UTERINE FIBROIDS (Leiomyomas)

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INTRODUCTION

Leiomyomas or Uterine Fibroids are noncancerous benign tumors reported as the most common gynaec disorder in reproductive females. The root cause of fibroid development is myometrium, a transformed single somatic stem cell that has undergone clonal expansion. It consists of a generous amount of extracellular matrix containing fibronectin, proteoglycan, and collagen.

It might develop as a single nodule or a cluster of nodules. Fibroid clusters can vary in diameter from 1 mm to 20 cm (8 inches) or even bigger. The growth and development of these uterine fibroids are assumed to be due to certain pathogenetic factors, including genetics, growth factors, steroids, microRNA, Chemokines, Cytokines, and extracellular matrix. Leiomyomas exhibit various clinical symptoms, including intermenstrual and excessive menstrual flow, dysmenorrhea, persistent pain in the pelvic region, and pressure sensations like bloating, increased urination frequency, and bowel trouble.

Additionally, they might impair reproduction, possibly causing infertility, early pregnancy loss, and problems in pregnancies. They are the main reason for hysterectomy (removal of the uterus). Earlier, fibroids went undetected in most women as they were asymptomatic. Clinical diagnosis analysis, which exclusively considers symptomatic individuals, significantly understates the true incidence.

CLASSIFICATION

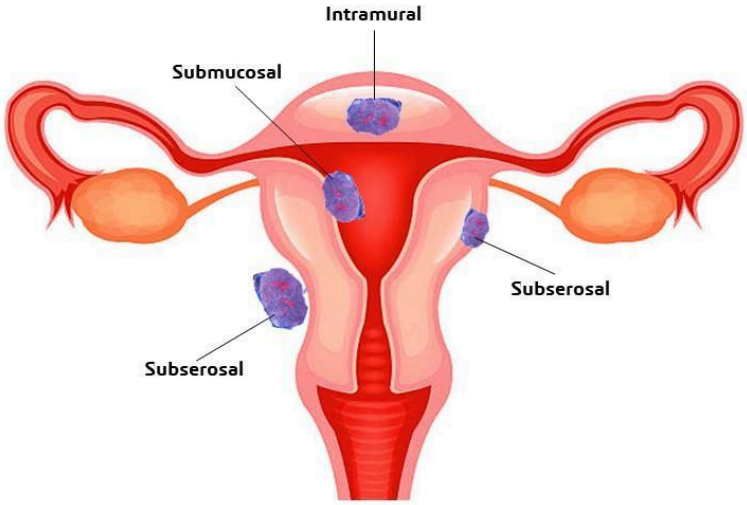

Fig 1: Types of Uterine Leiomyomas

Fibroids are classified as subserosal, intramural, or submucosal according to their location within the uterus. Leiomyomas, which grow on the outer layer or serosa of the uterus, are known as Sub-serosal leiomyomas. As it grows outside the uterus, it is asymptomatic. Subserosal leiomyomas can be Pedunculated (grow on a stalk attached to the uterus) or Sessile (broad-based). In the case of Intramural leiomyomas, it is found mainly within the uterine muscle

or myometrium, and it may disrupt the uterine cavity. About 95% of leiomyomas are tumors in subserosal and intramural regions. Submucosal leiomyomas are seen in the internal layer or mucosa of the uterus and can protrude toward the uterine cavity. Submucosal leiomyomas are symptomatic even at smaller sizes and can negatively impact fertility. Like Sub-serosal leiomyomas, submucosal leiomyomas can also be either pedunculated or sessile.

PATHOGENESIS OF UTERINE FIBROID FORMATION

Estrogen, Progesterone, Extracellular Matrix Components, Growth Factors, Cytokines, and Chemokine contribute to the growth and development of uterine fibroid.

Estrogen

A group of estrogen-related abnormalities in fibroids is caused by the complexity of the estrogen-responsive pathway and some etiologic factors. The development of fibroids in the presence of estrogen is through the initiation of progesterone receptor expression via Estrogen Receptor (ER) α, which results in the increased response of tumorigenic tissue toward progesterone signals. Compared to the normal myometrium, the existence of messenger RNA (mRNA) ERα and ERβ are higher in fibroid cells. Besides the Estrogen receptor's abnormal expression, its phosphorylation is also evident in fibroids. Various gene expressions including C-Jun and C-fos, progesterone receptor, connexin 43, IGF (insulin-like growth factor) receptors, progesterone receptor, and IGF1 (insulin-like growth factor 1) have also been regulated by estrogen. Activation of ATP-sensitive potassium channels by estrogen may promote cell proliferation in leiomyoma cells.

Progesterone

Progesterone stimulates the growth and development of uterine fibroids by cellular hypertrophy (an increase in the size of cells or tissue in response to various stimuli) and deposition of the extracellular matrix (ECM). In comparison to leiomyoma tissue, expression of progesterone receptor A (PR-A) and progesterone receptor B (PR-B) is found to be lesser in normal myometrium. Estrogen contributes to the activation of progesterone receptors via the initiation of activity of PR expression, which enables the expression of progesterone in leiomyoma. Progesterone is involved in the activation of signaling pathways in uterine fibroids, leading to rapid - membrane-initiated effects, which change the formation of a second messenger engaged in the transduction pathways of cell signaling. Progesterone receptors can quickly activate the Phosphatidylinositol-3-kinase (PI3K/AKT) pathway, which is mediated by progesterone, thereby initiating cell survival, proliferation, migration, differentiation, and apoptosis.

Extracellular Matrix Components

Uterine leiomyomas are characterized by excessive deposition of ECM (Extracellular matrix) constituents such as proteoglycans, fibronectin, laminins, and collagen.

The accumulation and function of ECM are controlled by steroid hormones, cytokines, and growth factors. Among cytokines and growth factors, PDGF, activin - A, TGF-α, and TGF- β can increase the ECM components by activating multiple signaling pathways. Moreover, estrogen and progesterone aid the increased production of ECM by modulating the expression and activity of certain growth factors (Transforming Growth Factor-β and Insulin Growth Factor), stimulating various signaling pathways. The deregulation of normal myofibroblast function causes the initiation of fibrosis. In response to uterine inflammation, myofibroblast cells create ECM which enhances major tissue homeostasis and repair mechanism.

Cytokines and Chemokines

TNF alpha (Tumor necrosis factor- α), interleukin-1 (IL-1), interleukin-6 (IL-6), and erythropoietin are only a few of the cytokines linked to the growth of uterine leiomyoma. Likewise, chemokines and their receptors (eotaxin, eotaxin-1, eotaxin-2, RANTES, CCR1, CCR3, CCR5, CXCR1, CXCR2, and mRNA) seemed to be intermediators of the aforementioned process. Compared to leiomyoma, MCP-1 mRNA levels are elevated in the myometrium, as estrogens and progestins slow down the production of MCP-1 protein, indicating that MCP-1 may exhibit antineoplastic activity in leiomyoma. Chemokines like IL-8 (Interleukin - 8) and Interleukin -8 receptors type A also showed elevated expression in leiomyoma, which can induce mitogenesis.

Growth Factors

Numerous growth factors, including PDGF, acidic fibroblast growth factor (aFGF), HB-EGF (heparin-binding epidermal growth factor), VEGF (vascular endothelial growth factor), EGF (epidermal growth factor), IGF, TGF-α, TGF- β, basic fibroblast growth factor (bFGF), and their receptors, also supplying to the growth of leiomyoma. Notably, bFGF and VEGF encourage angiogenesis in the growth of leiomyoma. By the activation of kinase pathways, PDGF and EGF appear to enhance polyploidization and DNA synthesis in cells of leiomyoma. PDGF has also modulated the frequency of proliferation in myometrium and leiomyoma cells.

Transforming growth factor (TGF)-β3 increases the gene expression associated with the extracellular matrix while decreasing the expression of genes related to its breakdown. Additionally, TGF-β may stimulate kinase pathways (Smad/ERK/MAPK) by modulating the several genes expression that affects the development and regression of leiomyomas. Similar to this, IGF promotes proliferation in uterine leiomyoma cells by activating the pathway of MAPK and taking part in the development of leiomyoma cells by increasing the expression of Bcl-2 protein in leiomyoma cells.

Myostatin and activin were also found in both leiomyoma and myometrium cells and hypothesized that these molecules might control the proliferation of myometrial cells after observing the elevated expression of these molecules in leiomyoma samples than in nearby myometrium. Myostatin and Activin were detected in leiomyoma and myometrium. Several studies inferred that myostatin and activin-A could control cell proliferation in the myometrium, which explains the increased expression level in leiomyoma samples in comparison to the myometrium.

Medication

A treatment method known as GnRH(Gonadotropin-releasing hormone) agonists was used to treat the fibroid by hindering the production of progesterone and estrogen. A progestin-releasing intrauterine device (IUD) provides relief from heavy bleeding, but it doesn't help to shrink the fibroids. It also intercepts pregnancy. A non-hormonal medication called tranexamic acid is provided to get relief from heavy menstrual periods. But it doesn't shrink fibroids or cure the condition.

There are particular procedures for removing uterine fibroids through a minimally invasive procedure. During Uterine artery embolization, embolic agents are inserted directly into the arteries contributing to the uterus, which cut down the blood supply to the fibroids, leading to the shrinking and dying of fibroid tissue. This technique is effective but may be risky if there is an insufficient supply of blood to other organs or ovaries. Uterine fibroids can be treated noninvasively with focused ultrasound surgery (FUS) guided by MRI. High-energy ultrasound transducers are employed inside an MRI scanner to carry out the surgery in MRI-guided focused

ultrasound surgery. The fibroid position is targeted and supplied with ultrasound waves in this technique. Thus, it heats and destroys the small areas of fibroid tissue.

Next is radiofrequency ablation; which destroys uterine fibroids by using radiofrequency energy to shrink the blood vessels feeding them. Laparoscopic or robotic myomectomy is practical if there are only a few fibroids. If the position of fibroids is inside the uterus, then hysteroscopic myomectomy can be considered an option. It includes the removal of fibroids by inserting instruments through the cervix or vagina into the uterus. Endometrial ablation is another procedure performed using a particular device that is inserted into the uterus, which utilizes heat, hot water, electric current, or microwave energy to eliminate the lining of the uterus. This procedure is effective in irregular menstrual flow but it exempts fibroids outside the interior lining of the uterus. Authentic surgical treatment includes Abdominal myomectomy and hysterectomy. In Abdominal myomectomy, abdominal surgical procedures are used to remove the fibroids, whereas, in Hysterectomy, it removes the uterus. Hysterectomy may also involve the removal of surrounding tissues and organs, such as ovaries and fallopian tubes. Hysterectomy is the only treatment that provides a permanent solution to uterine fibroids.

CONCLUSION

Uterine fibroids are common gynecological tumors that can cause several devastating symptoms and health issues in women for years. Anemia, infertility, pelvic pain/pressure, etc are the major health issues caused by the disease. Late diagnosis and lack of awareness make it more severe. By giving proper awareness among women about uterine fibroids and their symptoms, women can diagnose them earlier and access appropriate treatment. Early diagnosis can prevent the situation that necessitates a hysterectomy. A substantial gap in knowledge and understanding of the factors that contribute to the increased occurrence of symptomatic fibroids. Expanding

research on the disease pathway of uterine fibroids may lead to the development of novel drugs and curative treatments other than hysterectomy.

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