



The Incidence, Aetiology And Treatment of Leiomyoma in Nigeria

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Abstract

Leiomyoma are a significant source of morbidity in reproductive aged woman across the globe causing distressing symptoms and in infertility in some women. There does, however, appear to be an increased incidence of leiomyoma in women of black African ethnicity and especially those women in Nigeria. This review covers the incidence and possibly aetiology and treatment of leiomyoma in Nigeria.

Keywords: Nigeria; Uterine leiomyoma; Genetics; Aetiology; Treatment; Interventions

Introduction

Uterine leiomyoma, commonly known as uterine fibroids, is a benign tumor often found in women of all races across the world. There is a 3-4-fold likelihood of dominance among African women as opposed to what is seen in other races [1-4]. Leiomyoma occurs mostly in women of reproductive age and have been observed by some workers in 80% of women in Nigeria within the age range of 25 years and above. Leiomyoma generally begins with a small mass which further grows into a larger mass. There is generally a late presentation of patients at clinics as most leiomyoma is asymptomatic [5,6]. A study by Baird DD, et al. [7] showed a 60% incidence of leiomyoma among African American women at age 34 with a surge of greater than 80% when they attain age 50. This is in contrast to as what was observed in Caucasians who have 40% incidence at age 35 and 70% at 50.

The Aetiology of Leiomyoma

The aetiology of leiomyoma is currently unknown but many predisposing factors have been proposed such as age, race, nulliparity, early menarche, caffeine and alcohol consumption, positive family history, vitamin D deficiency, hormonal factors,

the use of chemical hair products, obesity and genetic factors [8-10]. The development of leiomyoma is thought to depend upon the female hormones oestrogen and progesterone. Studies have established the presence of oestrogen and progesterone receptors on the surface of leiomyoma along with higher mRNA and protein expression level when compared with the normal myometrium [11-13]. Varying degrees of symptoms have been observed in patients suffering from leiomyoma depending on the size and location of the leiomyoma [14]. The most common symptoms are menorrhagia with secondary anaemia, infertility, pregnancy loss, obstetric complications and pelvic pain [14]. In this review we focus on the genetic predisposition to leiomyoma, the current available therapeutic interventions and the potential of stem cells in the prevention of leiomyoma and optimization of the uterine endometrial environment.

The Genetic Basis of Leiomyoma

The pathogenesis of leiomyoma is not fully understood. Nevertheless, some insights have been documented such as the observation of Mehine M, et al [15] who linked leiomyoma with

complex multiple chromosomal rearrangements due to multiple chromosomal breaks and random reassembly. These chromosomal rearrangement result in tissue specific changes observed in leiomyoma which could be explained by the translocation of (High mobility group) HMGA 2 and RAD51B loci and mutation at the COLAA5- COLAA6 HMGA2 gene found in translocation 12:14 which has three DNA binding domains. These domains are responsible for the attachment of its protein to adenine-thymine (AT)-rich regions of DNA. This binding neither promotes nor inhibits the transcription process during myometrial stem cell division but alters the DNA structure to encourage complex formation of transcription regulatory proteins [16]. This single genetic mutation may alter key the signaling pathways such as those involving β -catenin and TGF- β . These are major cell proliferation regulators resulting in the inability of the cell to control its survival and senescence [17].

Other chromosomal changes have been directly linked to the pathophysiology of leiomyoma among which includes the observation that 40% of leiomyoma patients have tumor specific chromosomal mutations [18,19]. In familial leiomyoma transferable germline mutations have been observed to result in fumarate deficiency and a gene that could predispose women to leiomyoma has been mapped on chromosome 1q42.3-q43 [20-22]. Despite these observations it is not currently understood how fumarate deficiency promotes the growth of leiomyoma. One possible hypothesis is that mutation in fumarate hydratase in the citric acid cycle could result in leiomyoma development through the citric acid mediated mitochondrial dysfunction causing DNA damage, loss of energy dependent apoptotic function and inhibition of growth factor transcription [23]. In a study conducted by Mäkinen, et al. [24] 18 leiomyoma tissues and normal myometrium tissues were subjected to sequencing after which it was shown that 56% of the leiomyoma tissue (10 of 18) had a mutation in the gene that codes for the mediator complex subunit 12 (MED 12). The MED12 gene (Xq13.1) provides instructions to make a protein, mediator complex subunit 12, which regulates transcription through RNA polymerase II by linking transcription factors which influence whether genes are turned off or on [24]. Mis-sense and in-frame insertion-deletion mutations in the MED12 gene have been confirmed to contribute to the pathogenesis of leiomyoma. The MED12 mutation has been reported to be the most common form of mutation in leiomyomas contributing to about 70% of all cases [25].

In normal stem cells, the MED12 gene acts as a physiological modifier of β -catenin; however, when a mutation occurs, this function of the MED12 gene is lost. Moreover, TGF- β receptors are expressed in stem cells, which activate mitogenic protein kinase (MAPK) proteins, which regulate cell-cell interactions, renewal, and proliferation of stem cells [26].

In reproductive age women, myometrial smooth-muscle cells undergo cell division and involution under the influence of ovarian hormones or the hormones of pregnancy. A point mutation in MED12 resulting in a chromosomal rearrangement could also result

into increased expression of HMGA2, or some other gene defect in a somatic stem cell in the myometrium, may be the initiating factor [27].

It is agreed that leiomyomas are a monoclonal tumor of the myometrium and they have been reported to originate from somatic stem cell transformation influenced by ovarian hormones. This transformation is caused by somatic chromosomal aberration which could be inherited [28] resulting in a predisposition to leiomyoma in families.

The myometrial stem cells are actively dividing cells, responsible for the proliferation of the normal myometrial smooth-muscle cells and cell regeneration [29-31]. The presence of myometrial stem cells was first established in rodents and shortly after in humans in a study carried out by Arango et al., 2005. The presence of multipotent stem cells was observed in the mouse uterus by using flow cytometry and other observations showed that the smooth muscles of the uterus were replaced by adipose tissue upon deletion of β -catenin. These myometrial stem cells are in the G₀ phase (senescence stage) of the cell cycle and possesses low expression of oestrogen receptor alpha, progesterone receptor, callponin, and smooth line [30,32]. Hypoxia has been implicated in the ability to induce untimely proliferation and differentiation of myometrial stem cells which could lead to leiomyoma formation [30].

Leiomyoma have been investigated using flow cytometry and shown to possess multiple cell types which originate from a single parent cell line that contains multipotent stem cell [33]. Mas et al., [26] used flow cytometry assay to isolate leiomyoma stem cells and found that these stem cells were able to differentiate and self-renew into fibroid cells when xenotransplantation. These cells were observed to be responsive to signaling by progesterone and estradiol via the WNT/B-catenin pathway. In research recently completed at Harvard University lead by Markus Frank, stem cells that induce melanoma were identified and targeted using antibody that specifically binds the cancer stem cells and significant tumor regression was observed [34]. This idea could be applied to leiomyoma, where leiomyoma stem cells could be targeted specifically.

Interventions

Depending on the age, size and location of leiomyoma, intervention ranges from surgical to non-surgical procedures not limited to myomectomy by either hysteroscopy or laparoscopy, and radiography and ultrasonography to achieve uterine artery embolization (UAE) [35-39]. Drug therapies for the treatment of leiomyoma are not routine but they include the use of Gonadotrophin Releasing Hormone Agonists (GnRHa), Antiprogestins, selective progesterone receptor modulators (SPRMs), aromatase inhibitors, and the use of oral contraceptives. The GnRHa is effective in reducing leiomyoma size up to 40% in three months and as well a beneficial treatment prior to surgery. However, upon cessation of

therapy there is regrowth of leiomyoma [40]. Antiproggestins and SPRMs have been documented by Stein et al. [41] and Ouzounian S, et al. [42] to reduce leiomyoma size, regulate bleeding and manage pelvic pressure. Aromatase inhibitor has been documented to significantly improve clinical outcomes of leiomyoma and could also prevent future increase of leiomyoma mass [43-45].

Surgical Intervention in the Treatment of Leiomyoma

The gold standard for treatment of leiomyoma is surgical intervention. Various surgical procedures are available for the treatment of leiomyoma, these include:

Hysterectomy

This is the surgical removal of the uterus and any associated leiomyoma. Hysterectomy is especially useful for women who have completed child-bearing. Despite the great advantages of hysterectomy, it is not devoid of risk, morbidities and mortalities associated with surgical procedures [46].

Myomectomy

This is an option used by women who still desire to have children or who desire to retain their uterus and their fertility [47]. The major disadvantage of myomectomy is that about 50% - 60% of patient will develop another leiomyoma within period of 5 years [48].

Endometrial ablation: Endometrial ablation offers alternative to surgery in patients with more complicated conditions such as heavy or abnormal uterine bleeding. Most clinical studies on endometrial ablation excluded women with more significant leiomyoma [47,49].

Minimally Invasive Procedures (Uterine Artery Embolization and Uterine Fibroid Embolization)

Minimally invasive procedures are available in some Countries for the treatment of leiomyoma. They involve the delivery of some particulate emboli through the uterine arteries in order to block nutrient and blood supply to the leiomyoma vessels [50]. Various studies have shown that women who opt for this form of treatment do not need long hospitalization and morbidity is low. Patients resume their work quickly unlike those who underwent myomectomy and hysterectomy [51]. Even though uterine artery embolization is a good and cost-effective treatment option, it also comes with its own complications which include miscarriage, placenta praevia, pre-term labour and post-partum hemorrhage [47]. Limitations of using these techniques to treat patients with large leiomyoma should also be noted [52].

Magnetic Resonance-Guided Focused Ultrasound

This is a surgical procedure used in the treatment of uterine leiomyoma suitable for pre-menopausal women who no longer desire to give birth. It is a non-invasive procedure which uses the convergence of multiple ultrasound energies on the leiomyoma which leads to destruction of these tissues [53].

Non-Surgical Interventions

Progestin

Progestogens are natural, or artificial, hormones which may be capable of intervening in the development of leiomyoma. While the natural hormone progesterone augments epidermal growth factor, which stimulates fibroid growth, it also inhibits insulin-like growth factor-1, which may also additionally inhibit growth [54]. Progestogens as well known to down-regulate both oestrogen and progesterone receptors in leiomyoma. Reduction in the thickness of the endometrium can limit menstrual blood flow in women with leiomyoma [55].

Ulipristal acetate

Leiomyoma often grow during the reproductive years making one possible intervention to block gonadal steroid action. The full chemical name of ulipristal acetate is 17 α -acetoxy-11b-(4-N,N-dimethylaminophenyl)-19norpregna-4,9-diene-3,20 dione or CDB 2914. It binds to human progestin, glucocorticoid and androgen receptors but not oestrogen or mineralocorticoid receptors. It is a selective P receptor modulator (SPRM) with minimal in vivo anti-glucocorticoid activity as well as anti-proliferative activity on leiomyoma cells and the endometrium [56,57].

Donnez J, et al. [58] studied the actions of ulipristal acetate versus placebo before the surgical treatment of symptomatic leiomyoma. They showed a decrease in leiomyoma size following thirteen weeks of 5 mg and 10 mg of ulipristal acetate of 21.2% and 12.3%, respectively. The placebo group had a median 3% increase of leiomyoma size. Patients additionally experienced diminished uterine bleeding following treatment. Levens, et al. [59] showed that a 3-month administration of SPRM CDB-2914 reduced bleeding and leiomyoma size.

Aromatase inhibitors

Peripheral blood oestrogen concentration in leiomyoma is usually increased [60]. This is because of the secretion of oestrogen from the leiomyoma tissue. This paracrine secretion of oestrogen within leiomyoma may result in increased growth of the leiomyoma [61]. There is increased aromatase activity in leiomyoma related to the oestrogen secretion of the tissue [62].

The inhibition of aromatase (and therefore the reduction of endogenous oestradiol production) using anastrozole which is a selective, third-generation non-steroidal substance which has no effect on cortisol, aldosterone, androgens, progesterone or oestrogen. The use of anastrozole therefore does not induce weight gain, acne and hypertrichosis or alter the lipid profile [63-65].

Song H, et al. [66] have shown that the use of letrozole reduces fibroid volume by 46% and the use of a gonadotropin releasing hormone agonist by 32% after 12 weeks of treatment. Nevertheless, they did conclude that these results were not statistically significant. Significantly fewer women reported hot flushes in the letrozole

group than in the GnRHa group. Letrozole is an aromatase inhibitor which inhibits the conversion of androgen into estrogen.

Gonadotrophin Releasing Hormone (GnRH) Antagonists and Agonists

GnRH antagonists work by blockage of the hormone mechanism. GnRH agonists are useful pre-operatively to decrease leiomyoma and to limit anaemia related to uterine bleeding [67,68].

The principal advantage of the use of GnRH antagonists is their lack of the preliminary "flare" impact seen with GnRH agonist stimulation and supraphysiological amounts of follicle stimulating hormone, luteinizing hormone, and Oestradiol [69,70].

GnRHa is an artificially produced peptide which is structurally similar to the natural gonadotrophin releasing hormone. It can interact with the GnRH receptors to elicit biological functions. It has a half-life longer than the naturally produced GnRH and prolonged exposure leads to down regulation effect in hypogonadism which eventually brings about a state of hypoestrogenism by restraining pituitary ovarian function [71]. GnRHa is considered to be effective in the treatment of leiomyoma.

Currently, GnRHa is the solely approved short-term therapy by the FDA for the treatment of leiomyoma [72]. Luporon depot (leuprolide acetate for depot suspension) is a GnRHa approved by the FDA in 1999 which is effective in reducing leiomyoma [72]. GnRHa has side effects which include hypoestrogenism and menopausal symptoms such as vaginitis, tingling, vaginal dryness, breast enlargement and hot flushes [73].

Promising Therapies in Clinical Trial

Mifepristone

Mifepristone is an artificially produced steroid which has anti-progesterone and anti-glucocorticoids actions. It is synthesized from precursor norethindrone and it completely inhibits the progesterone receptor [74]. It suppresses the production of prolactin in both the leiomyoma and myometrium even if the patient does not have hyper-prolactinaemia. Some authors have suggested that prolactin levels should be used as a marker for the effectiveness of this therapy [75]. It has been shown that doses of mifepristone (2.5-5.0 mg/dL) was able to reduce the volume of leiomyoma up to approximately 50% [76].

Asoprisnil

Asoprisnil is a progesterone receptor modulator which has high binding affinity for the progesterone receptor and mild or moderate affinity for the glucocorticoid receptor. It has low affinity for the androgen receptor and no binding affinity at all for mineralocorticoid receptor [77]. It inhibits the appearance of growth factors TGF- β 3, IGF-1, EGF and their receptors in a cultured leiomyoma cell without affecting their appearance in myometrial cells [78]. Asoprisnil is known to moderately reduce uterine artery blood flow [79].

Pirfenidone

A phase II clinical trial of Pirfenidone has been completed. Pirfenidone is an effective inhibitor of leiomyoma growth and myometrial cell proliferation in vitro and it is known to reduce the mRNA level of collagen type I and III in a dose-dependent manner [80]. It is a pyridine molecule that shows antifibrotic effect in a variety of animal models [81].

Conclusion

There is clearly a high incidence of leiomyoma in Nigeria which also seems to extend to African race females living overseas. Leiomyoma is a significant cause of infertility in Nigeria and also has high morbidity for all child-bearing age females. The cause of leiomyoma in Nigerian women could include genetics, environment, pollution, nutrition, age and even life-style. Nigeria is a country with relatively high rates of pollution (domestic and industrial) and this could be significant factor in the development of leiomyoma especially that in Nigeria leiomyoma tend to increase with age which is directly proportional to the exposure of each individual to potential causative agents. There is clearly a genetic component associated with leiomyoma and this needs further research in women of all ages to perhaps develop a more effective and non-invasive therapeutic approach. It is unlikely that there is a single cause, it is more likely to result from a combination of effects. There are possible indications, from animal studies, that myometrial smooth muscle stem cells may have a role to play in the development of leiomyoma. Much more research is needed here to understand this mechanism and to possibly utilize stem cell technology in the treatment of leiomyoma. There are potential treatments available ranging from invasive surgery to new medications in clinical trial but at present these all have restrictions and drawbacks which makes it difficult to manage patients suffering from leiomyoma. Further research is needed to better understand leiomyoma and to develop new treatments or interventions which may prevent or minimize the development of leiomyoma on a global scale.

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Conflict of Interest

Authors declare no conflict of interest.

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