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PATHOPHYSIOLOGY OF FIBROIDS

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Abstract: *Fibroids are the commonest benign tumors of female genital tract. They are mainly composed of smooth muscle & fibrous connective tissue. Etiopathogenesis of fibroids is linked to hormones (estrogen & progesterone), genetic factors and some growth factors. Estrogen is the main predisposing factor-there is increased density of estrogen in fibroids compared to normal myometrium and increased concentration of aromatase leading to high local estrogen levels. The growth promoting effect of estrogen & progesterone has been shown to be mediated through local production of growth factors.*

Key-words: *fibroids, pathophysiology, growth factors.*

Fibroids/leiomyomas are the commonest monoclonal benign tumours & commonest benign solid tumours of uterus in females[1]. Their basic etiology is idiopathic & they seem to arise from myometrial transformation as a result of specific physiological & pathological conditions.[2]

Also known as uterine leiomyoma / myoma / fibromyoma. These terms are suggestive of its histology which is mainly smooth muscle & fibrous connective tissue (elastin, collagen, fibronectin, and proteoglycans). These tumors are rich in extracellular matrix.[3]

These neo-formations affect mostly women during their reproductive age group, with lifetime risk of 80%. [4]

Incidence: In African American - 60% by age of 35 yrs & 80% by 50 yrs. In white women, incidence is 40% by 35 yrs & 70% by 50 yrs of age.[5]

In a study by Cramer & Patel, the estimated prevalence based on clinical assessment was 33%, on ultrasonography 50% & histological examination of hysterectomy specimens was 77%.[2]

The term 'fibroid' is a misnomer as considerable collagen creates a fibrous consistency but it is not actually made of fibroblasts.[6]

Etiopathogenesis: The development of fibroids/ myomas can be linked to predisposing risk factors, initiators & genetic mechanisms, promoters & effectors.[7]

Role of hormones

Main predisposing factor earlier considered was estrogen so primarily called 'estrogen dependent tumor'. But now further studies have confirmed role of progesterone besides estrogen in its development.

Points in favour of hormone dependence[9] are-

- These tumors rarely occur before puberty and there is tendency to regress after menopause. Usually no new growth is seen post menopause.

- Obesity & early menarche commonly associated with the fibroids.
- There is an increased incidence in women with an ovulatory diseases like PCOS
- Increased growth is seen during pregnancy.
- Growth limited in child bearing period.

The proposed protective factors are: Smoking, increased parity, exercise.

Various mechanisms brought into light for the above stated risk & protective factors are as follows.

- Increased body mass index, early menarche: -due to increased overall lifetime exposure to estrogen & increased adipose tissue conversion of androgens into estrogen, decreased hepatic production of sex hormone binding globulin. One study found that the risk increases by 21% with each 10 kg increase in body weight. [9]

  Shikora[10] reported similar results in females with >30% body fat. Coculture of adipose cells & fibroid cells showed increased proliferation of fibroid cells.

- Chronic anovulation and sustained estrogen exposure as in PCOS.
- High doses of medroxy progesterone acetate in hormone replacement therapy causes increased growth of these tumors.
- Smoking alters estrogen metabolism, by lowering physiologically active serum estrogen levels. Nicotine inhibits aromatase enzyme, decreases conversion of androgens into estrogen by powerful induction effect on 2-hydroxylation pathway of estrogen so leads to decreased bioavailability of estrogen at target tissues.[11,12]
- Increased parity causes a break in chronic estrogen exposure resulting in remodeling of extracellular matrix during postpartum involution & specific expression of receptors for peptide & steroid hormones induced by pregnancy and parturition.[13]

Progesterone is the primary mitogen for growth & the role of estrogen is to upregulate progesterone receptors. Hence both the hormones work in syncrony

Several studies reported a rapid increase in incidence after 30 yrs of age due to time related hormonal changes or an enhanced symptomatology from already existing fibroids.[14]

Effect of estrogen

As compared to normal myometrium, there is an increased density of estrogen receptors in fibroid cells leading to increased estradiol binding. There is less conversion of estradiol into weaker estrone in these cells.[15, 16] It has been seen that there are higher levels of cytochrome P_{450} aromatase in fibroid cells than normal myocytes. This isoform catalyses conversion of androgens into estrogen in these tissues.[17]

Effect of progesterone

There is increased concentration of progesterone receptors A & B is myoma cells than normal myometrium. Highest mitotic counts occur at progesterone production peak.[7]GnRH agonists decrease the size whereas progestin along with GnRH agonists prevent the decrease in size of myomas.[17]

Leiomyoma growth is influenced by progesterone interaction with some growth factors; it upregulates the EGF (mitogenic) [18]and transforming growth factor- (TGF-) 3 (bimodal action) [19]expression. Some authors hypothesized that progesterone could stimulate leiomyoma cell growth and survival through upregulating B-cell lymphoma- (Bcl-)2 protein expression and downregulating tumour necrosis factor- (TNF-)α expression. [20]

Role of genetics[21]

40% of fibroids have chromosomal abnormalities mainly translocations between chromosome 12 & 14, deletion of chromosome 7, trisomy of chromosome 12. All these occur more commonly in cellular, atypical and larger fibroids. 60% have yet undetected mutations. More than 100 genes are up/ down regulated in these cells. Collagen type 1 & 3 are abundant but fibrils are in a disarray just like in a keloid formation.HMGA2 gene in translocation 12:14 is most common cytogenetic abnormality that occurs in about 20% of chromosomally abnormal lesions. This gene encodes a high

mobility group DNA binding protein and embryonic proliferation modulator. [22]

Markowski showed that antagonism of HMGA2 in vitro decreases leiomyoma cell proliferation.[23] However interesting fact to note is that genetic differences do exist between leiomyoma & leiomyosarcoma. Leiomyomas do not result in leiomyosarcomas, sarcomas generate from malignant degeneration of fibroids.

Heritable cancer syndrome hereditary leiomyomatosis & renal cell carcinoma predisposes to benign leiomyomas of skin & uterus & early onset renal cell carcinoma. [8]Alport syndrome, an X- linked progressive nephropathy is associated with leiomyomas due to defect in COL4A5 & COL4A6 genes.[24] Chr. 10q24.33 seems to have best association with leiomyomas.[25] Recent studies showed 70% fibroids have a series of mutations in transcending regulator complex subunit 12 (MED 12).[26,27]Studies directed at identifying epigenetic abnormalities in fibroids demonstrated abnormal hypomethylated ER-a.[28]

Follow up studies globally showed abnormal genomic methylation in myomas compared to implicating possible epigenetic contribution to genetic susceptibility of fibroid development.

Micro RNAs (MiRNAs) are small non-protein coding RNAs which regulate a large number of biological processes by target mRNAs for cleavage or transformal repression.[29] several reported MiRNAare let7, miR-21, miR-93, miR-200 signifying dysregulation.[30]

Fibroids are more prevalent in black compared to Caucasian & Hispanic population. It is unclear whether these ethical differences are genetic or due to known differences in hormonal metabolism, diet or environmental factors. Some authors have reported an inverse correlation between serum 25-(OH) Vit D levels and fibroid prevalence in black subjects.(31,32)

Role of growth factors

Growth factors, are polypeptides produced by fibroblasts & smooth muscles locally which result in increased growth by producing extracellular matrix.(33)

- Increase smooth muscle proliferation TGF-b, bFGF
- Increase DNA synthesis EGF,PDGF
- Stimulate synthesis of ECM TGF-b
- Promote mitogenesis TGF-b, EGF, IGF, PRL
- Promote angiogenesis VEGF, bFGF

TNF-a treatment increases human uterine myoma cell proliferation in a concentration dependent manner.(34,35) Ischaemic changes at the time of menstruation could be linked to release of vaso-constrictive substances. After vascular damage, bFGF is over expressed. Smooth muscle cells of myometrium react to injury with synthesis of extracellular fibrous matrix. It has been shown that estrogens may exert their growth-stimulatory effects on leiomyomas intermediated by cytokines, growth factors, or apoptosis factors.(36)

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