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REVIEW ARTICLE **OPEN ACCESS**

Uterine Leomyomas: Assessment and Management

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ABSTRACT
Most cases of uterine fibroids, a benign non-cancerous tumor, are observed in women who are fertile. Most women are asymptomatic despite the symptoms of dysmenorrhea, menorrhagia, excessive menstrual flow, abnormal uterine bleeding, increased pelvic pressure are seen. According to research and clinical investigations, the main determinant for the growth of uterine fibroids is the imbalance between the levels of the hormone's estrogen and progesterone. The risk of uterine fibroids is influenced by a number of variables, all of which have a detrimental effect on women's quality of life.
Keywords : *Abnormal uterine bleeding, Dysmenorrhea, Estrogen, Progesterone, Uterine fibroids, Pelvic pressure*

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INTRODUCTION

The most frequent clonal mass of uterine cells to affect women of child bearing age is a uterine myoma. [1,2,3]
The most typical presenting symptom is heavy menstrual bleeding, which can result in anemia, tiredness, and painful periods. [4,5,6,7,8,9], Uterine fibroids can cause uncomfortable and heavy bleeding, problems with daily activities and self-image, and reduced fertility.[10] They consist primarily of extracellular matrix (ECM) rich in proteoglycans, fibronectin, and collagen.[11]

ANATOMICAL CLASSIFICATION

For the purpose of facilitating clinical care and research, the FIGO classification system for the classification of abnormal uterine bleeding was created recently.[12]
According to their location and connection to uterine layers, myomata are divided into subgroups and different types.

(i) The most frequent type of leomyoma is intramural, however if a mass grows into another uterine layer, it may be classified as subserous or submucous myomas.[13,14]
(ii) When a tumour is directly next to the endometrium, it is referred to as a sub mucosal leomyoma.[13,15]A pedicle connects submucosal myomata to the myometrium and defines them as pedunculated when they extend into the uterine cavity.[13]
(iii) Just below the uterine corpus's peritoneal layer is where subserosal leomyomas are found.[13,15]

ETIOLOGICAL FACTORS

Alcohol and Caffeine

Most women have an increased risk of developing uterine fibroids when they consume coffee, alcohol, or smoke cigarettes.[16] Current alcohol consumers had a barely detectable higher chance of myoma diagnosis. [17]

Hormonal changes

Early hormone exposure throughout stages of development may be one of the potential causes of leiomyomas, causing epigenetic changes that last into adulthood and causing disease initiation or progression.[17] The main factor thought to encourage myoma growth is oestrogen. The objective of this review is to highlight the biochemical, histologic, and clinical data that support progesterone playing a crucial role in the development of uterine myomas.[18]

Genetic factors

Trisomy 12 was discovered, along with translocations between chromosomes 6 and 10, 12 and 14, and deletions of chromosomes 3 and 7. [19] Recent studies revealed that 70% of fibroids had a mutation in subunit 12 of the transcriptional regulator complex.[20] Chromosomal 10q24.33, STE20-like kinase, and

A-kinase anchor protein-13 (AKAP13) were the three susceptibility loci that Cha and colleagues discovered to be associated with uterine fibroids.[21]

RISK FACTORS

Fibroid formation is linked to risk factors, both reversible and irreversible. Age, race, endogenous and exogenous hormonal factors, obesity, uterine infections, and lifestyle factors (diet, caffeine and alcohol intake, physical activity, stress, and smoking) are among them.[22]

Parity

Though the mechanism is yet unknown, it has been discovered that pregnancy protects against the growth of uterine fibroids. According to certain theories, tiny lesions may undergo selective apoptosis during postpartum uterine remodelling.[23]

Menarche

Menarche after the age of 16 appears to reduce the risk of uterine fibroids, which has been linked to menarche before the age of 10.[19]

Genetic factors

The prevalence of chromothripsis in uterine fibroids shows that it contributes to the development and growth of the tumours[24]

Age

Pathologically confirmed fibroids are more common as people get older, peaking at age 50. Before puberty, myomas do not develop, and after menopause, their frequency declines.[25] According to various studies, fibroids were found to increase quickly after the age of 30, which may be caused by hormonal changes or a worsening of symptoms brought on by pre-existing fibroid.[26]

Obesity

A slight increase in the risk of fibroids is connected with a higher body mass index (BMI).[16] The metabolic syndrome is a group of conditions that includes central obesity, insulin resistance, high blood pressure, and hyperlipidemia, all of which are linked to an increased risk of fibroid development. [27,28] Every 10kg of body weight and BMI resulted in a 21% rise in the prevalence of fibroids.[29]

Lifestyle and Diet

Consuming a lot of green vegetables appears to be protective against myoma, whereas eating a lot of beef and gammon is related with the disease.[17] According to epidemiological research on fibroids, exercise prevents the development of fibroids.[30]

PATHOGENESIS OF UTERINE FIBROIDS

Fibroids and etiology involves a genetic mechanism. Uterine leiomyomata have not traditionally been regarded as a hereditary illness. But a lot of new clinical data suggests that at least some myomata have a hereditary cause. Actually, according to cytogenetic studies, roughly 40% of uterine fibroids have chromosomally changed DNA and exhibit cytogenetic abnormalities that are also seen in a number of other tumour forms. For instance, research discovered trisomy 12, translocations between chromosomes 6 and 10, deletions of chromosomes 3 and 7, and translocations between chromosomes 12 and 14. [31] The most prevalent cytogenetic anomaly, translocation 12:14, which affects 20% of chromosomally aberrant tumours, was discovered to contain the HMGA2 gene. This gene encoding protein with high mobility group DNA binding activity that regulates embryonic proliferation. [32] The HMGA2 gene is not expressed in the healthy myometrium, but it is in uterine leiomyoma and other human tissues with a proliferative phenotype, such as foetal tissues, lung, and kidney. [33] According to Markowski et al., in vitro HMGA2 antagonistic activity reduced leiomyoma cell growth. [34] Uterine leiomyomas, such as those from hereditary leiomyomatosis and renal cell cancer (HLRCC), can be used to identify heritable cancer syndromes. Patients with this syndrome are more likely to develop early-onset renal disease and benign uterine and cutaneous fibromas. cancer of the cell. The indicated gene is fumarate hydratase (FH), which encodes a Krebs cycle enzyme that converts fumarate to malate. [35] Due to a COL4A5 and COL4A6 gene deficiency, Alport syndrome is an X-linked progressive nephropathy accompanied by leiomyomas. [36] However, a recent study combining mRNA and miRNA differential expression between fibroids and myometrium found that the focal adhesion pathway was upregulated while the Wnt pathway was downregulated in fibroids. [37] The Beta – catenin immunohistochemistry data tends to indicate that the canonical Wnt pathway is not implicated in fibroids development, since Beta-catenin, when expressed, is located at the membrane in mutated cases; a localization which has been demonstrated to be indicative of a low transactivation activity. The Wnt/-catenin pathway does not appear to be constitutively activated in MED12 mutant tumours, according to the same authors, and they speculate that if MED12 mutations are involved in the development of uterine tumours, they are likely to play a minor role not by the activation of Wnt target genes in conjunction with catenin. [38][39]

DIAGNOSIS

Laboratory Investigations

- In order to determine if the patient needs surgery or not and whether you could need a blood transfusion, Hb is used to determine the degree of anemia.
- White blood cell (WBC) count or erythrocyte sedimentation rate(ESR) are used.
- For surgery or to treat anemia before surgery, blood grouping and cross-matching are performed.
- Before surgery, urinalysis is performed to check for UTIs as a potential source of post-operative infection. [40]

Further Investigations

a) Ultrasonography

Due to its accessibility and inexpensive cost, transabdominal and transvaginal ultrasonography has been used commonly. [41] Transvaginal ultrasounds can be used to detect fibroids as tiny as 5 mm in the hands of an experienced operator. When a patient is fat, transabdominal images are frequently of little use. Degenerate fibroids may look complicated and have sections that have undergone cystic transformation. [42] Circumferential vascularity is generally visible with doppler ultrasonography. [43] Although transvaginal sonography is reasonably trustworthy for the uterus with a total capacity of 375 mL or fewer than four fibroids. [44]

b) Sonohysterography with saline Infusion

For characterizing focal uterine masses identified on B-mode ultrasound images, saline infusion sonohysterography-based imaging is typically utilized as an additional or alternative imaging technique. It is also useful for identifying central intracavitary projections and scattered endometrial alterations. The deformation caused by insufficient saline injection is too tiny to produce images with a suitable signal-to-noise ratio. To get excellent strain images, care must be taken to deform the uterine wall just enough to be tolerated by the patient. It appears to have limited diagnostic accuracy in comparison to ultrasonography and MRI imaging, which are both less painful and more precise techniques for imaging. [45]

c) Magnetic resonance imaging (MRI)

The most effective approach for evaluating uterine fibroids has been described as magnetic resonance imaging, despite being more expensive, specifically for identifying the presence of tiny fibroids. With a sensitivity of 88%-93% and a specificity of 66%-91%, MRI is reliable for evaluating fibroids and distinguishing them from focal adenomyosis. [46] MRI can clearly show the uterine zonal anatomy, does not use ionizing radiation, and is more sensitive than ultrasound at detecting uterine myomas. [47] With MRI, fibroids as tiny as 5 mm in diameter can be seen, and submucosal, intramural, and subserosal fibroids are typically clearly distinguished from one another. It is also a useful tool for predicting and evaluating how fibroids will react to uterine artery embolization (UAE). [48] The "bridging vascular sign," which consists of blood vessels and/or signal spaces that stretch from the uterus to supply a pelvic mass, is a well-described MRI characteristic that is useful in the evaluation of big pelvic masses. [49]

d) Hysteroscopy

Intracavitary myomas and big endometrial polyps may necessitate differentiation via hysteroscopy. Hysteroscopy is often carried out in an outpatient setting without the need of anaesthesia. Hysteroscopy and endometrial biopsy may be coupled in cases of irregular bleeding or if the patient has risk factors for endometrial hyperplasia (obesity, chronic anovulation). [50]

MANAGEMENT

Medical Management

For brief periods of time, medical treatment is utilized as a "stand-alone" treatment for temporarily alleviating symptoms. Prior to surgery, medical intervention is utilized to minimize the size of fibroids, decrease bleeding, and raise the levels of hemoglobin. [51]

1. **Non-steroidal anti-inflammatory agents (NSAIDs)**

   NSAIDs are used as the first line of treatment for AUB and dysmenorrhea brought on by fibroids because of their affordability, lack of side effects, and widespread accessibility. [52] Ibuprofen (600-1800 mg daily) and naproxen (550-1100 mg daily) are best effective when started a day or two prior to the start of menstruation and followed throughout menstruation. Dysmenorrhea and menorrhagia have been proven to be improved by NSAIDs. In women who have a history of known NSAID hypersensitivity, active gastric or peptic ulcers, or renal illness, NSAIDs should be avoided. [53]

2. **Antifibrinolytics agents (tranexamic acid)**

An antifibrinolytic drug and blood clot promoter, tranexamic acid is a synthetic lysine derivative. In order to minimize menstrual blood flow and alleviate symptoms, it encourages pro-coagulant mechanisms by blocking fibrin breakdown at the surface of the plasminogen lysine receptor site. It is taken orally in a dose of two 650 mg tablets three times per day for up to five days. It is contraindicated for patients with color blindness, bleeding, previous instances of intravascular clotting, or allergy to the drug due to its uncommon and minor side effects, which include gastrointestinal and musculoskeletal complaints. [54]

3. **Combined hormonal contraceptives**
   AUB is frequently treated with combined estrogen-progesterone contraceptives, including in women with uterine fibroids, whether they are taken orally, vaginally, or as transdermal patches. [55] They primarily have a tendency to maintain a thin endometrium and reduce the amount of endometrial loss throughout the menstrual period. They improved hemoglobin concentration, quality of life, and fibroids-associated AUB, but they weren't as effective as progestin-releasing intrauterine devices (IUD). Before proposing the use of any combined hormonal contraceptives, medical eligibility requirements such as age, smoking, history of venous thrombosis, and aura migraines should be discussed with the patient. Side effects such as nausea, headaches, and irregular bleeding should also be discussed. [56]
4. **Progestins**
   Oral progestins (5–10 mg of norethindrone acetate, 10 mg of medroxyprogesterone, and 40 mg of megestrol daily) and progesterone-releasing IUDs are the most often used progesterone-only therapies for AUB. [57] This class of drugs reduces menstrual blood loss by suppressing the endometrium's development that is driven by estrogen. The side effects are mood swings, acne, breast soreness, irregular bleeding, and gastrointestinal issues. Levonorgestrel-releasing IUDs, which act locally on the endometrium and have little side effects and systemic absorption, can alleviate menorrhagia and anemia in up to 50%–60% of individuals with AUB at six to twelve months. [58]
5. **Selective progesterone receptor modulators and anti-progestins**
   SPRMs and anti-progestins thin the endometrial lining, activate apoptosis, and prevent the growth of fibroid cells at the level of peripheral progesterone receptors. In preliminary investigations, ulipristal acetate (5–10 mg orally once daily) was linked to 25%–50% fibroid shrinking and higher than 90% control of uterine blood loss. The use of an effective method of birth control is advised because anovulation was observed in 80% of women receiving the current doses of ulipristal acetate. Significant liver dysfunction and severe asthma are contraindications to this drug. The mifepristone daily doses of 12.5 to 50 mg revealed a 40%–50% reduction in uterine/fibroid volume. [59] 6
6. **GnRH agonists and antagonists**
   Leuprolide acetate is the most used GnRH agonist and is administered intramuscularly for 3-6 months as a 3.75 mg once a month or 11.25 mg every three months dose to treat uterine fibroids before surgery. After triggering the release of gonadotropins initially (the "flare effect"), GnRH agonists cause the pituitary to downregulate, which reduces the amount of gonadotropins and gonadal steroids produced and prevents the growth of fibroids. In the majority of women (>98%), GnRH agonists cause amenorrhea and are linked to a 35%–65% reduction in fibroid size within 3 months of therapy commencement. However, GnRH agonists without add-back therapy are linked to side effects including as hot flushes, mood swings, dryness in the vaginal cavity, decreased libido, sleep difficulties, and bone loss when used long-term (>6 months). Currently, it is difficult to employ GnRH antagonists such as cetrorelix and ganirelix acetate. They are more expensive than GnRH agonists and need daily injections although having an instant clinical response. [60]
7. **Iron supplementation**
   Due to the fact that fibroids are frequently accompanied by severe and extended menstrual flow, they might result in iron-deficiency anemia, for which iron supplementation is a valid alternative treatment. There are several oral formulations using iron dextran, iron sucrose, or ferric gluconate that provide 150–200 mg of elemental iron daily. When administered intravenously, iron can also result in allergic reactions (urticaria and pruritus) and musculoskeletal pain. Gastrointestinal problems are the most frequent side effects of dietary iron. In unstable individuals or after an unsuccessful iron treatment, blood transfusion may be the last option. [61]
8. **Aromatase inhibitors**

By preventing the aromatization of androgens to estrogens, aromatase inhibitors like letrozole (2.5 or 5 mg orally once a day) and anastrozole (10 mg orally once a day) cause a hypoestrogenic state, which causes the endometrial lining to thin and menstrual flow to decrease. According to a Cochrane review on the effectiveness of aromatase inhibitors, fibroid size can be reduced by 40%–50%, and menorrhagia, dysmenorrhea, and menstrual cycle duration can all be improved. [62]

Interventional radiology procedures

For women who reject surgery or are not suitable surgical candidates, UAE and MRgFUS are effective minimally invasive therapies for fibroids.

Uterine artery embolization (UAE)

Tris-acryl gelatin microspheres or non-spherical polyvinyl alcohol are used in the minimally invasive angiographic procedure known as uterine artery embolization (UAE) to cut off the uterine blood supply, which results in ischemic necrosis of the fibroid. [63] To access and embolize the uterine arteries bilaterally, a tiny catheter is inserted via the right common femoral artery while the patient is under light anesthesia. Contraindications to this surgery include current pregnancy, suspected malignancy, and active pelvic infections. Women who had UAE expressed relief in bulk symptoms, a 42% reduction in fibroid size at three months, and a shorter menstrual cycle. Post-embolization syndrome is one distinctive side effect of UAE. [64]

Magnetic resonance guided focused radiofrequency ablation (MRgFUS)

High intensity focused ultrasound (HIFU), also known as MRgFUS, is a fibroid-specific therapy that is accessible but not widely utilized. It causes fibroid coagulative necrosis and regression using high intensity transabdominal ultrasound pulses. [65] Pacemakers and other MR scan contraindications prevent patients from participating in this operation because it is done under dynamic real-time MRI supervision. Pedunculated, gadolinium-unenhanced, or very big fibroids (>10 cm), post-menopausal state, and severe adenomyosis are further contraindications to this procedure. Around 71% of women who had MRgFUS said their symptoms had improved six months later. The two most common hazards of MRgFUS are reversible pelvic neuropathy and local skin burns. [66]

Surgical management

Myomectomy

Uterine-sparing surgery known as a myomectomy involves removing the fibroids while leaving the uterus unharmed. It is most frequently recommended to patients who hope to become fertile in the future, but it is also an option for women who have finished having children and want to keep their uterus. Up to 80% of women who undergo a myomectomy see a temporary decrease in uterine size and an improvement in their symptoms. [67] The preferred method for removing smaller type 0 or type 1 submucosal fibroids is hysteroscopic myomectomies. The recommended treatment for intramural and subserosal fibroids should always be laparoscopic myomectomy. This method is associated with reduced post-operative pain, less blood loss and morbidity, and shorter hospital stays. [68]

Hysterectomy

The surgical excision of the uterus, along with or without the ovaries and tubes, is known as a hysterectomy and used for removal of symptomatic fibroids. Vaginal and laparoscopic hysterectomies are advised since they are linked to a shorter hospital stay, a quicker recovery, and higher patient satisfaction. [69]

Laparoscopic radiofrequency volumetric thermal ablation

An electro-surgical probe is introduced inside the fibroid during radiofrequency volumetric thermal ablation (RFVTA), a laparoscopic outpatient operation carried out under ultrasound guidance. This method causes coagulative myolysis. [70]

Endometrial ablation

Pre-menopausal women who have finished childbearing are good candidates for endometrial ablation as a treatment option for fibroid-associated AUB. Devices for destroying the endometrium include thermal balloons, microwaves, hydrothermal ablation, bipolar radiofrequency endometrial ablation, and endometrial cryotherapy. Endometrial ablation has a low incidence of complications, such as uterine bleeding and perforation (1%–2%), and can effectively reduce uterine bleeding by up to 90%. [71]

Diet and lifestyle strategies

- The risk of uterine fibroids is raised by obesity and excess weight because estrogen is produced in large quantities by fat cells. Weight loss may aid in preventing or reducing the size of fibroids.
- Foods to be avoided - white rice, pasta, and flour, soda and other sugary drinks, corn syrup, boxed cereals, baked goods like cakes, cookies, and doughnuts, chips.
- Foods to eat - raw and cooked vegetables and fruit, dried fruit, whole grains, brown rice, lentils and beans, whole grain bread and pasta, fresh and dried herbs, green tea.
- Dairy products like milk could aid in reducing fibroids. Calcium, magnesium, and phosphorus are all abundant elements in dairy products.
- Other remedies - warm compresses or applying local heat, warm baths, yoga and exercise, massage therapy.
- Vitamin A, vitamin D, curcumin, resveratrol, isoliquiritigenin, epigallocatechin gallate, and Euonymus alatus are nutritional supplements with some proof of therapeutic benefit in the additional prevention of uterine myomas. [72]

CONCLUSION

Nearly 40% of women experience considerable morbidity from uterine fibroids during their reproductive years, and occasionally even after menopause. Therefore, finding any etiological hints in variables like food, stress, and environmental impacts is of great interest. Myomectomy and hysterectomy were once the only surgical options available for treating fibroids. Vascular embolization has changed the game and made it possible for women to maintain their fertility without having surgery. The FEMME (A Randomized Trial of Treating Fibroids with either Embolisation or Myomectomy to Measure the Effect on Quality of Life among Women Wishing to Avoid Hysterectomy) trial is looking into this issue further. The creation and adoption of novel procedures have significantly enhanced minimally invasive therapy of fibroids.

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CONFLICT OF INTEREST

None

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