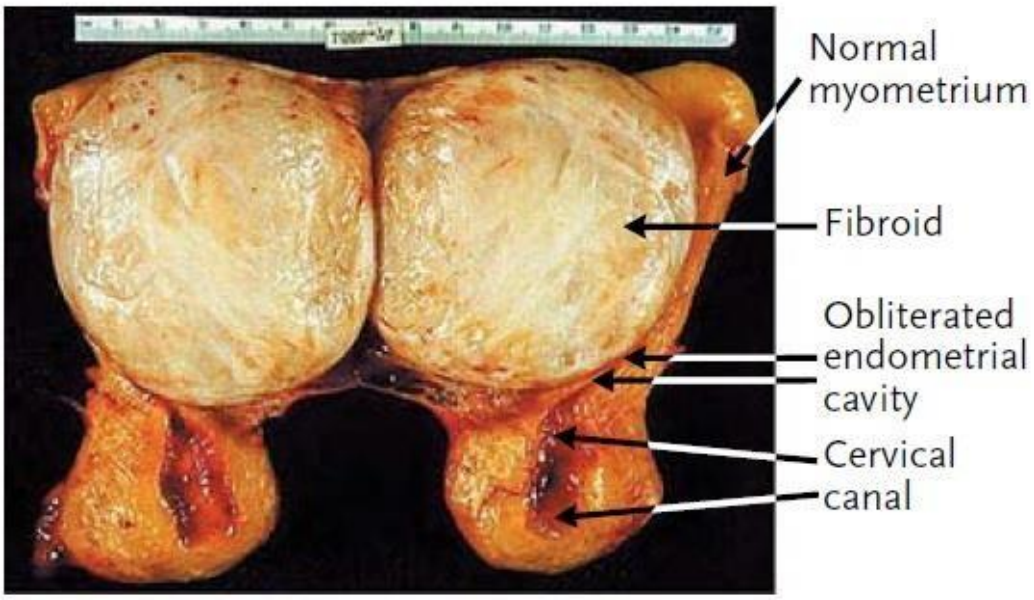

Figure 3: *Uterine fundus occupied by a single large fibroid* [(13)] .

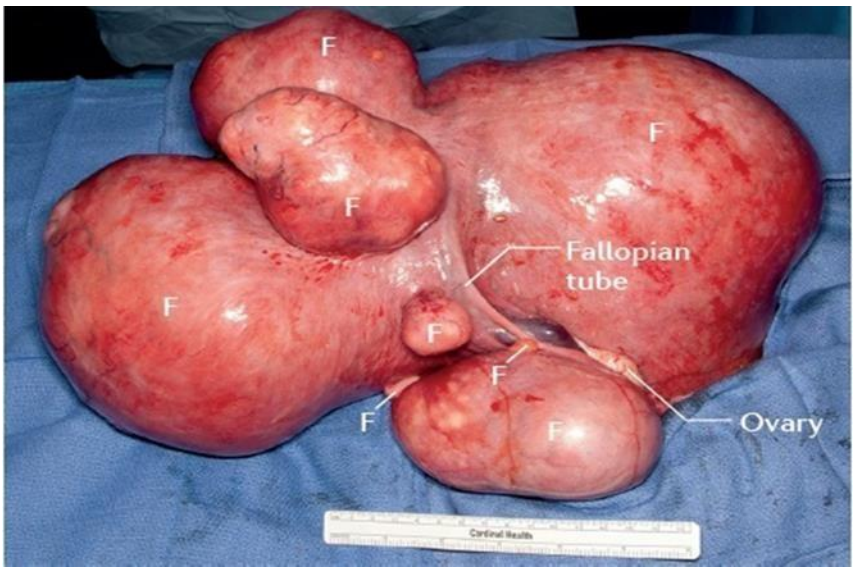

Figure 4: *Uterus with multiple fibroids* [(13)] .

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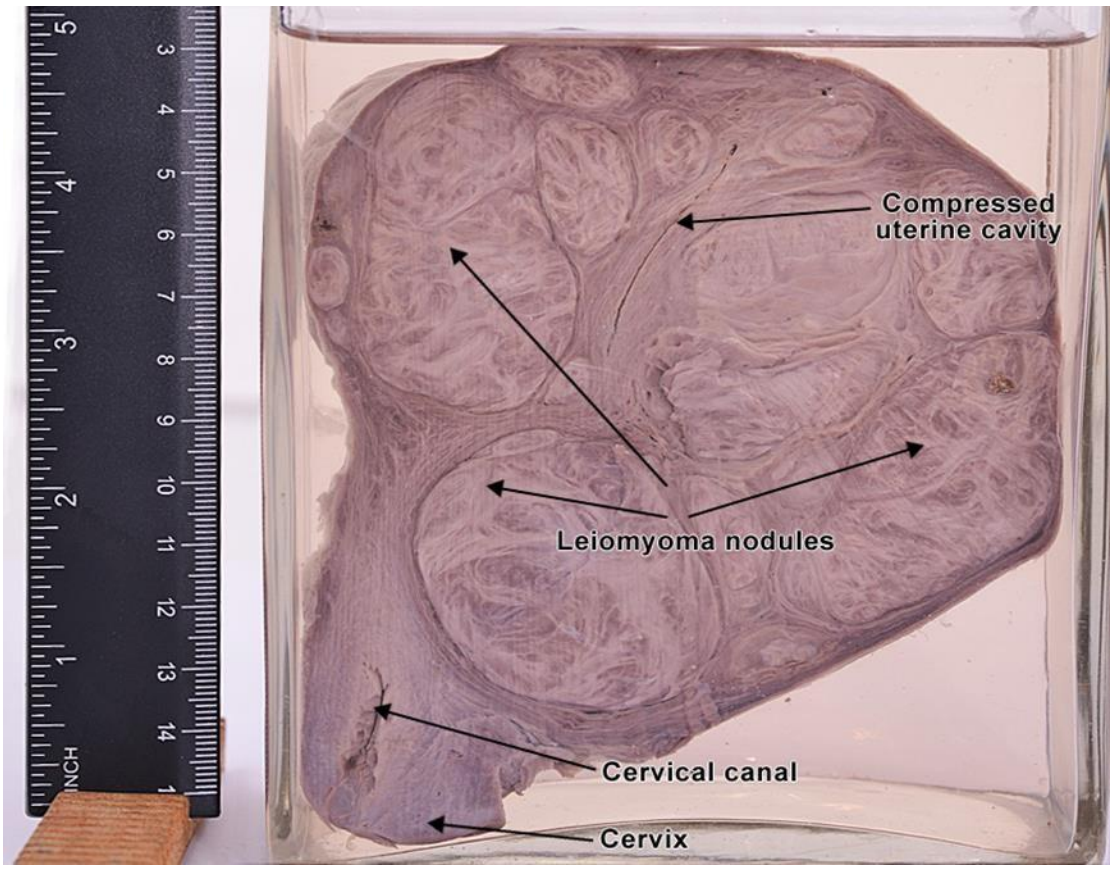

Figure 5: *Cut surface of uterine body with multiple leiomyoma nodules*. Leiomyomas so present bleeding areas, cystic degeneration and calcifications. The uterine cavity is compressed [(12)].

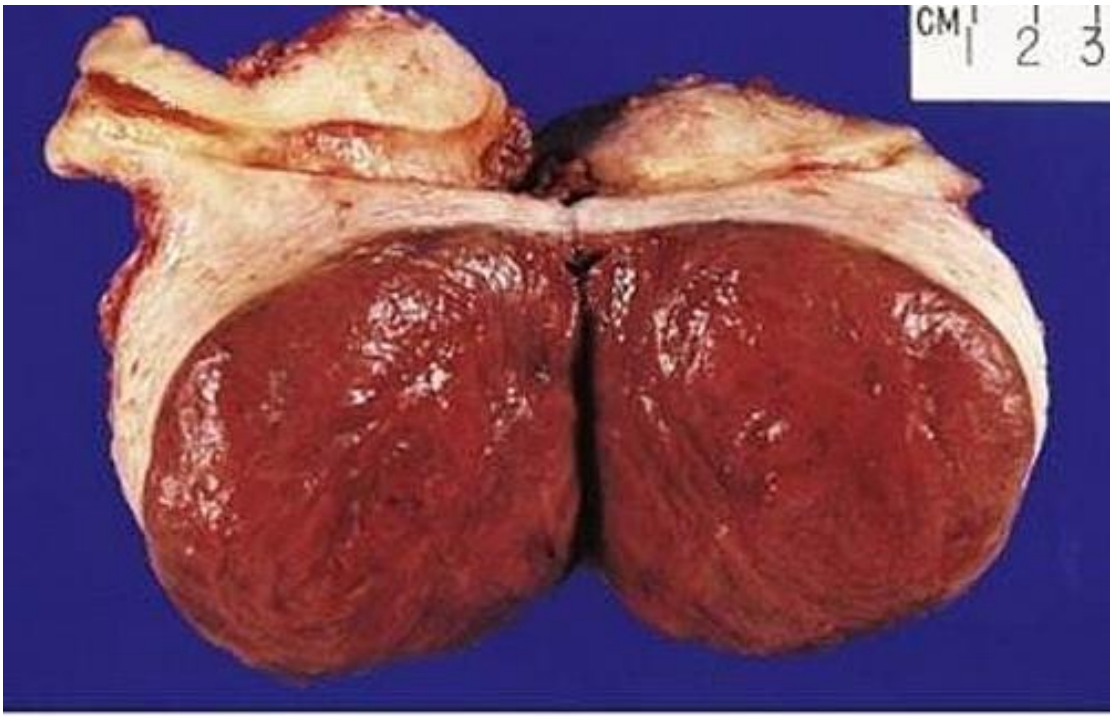

Figure 6*: Red degeneration of uterine fibroids*[(12)]

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5. Pathophysiology

The mechanisms which are responsible for the pathogenesis of uterine leiomyoma are not very clear. Uterine fibroids is defined as clonal smooth muscle cell tumor which are enlarged as a response to gonadal steroids and have typical rearrangements of chromosome essential for their development (14) [Figure7].

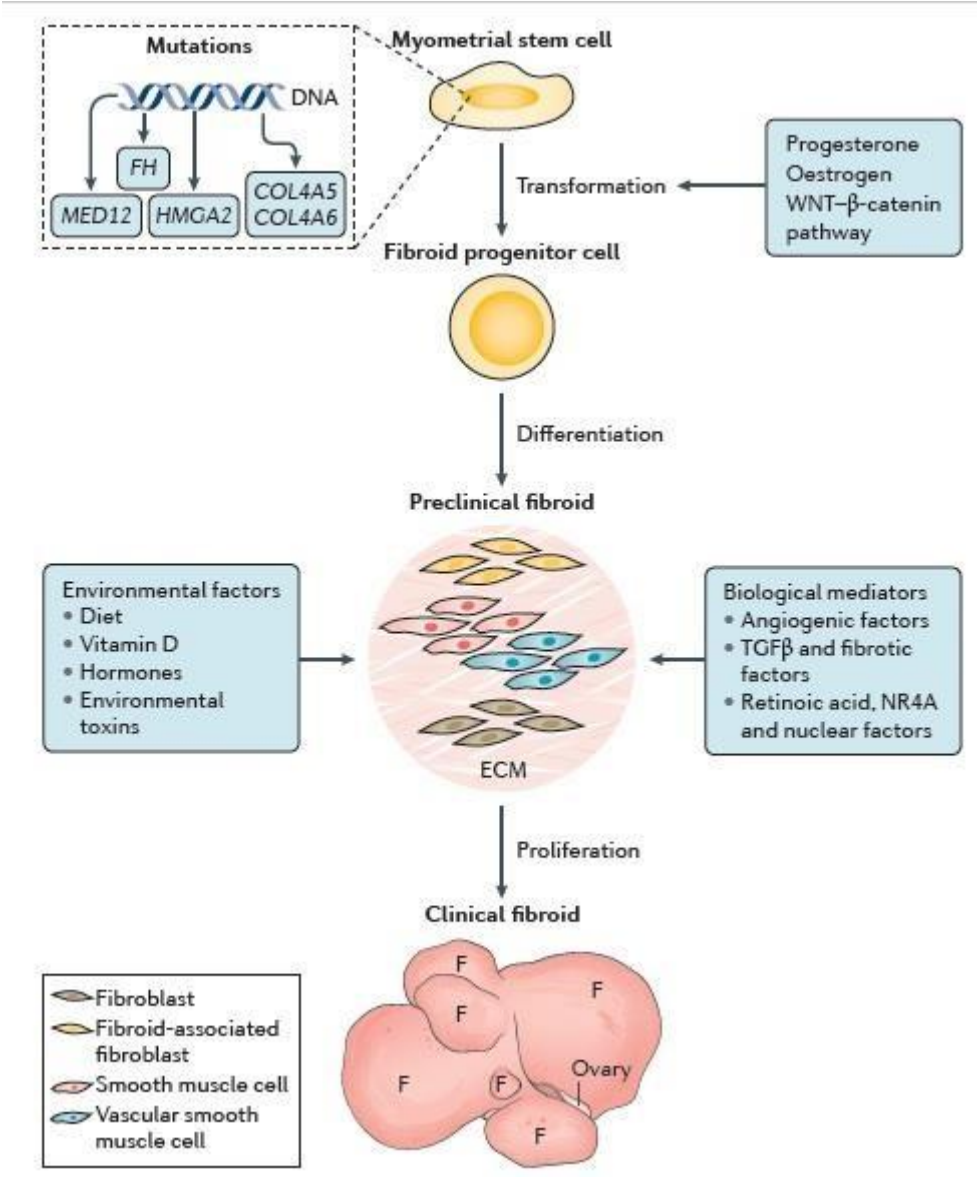

Figure 7: *recent ideas in the pathogenesis of uterine fibroids*.NR4A, nuclear receptor 4A; TGFβ, transforming growth factor-β (14).

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5.1. Leiomyoma formation

5.1.1. Fibroid stem cell

A solitary somatic stem cell of the myometrium undergo transformation into fibroid progenitors cell which is the origin of each fibroid and this transformation is under the control of ovarian hormones . The fibroid components such as the smooth muscle cells, vascular smooth muscle cells and two forms of fibroblasts (fibroblasts and fibroid-associated fibroblasts) are formed through differentiation of the fibroid progenitor cell . Genetic studies propose that fibroids are monoclonal, meaning these cells are derived from the fibroid progenitor cell [14].

Multipotent somatic stem cells present in human and mouse myometrial tissues . This subset of tissue cells undergoes self-renewal and produces daughter cells under the influence of ovarian hormones ; this process is accountable for regeneration . However, stem cells derived from fibroid tissue - not the myometrium - (Mutated myometrial or fibroid stem cell) carry MED12 mutations, which proposes that as a minimum one genetic thump firstly transforms a myometrial stem cell, which afterward interacts with the surrounding myometrial tissue to produce a fibroid tumor [Figure 8] [15, 16].

5.1.2. Ovarian hormones

The stem cells of fibroid determine low levels of estrogen and progesterone receptors when compared with the main fibroid-cell population or with normal myometrial cells, . The myometrial cells with elevated levels of the progesterone and estrogen receptors and their ligands are necessary for the growth of fibroid stem cells , signifying that the achievement of steroid hormones on fibroid stem cells is mediated by myometrial cells in a paracrine fashion [Figure 9] [16].

5.1.3. WNT–β-catenin pathway

WNT–β-catenin pathway seems to shows a key role in regeneration and differentiation of stem cells in myometrium and fibroid tissues. Over expression of activated β-catenin in uterine mesenchyme during embryonic progress and in adult mice contributes to fibroid like tumors in the uterus [16].

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The biologic functions of β-catenin are regulated by complex mechanisms. Secreted WNT proteins attach to cell-surface receptors of the Frizzled family of receptors . This will lead to triggering of a cascade of proteins causing low degradation of β-catenin in the cytosol and finally the amount of β-catenin that influences the nucleus will be changed. The cytoplasmic β-catenin that run away from degradation is capable to enter the nucleus and act together with chromatin and the family of T-cell transcription factor (TCF) proteins to adjust the expression of a big number of genes and modify key cellular functions, such as cell differentiation , tumorigenesis, and cell fate. The ovarian hormones play role by interacting with the WNT–β-catenin pathway to quicken the process of tumorigenesis [17,18]. This pathway be able to trigger transforming growth factor-β3 (TGFβ3) expression , which makes the expression of fibronectin (an ECM protein) and cell production in preclinical fibroids extra than in the myometrium [Figure 9] [14].

5.1.4. Genetic hit

Mutations of the mediator complex subunit 12 (MED12) seem to drive fibroid formation. This Mutations touch the interaction linking MED12 and cyclin C, which orders β-catenin transcriptional action. Fibroids with MED12 mutations contain high ranks of WNT4–β-catenin associated with those without these mutations [14]. The mutations of MED12 have also been linked to improved expression of the TGF-β receptor, thus cause activation of its downstream signaling. This in sequence activates SMAD and MAPK family proteins, mediating stem-cell self-renewal and creation [Figure 9] [16].

Definite karyotypic readjustments were found in fibroids lead to deregulation of specific genes such as high mobility group A2, HMGA2. It was previously supposed that this type of chromosomal translocation is partial to malignant tumors but currently is known to have a role in the pathogenesis of fibroid [14]. In uterine leiomyoma and in other human tissues with a proliferative phenotype HMGA2 gene is expressed , but not in the normal myometrium [19] .In fibroid cells, HMGA2 seems to inhibit senescence by decrease the expression of cyclin-dependent kinase inhibitor 2A (CDKN2A), which encodes ARF (p14) . Intact ARF (p14) keeps senescence in fibroids. HMGA2 might interact with let-7 (a microRNA precursor) and possibly lead

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to repression of HMGA2 which causes inhibition of cellular production. Fibroids have the prospective to be either lacking in let-7, like in larger fibroids, or express amplified levels of let-7, like in smaller fibroids. The merger of several studies led to the suggestion that modifications in the let-7 HMGA2– ARF (p14) pathway might enhance the self-renewal ability and decline senescence of fibroid progenitor cells (14).

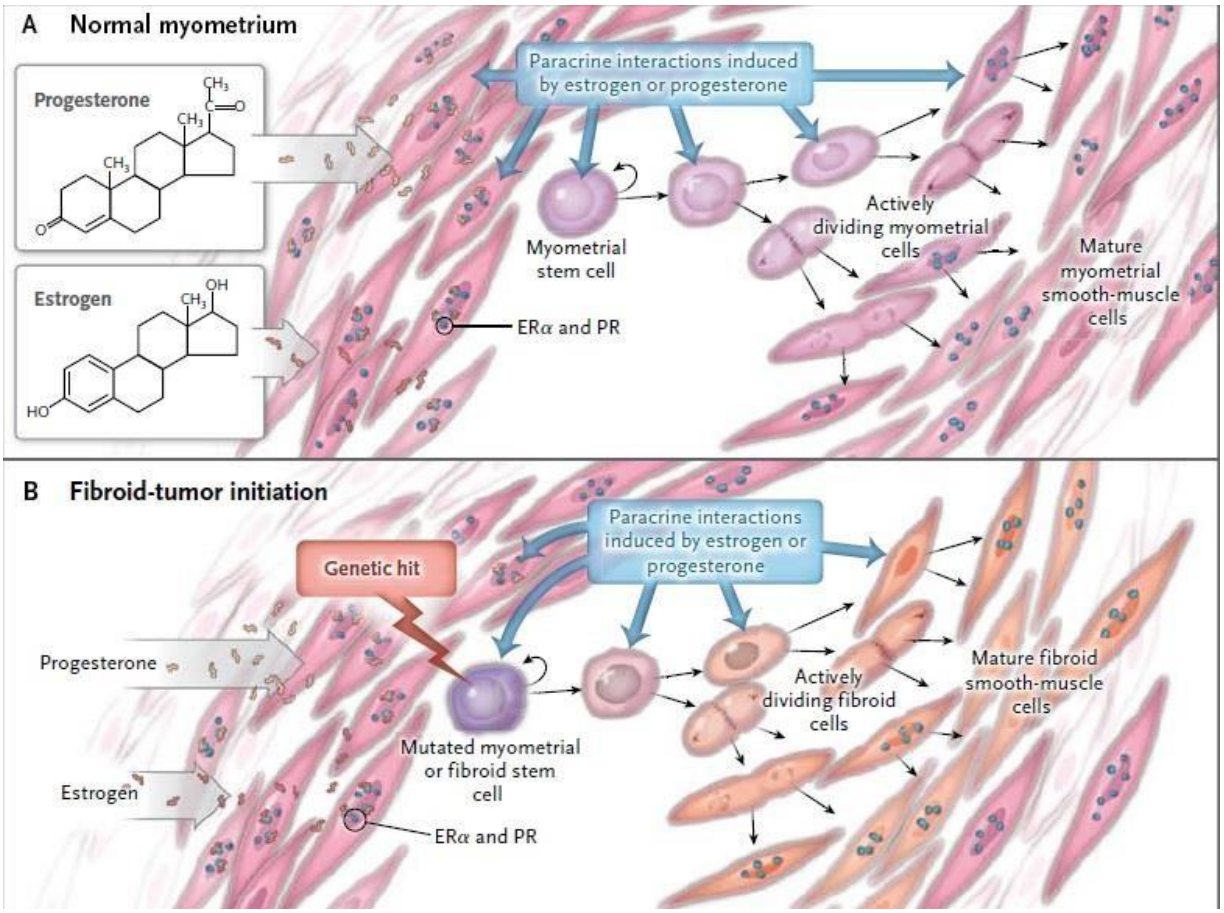

Figure 8: Tumorigenesis of Fibroids. Normal myometrial tissue contains populations of stem cells with the ability for self-renewal accountable for the proliferation of normal myometrial smooth-muscle cells (Panel A) Paracrine factors, such as WNT ligands, that are released by mature cells may act on stem cells to induce their self-renewal and proliferation. A genetic hit, such as a MED12 mutation or a chromosomal rearrangement affecting HMGA2, may transform a myometrial stem cell into fibroid stem cells (plane B) (16).

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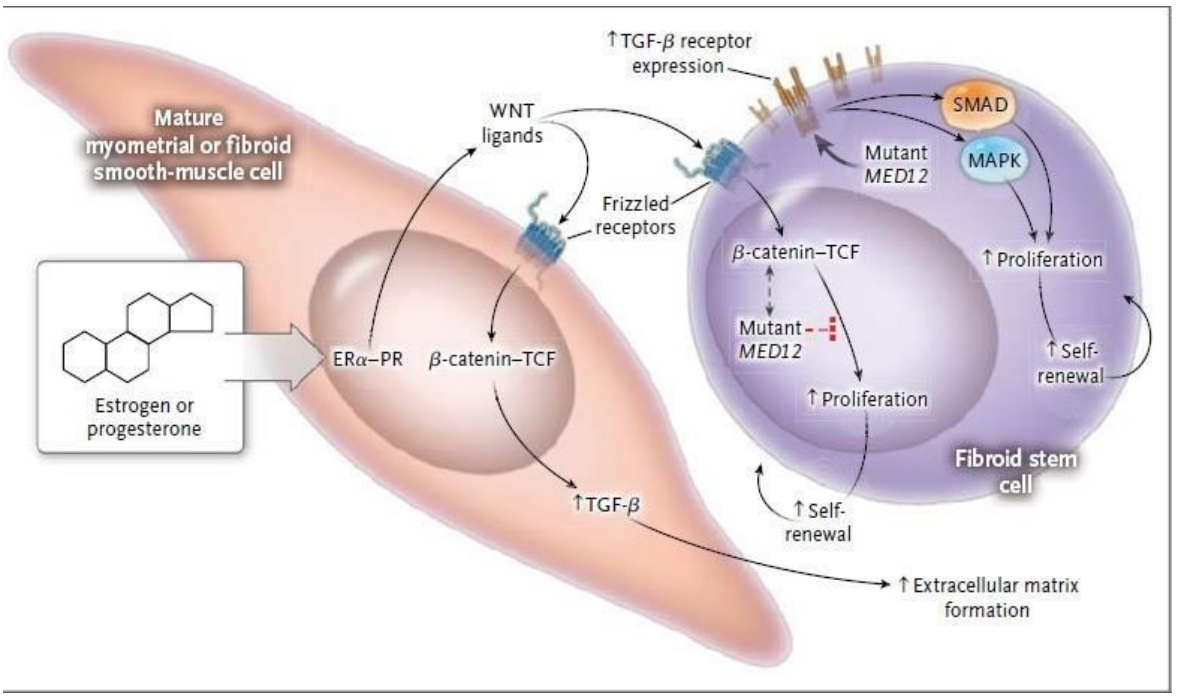

Figure 9: Interactions among Ovarian Hormones, the β-Catenin and TGF-β Pathways, and MED12 in Fibroid Cells. Estrogen and progesterone may increase secretion of WNT ligands from mature smooth muscle cells surrounding the stem cells. In both cell types, WNT, acting through the Frizzled family of receptors, activates the β-catenin–T-cell transcription factor (TCF) pathway, which induces the production of transforming growth factor β (TGF-β) in mature cells and leads to excessive formation of extracellular matrix. In stem cells, nonmutant MED12 may act as a physiologic modifier of β-catenin action, whereas mutant MED12 (or the absence of MED12) may linked to increased expression of the TGF-β receptor, which leads to the activation of (SMAD) and (MAPK) family proteins, mediating stem-cell self-renewal and proliferation [16].

5.2. Fibroid growth regulators

5.2.1. Receptor in nuclei

Progesterone, Estrogen and their receptors (ER and PR, respectively) have extensive been measured as key regulators of fibroid biology [Figure 10]. After the differentiation of fibroid progenitor cells together ERα and ERβ are stated in fibroids [14]. Progesterone receptor (PR) levels are maintained by Estrogens , and thus progesterone through its receptor may promote the growth of leiomyoma . The growth-stimulatory effects of estrogens on leiomyomas are intermediated by cytokines, growth factors, or apoptosis factors [19]. An important regulator of

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estrogen response in leiomyomas is the enzyme aromatase. Aromatase is the enzyme responsible for alteration of androgens to estrogens and is up regulated in leiomyoma cells related with normal myometrium [20, 21].

Progesterone receptors are also up regulated in leiomyomas compared to usual myometrium [22]. Early readings postulated that progesterone acted on leiomyomas as a smooth muscle cell mitogen while current studies suggest that it hinders apoptosis through making the antiapoptotic factor Bcl2 [23].

Females who have elevated levels of testosterone have higher degrees of fibroids. This might result from the effect of the androgen receptor which cause overexpression of aromatase, [14].

There are new facts to suggest that the NR4A nuclear receptor (constitutively dynamic orphan receptors) have been overexpressed in fibroids and playing a key role in fibroid pathogenesis and both ECM deposition and cellular production [14].

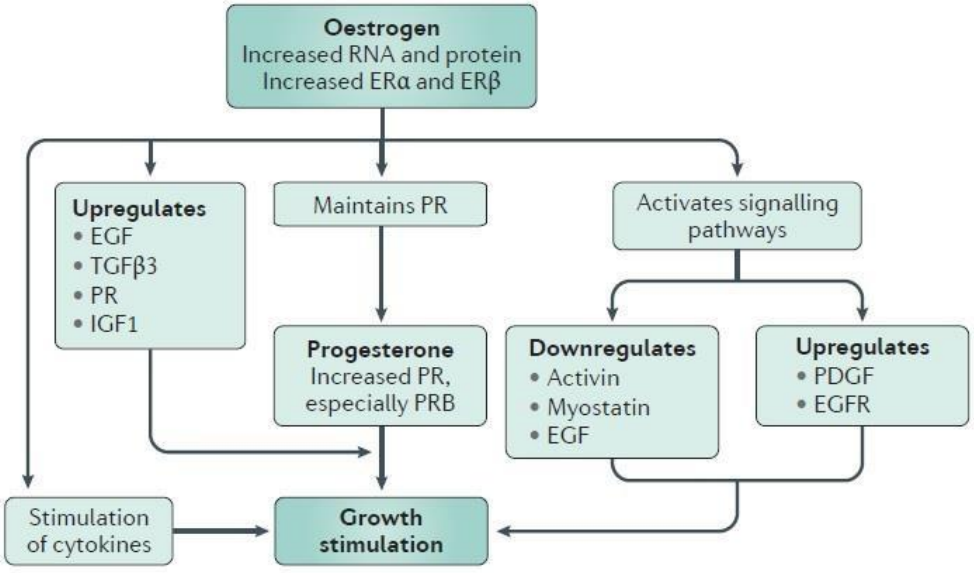

Figure 10: The effect of sex steroids in fibroid growth regulation. EGF, epidermal growth factor; EGFR, EGF receptor; ER, estrogen receptor; IGF1, insulin- like growth factor 1; PDGF, platelet-derived growth factor; PR, progesterone receptor
; TGFβ3, transforming growth factor-β3 [14].

5.2.2. Angiogenic factors

In leiomyoma and myometrial cells fibroblast growth factor (bFGF) and its receptors

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FGFR-1 and FGFR-2 expression have been reported . The countenance of FGFR-1 in the tumors is more distinct compared with myometrium. This factor stimulates angiogenesis and causes production of smooth muscle cells.

Vascular endothelial growth factor (VEGF) mRNA and VEGF protein expression have currently been documented in the smooth muscle cells of both myometrium and leiomyoma. (24). Heparin-binding regions are present in the VEGF . This can facilitate binding to the extracellular matrix, which may thus function as a pool for this factor as with the other heparin binding factors bFGF and PDGF. VEGF kindles angiogenesis. Angiogenesis is necessary for actively growing tumors, and it has been stated that VEGF is the most active agent known for increasing capillary permeability, which growing the nutrient supply and increase the growth of fibroids . By subsidiary effect VEGF could also induce the production of endothelial cells. In addition VEGF acts synergistically with fibroblast growth factor (FGF) . The grouping of these two angiogenic factors having a synergistic effect on angiogenesis (25).

5.2.3. The TGFβ pathway

The TGFβ path has been documented as a vital organizer of cell growth in fibroids through inflection of tissue remodeling and inflammation. TGFβs are identified to have an significant role in healing of wound and repairing of tissue . High or sustained production of TGFβs or abnormalities in their receptors can lead to the development of fibrosis (26). The mien of local anticoagulant factors (such as plasminogen activator inhibitor 1, antithrombin III and thrombomodulin) might destroy by TGFβ3 in neighboring endometrial cells, which leads to dense menstrual bleeding (14).

5.2.4. Membrane receptor system

The prolactin-releasing peptide receptor, looks to be unusually expressed in fibroids. These receptors situated upstream of the automatic target of rapamycin (mTOR) , and the damage of the repressor RE1-silencing transcription factor might take part in pathogenesis of fibroid. Prolactin is upregulated in fibroids and its receptor has as well been recognized in fibroid, myometrial and endometrial tissue (14).

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5.3. Extracellular Matrix (ECM):

.Leiomyomas is a fibrotic process characterize by abnormalities of amount and topology of the ECM. The collagen subtypes, fibronectin, and proteoglycans are the main constituents of ECM. There is upregulation of the mRNA and protein for major extracellular matrix components, primarily type I and III collagen [27]. . The ECM in leiomyomas indirectly stimulates intercellular signaling and thus it does not appear to be passive nonfunctioning component. The tissue tension increases as a result of the abnormal composition, fluid content and stiffness of the tumor. This induces mechanical signaling transmitted from the fibers in the ECM to intracellular components through transmembrane receptors. This complex mechanical signaling network involves changes in physical linkages with the cytoskeleton and cell shape in addition to distorted stiffness and ECM [28].

6. Risk Factors

Age: Myomas do not happen before puberty. Their incidence decreases with menopause. It has been reported that fibroid incidence increases after the age of 30, this might be result from increasing formation or increasing myoma growth secondary to changes in the hormones level during this time [29, 30].

Ethnicity: Black women are considerably more probable to have uterine fibroid than white women [4] .This racial variations could be due to differences in the biosynthesis and/or metabolism of estrogens . Black women have elevated level of aromatase enzyme which is responsible for the aromatization of androgens into estrogens and this produces high levels of estrogen in tissue [31]

Parity: Pregnancy produce defensive effect against the development of uterine fibroids, however the mechanism remains indistinct. It has been recommended that during post-partum uterine remodeling, small lesions perhaps subject to selective apoptosis. In addition fibroid tissue may be liable to ischemia during both parturition and uterine remodeling [1, 5].

Early menarche: The risk of developing fibroids increased in women with early menarche (<10 years old) due to longer exposure to circulating ovarian hormones over a lifetime [32,

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33).

Family history: Women reporting myomas in two first-degree relatives are more probable to have VEGF expression strongly when compared with women have myomas but without family history (34).

Obesity: high BMI is significantly documented in women with myomas. In obese women high levels of estrogens in the blood resulted from the aromatization of androgens by peripheral fatty tissues and decreased sex hormone binding globulin production by the liver so that the bioavailability of estrogens and androgens will increase (35) .

Alcohol: Alcohol consumption is associated with higher endogenous levels of estradiol and estrone (36) Alcohol stimulates aromatase activity, increasing estrogen levels. Alcohol might also interact with luteinizing hormone production from the pituitary gland, increasing estradiol release from the ovaries (37) .Long-term alcohol consumption may also affect immune system and may control production of pro-inflammatory cytokines. Since the endogenous levels of hormone can be changed due to the effect of alcohol especially beer, the risk of developing fibroids is increased (32).

7. Clinical Manifestations

In general symptoms associated with uterine leiomyomas can be classified into three different categories (38):

7.1. Heavy or prolonged menstrual bleeding

Heavy and/or prolonged menses is the characteristic bleeding form with leiomyomas . In many women with fibroids dysmenorrhea is reported and appears to be associated with heavy menses. The location of the fibroid determined the incidence and amount of uterine bleeding . The size of fibroid is of lesser importance. Significant heavy menstrual bleeding is frequently associated with submucosal myomas that project into the uterine cavity. The mechanism(s) of abundant menses in women with leiomyomas are uncertain but may include uterine vasculature abnormalities, molecular dysregulation of angiogenic factors , or impaired endometrial hemostasis(38 ,39).

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7.2. Bulk-related symptoms

Uterus with fibroid is enlarged and become irregular in shape. This causes certain symptoms due to pressure from myomas at particular locations.

generally, the common symptoms in women with fibroids is pelvic discomfort which is expected to be chronic, irregular, boring pressure or pain. A various group of urinary symptoms can be seen in up to 60 percent of women with fibroids including frequency, difficulty emptying the bladder, or, rarely, complete urinary obstruction . When Fibroids set pressure on the rectum , bowel symptoms include constipation, and severe abdominal pain may result associated with breaking down of the fibroid tissue (degeneration) or torsion of a pedunculated tumor . An increase in thromboembolic risk may result from very large uterus which compresses the vena cava [40,41].

7.3. Reproductive dysfunction

When leiomyomas distort the uterine cavity (submucosal or intramural) conceiving pregnancy is became difficult and risk of miscarriage is increased. The mechanisms by which fibroids may cause loss of pregnancy are uncertain but may include the interference of fibroid with the development of placenta and normal uteroplacental circulation and increased in contraction of myometrium that caused by rapid fibroid growth [42].

Leiomyomas are expected to report for 1 to 2 percent of infertility. Submucosal fibroids that grow just below the inner lining of the uterus (endometrium) can modify the lining of the uterus and interfere with the implantation [43]. As well, leiomyomas have been correlated with unfavorable pregnancy outcomes (e.g., fetal growth restriction, abruption of placenta, and preterm labor and birth) [42].

8. Evaluation

8.1. History

A medical history have to focus on the duration of fibroid, severity of symptoms related to fibroids such as heavy or prolonged menstrual bleeding , pelvic pain , recurrent

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miscarriage and infertility . Surgical history and medications that may aggravate the symptoms of a pelvic pain and uterine bleeding should also include (44).

8.2. Physical examination

Palpation for a pelvic- abdominal mass should be included in the abdominal examination of fibroid. Vital signs are taken, as suitable. Fibroids are not often associated with fever, except in some women with degenerating fibroids. In case of heavy menstrual bleeding , women may become anemic, but in otherwise healthy reproductive-age women, a significant change in blood pressure or heart rate is uncommon as part of the clinical presentation (44).

8.3. Imaging and endoscopy

Step one: Pelvic ultrasound

Pelvic ultrasound is the first-line study used in imaging the uterine fibroids owing to its availability , safety and low cost. In very big uteri or when there are many tumors precise localization of fibroids is restricted. Fibroids are seen on ultrasound usually as identical, hypo echoic, well-circumscribed round masses, often with shadowing. In degenerative leiomyomas complex appearance can be seen and this confirm areas of cystic change (calcification).In obese women Transvaginal ultrasound provides better visualization than abdominal ultrasound (45).

Step two: Evaluate the uterine cavity

- Saline infusion sonography (sonohysterography) : saline is infused into the uterine cavity when pelvic ultrasound is performed . This can allow very clear ultrasound images to be taken for the lining of the uterus and in this case thickening of the endometrium or polyps can be simply seen. Use of this technique allows detection of submucosal lesions and intramural myomas that project into the cavity (46).
- Hysteroscopy *is* useful for visualizing the endometrial cavity. This allows evaluation for submucosal or protruding myometrial fibroids and can characterize the extent of protrusion. Once the whole fibroid is visualized rising from a pedicle, or has a broad base, the lesion is hysteroscopically classified as intracavitary. The ultrasound and

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sonohysterography more precisely predicts the size of the myoma compared with hysteroscopy [44].

Step three: Additional imaging

Magnetic resonance imaging (MRI) is one of the most effective method for visualizing the location and size of all uterine myomas. In this technique magnetic field and pulses of radio wave energy to create pictures of organs and structures inside the body are used. Due to the cost of this method, its utilize is kept for procedural planning. MRI is proficient in differentiating adenomyosis from uterine leiomyomas and Leiomyomas with small diameter (5mm) can be imagined with it [44].

9. Differential diagnosis

Leiomyomas may be associated with menstrual irregularities, pain, and infertility; therefore, a careful work-up of symptom-based differential diagnoses is valid [4] [Table.1].

Table 1. Differential Diagnoses for Symptoms associated with Uterine Leiomyomas [4].

Presenting symptom	**Differential diagnosis**
Pelvic and /or abdominal pain	Ectopic pregnancy Ovarian cyst include ruptured or hemorrhagic cyst Adrenal torsion Pelvic inflammatory disease Endometriosis Adenomyosis
Pelvic mass	Ovarian or endometrial carcinoma Uterine sarcoma Leiomyosarcoma Ovarian cyst fibroma of ovary
Menstrual irregularities	Endometrial hyperplasia Endometrial polyp Poly cystic ovary syndrome abnormalities of coagulation

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10. Management

10.1. Medical therapy

10.1.1. Non-hormonal

- It has been found that NSAIDs are effective in reducing the painful menses and severe menstrual bleeding related with fibroids. NSAIDs are not expensive and are available without a prescription in most countries [47].
- Tranexamic acid has been exposed to cause a important effect in reducing blood loss. Additionally, it is well tolerated and considers safe [48-51].

10.1.2 Hormonal

- Oral contraceptives are efficient in decrease menstrual bleeding in the short-term and may prevent the development of uterine fibroids. The theoretical mechanism of action is through atrophy of endometrium [52,53].
- Levonorgestrel intrauterine system (LNG-IUS*)* has significant effect in reducing the intense menstrual bleeding detected in women with fibroids in which the fibroids do not deform the endometrial cavity although with no reduction in fibroid size [54,55].
- GnRH agonists consider useful therapy for uterine fibroids and are usually utilized before surgery for period of 3–6 months in combination with iron therapy .They show slow onset of action since they initially stimulate the pituitary gland and ovaries and this phenomenon recognized as the flare effect, followed by down regulation of GnRH receptors resulting in hypoestrogenic symptoms. Treatment with GnRH agonists might improve the heavy menstrual bleeding, anemia, dysmenorrhea and produce significant reduction in uterine size, thus improve the symptoms of myoma [56,57].
- Selective Progesterone receptor modulators (SPRMs), for instance Ulipristal acetate, are gradually more used for medical treatment of fibroids .SPRMs are used before operation and as a short-term treatment in nearly all of the world. They are valuable at decreasing both uterine and fibroid size, additionally to intense menses, anemia and pain and largely improve in quality of life [58, 59].

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10.2. Surgical therapy

- Endometrial ablation (EA) is the choice for management of bleeding abnormalities .It is a simply invasive surgical method used for the destruction of the lining of the endometrium. It is useful for women who do not want pregnancy in the future [50, 60].

- Myomectomy *is* the choice for women who hope to keep their uterus. Even though myomectomy is a successful treatment for menorrhagia and pelvic pressure, the disadvantage of this surgery is the higher risk of blood loss and longtime of operation with myomectomy than with hysterectomy. Fibroids have a 15% recurrence rate in myomectomy and 10% of women undergoing a myomectomy will ultimately need hysterectomy within 5 to 10 years [61, 62].

- Hysterectomy *is* another effectual choice for women with fibroid related with intense bleeding who do not want pregnancy in future. The removal of the risk of the growth of new fibroids and treating other diseases including adenomyosis are the main advantages of hysterectomy. The freedom from problems in the future makes hysterectomy good choice For many women who have finished childbearing [50 ,63].

10.3. Interventional therapy

- Uterine artery embolization (UAE) is a slightly invasive option for controlling of leiomyoma-related symptoms in which a small particle delivered to block the uterine blood supply using catheter causing shrinkage of fibroids. It is an effective choice for women who wish to preserve their uterus or avoid surgery because of medical comorbidities or personal preference [64 -66].

- Magnetic resonance guided focused ultrasound surgery (MRgFUS*).* In this therapy focused ultrasound energy directed through the intact anterior abdominal wall to minimize and soften fibroids. Sustained symptoms relief for up to 5 years after treatment with MRgFUS and successful pregnancy outcomes are the main advantages of this therapy [50, 67, and 68].

- Radiofrequency myolysis is a technique in which radiofrequency energy delivered to myomas in an attempt to dehydrate them directly.

Laparoscopic and ultrasound visualization are performed for mapping of myomas.

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When a myoma is targeted for ablation, the RF probe is inserted percutaneous under laparoscopic supervision through a 2-mm skin incision. Advantages of this technique are rapid recovery, better quality of life, and actual symptoms relief [69, 70].

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