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## Chapter

# Physiopathology and Management of Uterine Fibroids

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## Abstract

Uterine fibroid is the most encountered benign tumour in women of reproductive age. It causes spontaneous abortions, missed abortions, painful red degeneration or infarction of the fibroids, abnormal foetal presentation, obstructed labour, and an increased likelihood of premature deliveries, caesarean deliveries, postpartum haemorrhage in pregnancy, whereas, in the non-pregnant women it is associated an irregular menstrual cycle sometimes associated with heavy menstrual bleeding, infertility, constipation, urinary incontinence, and leiosarcoma transformation. Till date is pathophysiology and management both in the non-pregnant and pregnant woman have not been well described. In this chapter, we present contemporary evidence to help elucidate this enigma.

**Keywords:** uterine fibroid, leiomyoma, pathophysiology, management

## 1. Introduction

Leiomyomas also called uterine myomas, uterine fibroids, or fibromyomas are discrete, rounded, firm, white to pale pink, benign myometrial tumours composed mostly of smooth muscle with varying amounts of fibrous connective tissues [1]. Uterine fibroids or leiomyomas are benign tumours of the uterine smooth muscles. They are benign clonal neoplasms that contain an increased amount of extracellular collagen, elastin and are surrounded by a thin pseudo-capsule. They may enlarge to cause significant distortion of the uterine surface or cavity. Their size will then be described in menstrual weeks, as in a pregnant uterus [2].

Most fibroids are asymptomatic; usually asymptomatic in pregnancy but may interfere with conception and may cause spontaneous abortion, missed abortions, painful red degeneration or infarction of the fibroids, abnormal foetal presentation, obstructed labour, and an increased likelihood of premature deliveries, caesarean deliveries, postpartum haemorrhage and, whereas, in the non-pregnant state its signs and symptoms are menorrhagia, metorrhagia, menometorrhagia, infertility, constipation, urinary incontinence, and leiosarcoma transformation [3]. Uterine fibroids can occur in the non-pregnant woman and then continue into pregnancy/may develop de novo in pregnancy. In both circumstances, the physiopathology is the same but specific considerations may be taken in its management.

## 2. Epidemiology

Evidence from the contemporary literature reports that the prevalence rate of uterine fibroid varies between 16.7% - 30% of reproductive-age women and there is a two-fold increase in the prevalence in Afro American women [4, 5]. Also, their incidence tends to peak at the age of 35 years and almost 50% of African women will have uterine fibroid by their 5th decade of life [1]. Leiomyomas are the most frequent pelvic tumours and occur in about 20 to 25% of reproductive-age women. Uterine fibroids and the severity of their symptoms have a predilection for the black ethnicity. Huyck KL et al. in 2008 demonstrated that the odds of having severe symptoms from uterine fibroids are more than five times greater in black African women than in Caucasians [6]. Furthermore, black women develop the disease five to six years earlier and their peak age at diagnosis is 40–44 years [7] as opposed to a peak age of incidence of 35 years observed in Caucasians [1]. Also, almost 50% of African women will have uterine fibroid by their 5th decade of life [1].

Risks factors of uterine fibroids include African-American ethnicity, early menarche (less than 11 years) and high body mass index [8, 9]. Moreover, the length of the menstrual cycle has an inversely proportional relationship with fibroids: a shorter cycle is positively correlated with an increased likelihood to develop fibroids [10, 11]. A similar inverse association is observed with use of oral contraceptives, the duration of tobacco smoking and the development of fibroids [12]. On the other hand, multiparity and the late ages of last pregnancy are other protective factors for uterine fibroids [11].

## 3. Anatomical Classification of Uterine Fibroids

According to their anatomic locations, there are three different types of leiomyomas:

- **Subserosal or subperitoneal** leiomyomata are the most common and are usually asymptomatic unless very large. They originate in the myometrium and grow out toward the serosal surface of the uterus, lying beneath the peritoneum [1]. They may lie just at the serosal surface of the uterus or may become pedunculated. They become parasitic when they derive their entire blood supply outside of the uterus, from omental vessels. Sometimes, their pedicles may atrophy and resorb. When they arise laterally, subserous tumours may extend between the two peritoneal layers of the broad ligament to become intraligamentary leiomyomas.
- **Intramural or interstitial** myomas are located within the uterine wall of the myometrium and may distort the shape of the uterine cavity and surface. They may manifest with swelling of the abdomen, menorrhagia and infertility.
- **Submucosal fibroids** are the most symptomatic. They originate in the myometrium and grow toward the endometrial cavity, protruding into the uterine cavity that they tend to compress. Their impact on the endometrium and its blood supply most often lead to irregular uterine bleeding. Other symptoms commonly associated are dysmenorrhea, infertility and recurrent abortions [13]. This type of fibroids may also develop pedicles and protrude fully into the uterine cavity. Occasionally they pass through the cervical canal while still attached within the corpus by a long stalk. There, they are subject to torsion or infection.

- **Cervical leiomyomas** are a rare type. They are sometimes mistaken to vaginal leiomyomas, which may present with the same clinical features [14]. They cause early pressure effects in regions of bladder neck, infection, dyspareunia and infertility.
- With respect to the location of the fibroids, 89.4% submucous, 10.6% subserous and 74.5% were intramural according to a study done in Cameroon [15].

#### FIGO classification of uterine fibroids (PALM-COEIN)

Stage 0: a sub-mucosal pedunculated intra-uterine cavity fibroid  
Stage 1: a sub-mucosal located less than 50% intra-murally  
Stage 2: a sub-mucosal located greater than 50% intra-murally  
Stage 3: a fibroid which is 100% interstitially or intra-murally located in contact with the endometrium  
Stage 4: a fibroid which is completely interstitially or intra-murally located  
Stage 5: a sub-serosal fibroid which is greater than or equal to 50% intra-murally located  
Stage 6: a sub-serosal fibroid which is less than 50% intra-murally located  
Stage 7: a sub-serosal pedunculated fibroid  
Stage 8: others, parasite (round cervical ligament, large ligament).

## 4. Physiopathology of Uterine Fibroids

The cause of uterine leiomyomata is idiopathic till date. However, several hypotheses have been postulated, namely:

- i. Glucose-6-phosphate dehydrogenase studies suggest that each individual leiomyoma is unicellular in origin that is monoclonal [2]. Hence, this implies a genetic probability for the growth of uterine.
- ii. In increment in the exposure of circulating oestrogens is another hypothesis for the growth of uterine fibroids. Effectively, leiomyomas contain oestrogen receptors in higher concentrations than the surrounding myometrium. But at lower concentrations than the endometrium, this oestrogen may contribute to tumour enlargement by increasing the production of extracellular matrix. On the other hand, progesterone increases the mitotic activity of myomas in young women. It may allow for tumour enlargement by down-regulating apoptosis in the fibroids [16]. They usually decrease in size after menopause and whenever myomas grow after menopause, malignancy must be seriously considered [17].

Malignant transformation of leiomyomas is very rare, seen in 0.04% women having uterine fibroids. In a review of 13,000 leiomyomas, 38 cases (0.29%) demonstrated malignant manifestations. A second study reported that malignant change developed in less than 0.13% of uterine leiomyomas [17]. The diagnosis of leiomyosarcomas is based on the counts of 10 or more mitotic figures per 10 HPFs. Atypical leiomyoma is differentiated from leiomyosarcoma by a lack of necrotizing tumour cells and a mitotic count less than 7 per 10 HPFs. Nuclear atypia makes the difference with mitotically active leiomyoma [18]. Secondary changes may occur when the fibroids tend to outgrow their blood supply. These degenerations include necrotic, haemorrhagic (red degeneration) or septic for the acute ones. Chronic degeneration may be atrophic, hyaline (65%), cystic, calcific (10%), myxomatous (15%), or fatty [1].

## 5. Diagnoses

### 5.1 Clinical features

Most at times, leiomyomas are asymptomatic. Symptoms are found only in about 35–50% of the patients. They vary according to the type, location, size, number and vascular supply of the fibroids. These include:

- Abnormal bleeding from the uterus
- Pain symptoms
- Pressure effects
- Reproductive dysfunction

**Bleeding from the uterus** is the most common symptom. It may either be during the menstrual periods when the patient will have heavy and prolonged menses called menometorrhagia [16] or it may manifest as light spotting before and after the menses. The incidence of abnormal uterine bleeding was 47.7% in a study done by Okogbo et al. in 2011 in Nigeria [19]. This abnormal bleeding is due to the development or dilatation of endometrial venules which increase the flow during cyclical sloughing or to the increase in size of the uterine cavity by the fibromyomas [17].

**Pain** may either be due to red degeneration, infarction or torsion of a uterine fibroid, or may stem from attempts to expel a pedunculated submucosal fibroid [1]. A sensation of pelvic heaviness or fullness or a feeling of a mass in the pelvis is particularly characteristic of large tumours. These may press on nerves within the bony pelvis, creating pain that radiates to the back or lower extremities.

**Pressure effects** may either be anteriorly on the bladder, causing mainly frequent micturition, and urinary incontinence. Laterally, myomas may compress the ureters, leading to hydronephrosis. When the base of the bladder is involved, urinary retention may occur. Posteriorly, fibroids may increase the rectal pressure or cause constipation or tenesmus. It should be noted that these pressure symptoms are quite unusual and are difficult to directly relate to fibroids.

The relationship between fibroids and **infertility** is not clear. Fibroids may have a detrimental effect on fertility in up to 10% of the cases [20]. Infertility may result because of impaired implantation, tubal function or sperm transport.

### 5.2 Diagnostic tests

The diagnosis of uterine fibroids is made from the signs and symptoms, pelvic examination, laboratory investigations and imaging.

Most leiomyomas are discovered by routine pelvic examination, when a firm mass of an irregular shape is felt in the uterus. To confirm the diagnosis different types of imaging techniques are used:

- **A Pelvic ultrasound scan** is the test of first choice. Here, three-dimensional scan is preferred to a two-dimensional scan due to its higher resolution which helps to rule out a pregnancy, other pelvic masses, a congenital uterine malformation [21].
- **A magnetic resonance imaging** is the gold standard test which is highly accurate in depicting the size, number and location of myomas to choose the therapeutical modality.

- **Saline sonohysterography** can identify and characterise the location of submucosal myomas missed on classical abdominal or transvaginal ultrasound.
- **Plain X-Rays of the lower abdomen and pelvis** usually identify only calcified fibroids and sometimes large fibroids may be seen as soft tissue or calcified masses displacing bowel gas [22].
- **Hysterosalpingography** may be useful in the infertile patient. It evaluates the contour of the uterine cavity and the patency of fallopian tubes but does not evaluate the exact location of fibroids.
- **CT scan** is not the investigation of choice, fibroids may be detected incidentally while investigating for another condition.

**Laboratory investigations** may reveal anaemia as a consequence of the menometrorrhagia of fibroids and depletion of iron stores or leucocytosis and raised C-reactive proteins in case of acute degeneration or infection.

Differential diagnoses of leiomyomas include pregnancy, adenomyosis, leiomyosarcoma, or solid ovarian neoplasms. Other conditions to be considered include sub involution, congenital anomalies, adherent adnexa, omentum or bowel benign hypertrophy, and sarcoma or carcinoma of the uterus [1]. The most common symptom of leiomyomata, recurrent abnormal bleeding, may be caused by any of the numerous conditions that affect the uterus. The definitive diagnosis in cases of uterine bleeding usually can be established by endometrial biopsy or fractional D&C [16].

## 6. Management

When uterine fibroids become symptomatic, medical or surgical treatment is offered to the patient, depending on her age, symptoms and future fertility desires.

A. Medical therapy includes:

- **Progestins:** Progestational therapy using norethindrone, medrogestone, and medroxyprogesterone acetate has been successful. These compounds produce a hypo-estrogenic effect by inhibiting gonadotropin secretion and suppressing ovarian function [17]. A small randomised controlled trial presented weak evidence of a reduction in fibroid size among women receiving lynestrenol compared with women receiving leuprolide acetate [13].
- **25 mg mifepristone** produces reduction in leiomyoma size and uterine volume and produces symptomatic improvement in women with fibroids [23].
- **Gonadotrophin Releasing Hormone (GnRH) agonists** have proven very useful for limiting growth or temporarily decreasing uterine fibroid's size. GnRH agonists induce hypogonadism through pituitary desensitisation, down-regulation of receptors, and inhibition of gonadotropins. They are however not suitable for long term use because they are associated with menopausal symptoms and bone loss but are likely to be beneficial preoperatively [24].
- **Oestrogen Receptors Modulators and Antagonists:** Because co-administration of oestrogen with progesterone was essential for growth and maintenance, inhibition of oestrogen receptors should also be an effective treatment for Leiomyomas [22].

B. Surgical therapies include:

- **Myomectomy:** There may be a beneficial effect of surgical resection of myomas to enhance fertility or successful pregnancy outcome [25]. It can be achieved using the following surgical procedures: open surgery, laparoscopy, robotic, transvaginal, and hysteroscopic surgery. The location and size of the myoma(s) dictates the specific surgical approach. Total abdominal myomectomy maintains fertility compared with hysterectomy but increases recovery time and postoperative pain compared with laparoscopic myomectomy [24]. However, there is high chance of recurrence with myomectomy, while hysterectomy is definitive. A rare complication of laparoscopic myomectomy is the occurrence of parasitic leiomyomas. They usually regress after menopause but in extremely rare cases they can calcify and present in a post-menopausal woman with atypical signs and symptoms [26].
- **Hysterectomy:** It is the procedure of choice whenever surgery is indicated for leiomyomas and when childbearing has been completed. It should also be considered in the event of a rapidly enlarging fibroids, in which a reasonable likelihood of malignancy exists. Different types of hysterectomies exist: laparoscopically-assisted vaginal hysterectomy, total vaginal hysterectomy, total abdominal hysterectomy and total laparoscopic hysterectomy. Total abdominal hysterectomy is considered to be beneficial in reducing fibroid-related symptoms, but total vaginal hysterectomy and total laparoscopic hysterectomy may have lower risks of complications, and shorter recovery times [18]. In 2010 Demir RH and Marchand GJ published a case report in which they resected a huge uterus weighing 3200 g via laparoscopic-assisted hysterectomy, laparotomy can be avoided in almost all instances of hysterectomy for benign disease for an experienced laparoscopic surgeon [27].
- **Uterine artery embolization (UAE):** It is the occlusion of the uterine artery, which reduces the blood supply to the uterus and ultimately to the uterine fibroids. There is evidence that uterine artery embolization patients are more likely to report greater improvements in symptoms, fewer complications and less additional interventions than myomectomy. Meanwhile, patients who undergo a myomectomy are more likely to have a conserved fertility [28, 29]. Complications of the technique include infections, complications of angiography and very rarely, uterine ischemia. However, there are no increased serious complications after UAE in patients with a large fibroid burden [30].
- **Laparoscopic occlusion of the uterine vessel:** It consists of cauterising the uterine artery at laparoscopy, with or without concurrent myomectomy. Based on the study of Helal et al. in 2010, both laparoscopic occlusions of the uterine vessel and embolization improve symptoms associated with uterine fibroids [31]. The laparoscopic procedure resulted in less postoperative pain and nausea and shorter hospital stays, although significantly more participants experienced heavy menstrual bleeding six months after laparoscopic occlusion, indicating a more favourable effect after uterine leiomyoma embolization. Thus, laparoscopic uterine artery occlusion is likely to attract considerable interest as an effective alternative to hysterectomy treatment of symptomatic uterine leiomyomata.

- **MRI-guided focused ultrasound surgery.** It was approved by the Food and Drug Administration (FDA) in October 2004 for the treatment of leiomyoma in premenopausal women who have completed childbearing. This outpatient procedure uses MRI for real-time thermal monitoring of the thermoablative technique, which concentrates multiple waves of ultrasound energy on a small volume of tissue to be destroyed [16]. Careful patient selection and use of pre-treatment imaging are important components for predicting the success of MR-guided focused ultrasound surgery of uterine leiomyomas [32]. Overall, there is reasonable tolerance, improvement in quality of life, and modest change in fibroid size. However, 11% of women experience worsened symptoms during more than a year of follow-up and 28% elect further treatment including myomectomy and hysterectomy [13].

## 7. Uterine Fibroids and Pregnancy.

The prevalence of leiomyomas in pregnancy varies between 10.7% to 16.7% [5, 33]. It's higher in African American women followed by Caucasians, Hispanic and Asian women [33]. According to a study done by Hasan et al. in 2010, fibroids are part of the factors predictive of bleeding in the first trimester of pregnancy and are also potential important predictors of heavy menstrual bleeding heaviness [34]. This is due to the oedema, increased vascularity and hypertrophy of uterine muscles that lead to the increase in size of fibroids during pregnancy. However, Laughlin et al. in 2010 think there could be a direct protective effect of pregnancy on fibroids after delivery. In their study of 171 postpartum women, they found that 36% of fibroids resolved to an undetectable level and those that remain were reduced in diameter by a median of 0.5 cm [35].

Generally, the effects of fibroids on pregnancy and labour are:

- Spontaneous abortion, especially with sub-mucosal leiomyomas due to the distortion of the uterine cavity and impairment of the vascular supply to the implanted ovum [36].
- Ectopic pregnancy if it interferes with the passage of the ovum.
- Incarceration of a retroverted gravid uterus in case of posterior wall uterine fibroid.
- Placenta praevia due to interference with implantation of the ovum in the upper uterine segment.
- Malpresentations; in the study of Tchente et al. in 2008, breech presentation was two times more encountered in pregnant women with fibroids [15].
- Abdominal discomfort if the tumour is large.
- Torsion of the uterus which is very rare and is found in subserousal fundal myoma.
- Premature or threatening premature delivery probably due to the stretching of the uterus by the fibroids or the liberation of prostaglandins and fever in red degeneration [15].

- Prolonged labour due to inertia from interference with normal uterine contractions.
- Obstructed labour in cervical myoma or pedunculated subserous myoma impacted in the pelvis.
- Postpartum haemorrhage due to interference with sub involution of the uterus and increased vascularity.
- Puerperal sepsis.

The management of uterine fibroids in pregnancy depends on the signs and symptoms:

In the majority of cases, no treatment is required. In case of pain, bed rest and narcotics are almost always successful [16]. Tocolytics may be necessary to control the uterine contractions in threatening premature labour. Myomectomy is generally contraindicated during pregnancy due to increased vascularity that may lead to haemorrhagic complications. However, laparoscopic myomectomy may be considered safe if done in early pregnancy but only in the hands of experienced laparoscopic surgeons [37]. Indications for it include red degeneration not responding to medical therapy, torsion of a pedunculated myoma or internal haemorrhage from rupture of a surface vein [36]. In case of obstructed labour, caesarean section is indicated but myomectomy is contraindicated. In the post-partum period, prophylactic antibiotics should be given. Also, the women should be carefully observed for post-partum haemorrhage.

## **8. Conclusion**

Uterine fibroids are the most frequent benign uterine tumours in females of reproductive age. Although benign in character they are associated with adverse outcomes such as miscarriages, aseptic necrobiosis, foetal mal-presentation, obstructed labour, premature births, caesarean sections, postpartum haemorrhage in pregnancy, and an altered menstrual cycle, heavy menstrual bleeding, infertility, constipation, urinary incontinence, and malignant transformation in non-pregnant women. Through this chapter the authors sought to contribute to the scarce evidence on its idiopathic pathophysiology and present all its available management options.



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