Obstetrics and Gynecology International

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Editorial Board

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Editorial

Complications of Uterine Fibroids and Their Management

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Uterine fibroids are the most common gynaecological tumours found in women. These tumours are said to be present in 80% of Caucasian women and are even more common in women of African origin. In 50% of women with fibroids symptoms usually occur, leading to complications from the presence of these fibroids. Although they are mainly a problem in the reproductive years, there are reports of problems from fibroids in postmenopausal women.

The management of patients with fibroids is quite variable including conservative oral and parenteral treatment, conservative and radical surgery, and newer techniques such as uterine artery embolisation and radiofrequency ablation. All of these techniques can also cause complications for the patient, and as a result careful evaluation of patients must be done to decide on the correct treatment option for a particular patient.

The focus of this special issue is to highlight the complications which are caused by fibroids and also those which can arise as a result of the treatment options available. This is intended to assist clinicians and their patients in making informed decisions about the management of this common problem.

The journal is the effort of a truly international group of clinicians giving varied experiences from across the world.

The paper entitled "*Complications of uterine fibroids and their management*" is from Jamaica and outlines the entire spectrum of complications of fibroids and their treatment. This is a good review of the modern methods available and should be helpful to clinicians to assist them in counseling their patients.

The paper entitled "*Innovative oral therapy for uterine leiomyomas*" is a collaborative effort of clinicians from Egypt and the United States of America (USA) reviewing the use of oral therapy for the treatment of fibroids. This paper gives an update on the modern use of drugs to treat fibroids to avoid surgery.

The paper entitled "*Surgical management of uterine fibroids at Aminu Kano Teaching Hospital*" is from Nigeria, and this paper discusses use of myomectomy versus abdominal hysterectomy in their setting. The authors have outlined their experience and given the reader an idea of their methodology and complication rates comparing the two procedures.

The paper entitled "*Intrauterine adhesions following conservative treatment of uterine fibroids*" is from Sweden and Spain discussing the complication of intrauterine adhesions reminding readers how to diagnose and treat this often forgotten complication of surgical treatment of fibroids.

The paper entitled "*Indications and outcomes of uterine artery embolization in patients with uterine leiomyomas*" is from Japan, and the paper entitled "*Complications associated with uterine artery embolisation for fibroids*" is from the United Kingdom. Both papers discuss their experience with uterine artery embolisation. The complications from both sites are outlined.

The paper entitled "*Radiofrequency ablation for treatment of symptomatic uterine fibroids*" is from the United States and the United Kingdom and reviews the use of radiofrequency ablation to treat fibroids. This is an excellent review detailing

older now archaic methods and outlining the more modern safer techniques used in their setting.

Overall this journal is an excellent resource for physicians who wish to review uterine fibroids as well as all the methods available to treat them. The complications of fibroids are outlined in detail, and the different treatment modalities and possible complications are also outlined. This should become a standard compendium on fibroids for students and physicians for the benefit of increasing knowledge for examinations as well as the proper counseling and management of patients.

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Review Article

Innovative Oral Treatments of Uterine Leiomyoma

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Uterine fibroids (leiomyoma), the benign tumors of the uterine wall, are very common cause of morbidity in reproductive age women usually in the form of excessive vaginal bleeding, chronic pelvic pain, miscarriage and infertility. These tumors are the leading indication for hysterectomy in the United States. Uterine fibroids are about 4 times higher in blacks compared to whites and constitute a major health disparity challenge. The estimated cost of uterine fibroids is up to $34.4 billion annually. Additionally, women who suffer from this disease and desire to maintain their future fertility have very limited treatment choices. Currently, there is no effective long-term medicinal treatment for uterine fibroids. While surgery has traditionally been the gold standard for the treatment of uterine fibroids, there is growing interest towards orally administered medications for the management of leiomyoma-related symptoms. In this review, we will discuss these promising innovative oral medical treatments in detail.

1. Introduction

Uterine leiomyomas are the most common benign pelvic tumors in women [1, 2]. They are monoclonal tumors of the smooth muscle cells of the myometrium and consist of large amounts of extracellular matrix that contain collagen, fibronectin and, proteoglycan [2, 3]. A thin pseudocapsule that is composed of areolar tissue and compressed muscle fibers usually surrounds the tumors [4]. Leiomyomas may enlarge to cause significant distortion of the uterine surface or cavity. Dark skinned women, such as African Americans, also had higher numbers of leiomyomas and tended to have larger uteri, which in turn may explain the higher incidence of in-hospital complications or blood transfusion requirements in AA women compared to white women [5, 6]. The overall incidence of uterine leiomyomas is estimated to be 3-4 times higher in African American women compared to Caucasian women [7–10]. Recent data have also confirmed that the age-standardized rates of ultrasound- or hysterectomy-confirmed leiomyoma were significantly higher in black women compared to white women [11]. Although they are benign, they commonly result in severe symptoms, such as heavy, irregular, and prolonged menstrual bleeding as well as anemia. Uterine leiomyomas have also been associated with numerous other medical disorders, such as infertility, recurrent abortion, and preterm labor [12]. These clinical complications negatively impact women's health. Uterine leiomyomas are the most cited indication for the more than 600,000 hysterectomies that are performed in the US annually, and this major surgery is associated with morbidity and mortality as well as a huge economic impact on healthcare delivery systems that is estimated to be approximately $34.4 billion/year [13] (Table 2).

2. Current Treatment Options for Uterine Leiomyomas

Treatment options for leiomyoma vary; treatment strategies are typically individualized based on the severity of the symptoms, the size and location of the leiomyoma lesions, the patient's age and their chronological proximity to menopause, and the patient's desire for future fertility. The usual goal of therapy is the relief of the symptoms (Table 1). The treatment options range from the use of acupuncture (ancient Chinese method) to the total removal of the uterus and

Table 1: The clinical presentation of uterine leiomyomas.

(i) Asymptomatic
(ii) Abnormal uterine bleeding
(a) Menorrhagia
(b) Anemia
(iii) Pelvic pressure
(a) Urinary frequency
(b) Urinary incontinence
(c) Difficulty with urination
(d) Hydronephrosis
(e) Constipation
(f) Tenesmus
(iv) Pelvic mass
(v) Pelvic pain
(vi) Infertility
(vii) Obstetric complications
(viii) Pregnancy related
(a) Myoma growth
(b) Red degeneration and pain
(c) Spontaneous miscarriage
(ix) Malignancy
(x) Rare associations
(a) Ascites
(b) Polycythemia
(c) Familial syndromes, renal cell carcinoma
(xi) Benign metastasizing

its myoma contents (hysterectomy) [14]. To date, there is no definitive oral therapeutic agent for the treatment of uterine leiomyomas, which is a reflection of the remarkable lack of randomized clinical trial data that demonstrate the effectiveness and safety of medical therapies in the management of symptomatic leiomyomas [15].

3. Oral Medical Agents for the Treatment of Uterine Leiomyomas

Currently, there are no definitive FDA-approved agents for the oral medical treatment of uterine fibroids. However, there are several candidate agents that can be used in addition to other approaches in the management of this common benign tumor.

However, there are several candidate agents that can be used with varying degrees of success. Increasing knowledge of the mechanism of action of more recent candidate agents such as Vitamin D, Green tea extract, and Elagolix (oral GnRH antagonist) as well as that of older agents such as selective estrogen receptor modulators (SERMs), antiprogestins, aromatase inhibitors, cabergoline, danazol, and gestrinone may lead to the development of an oral agent with the ability to shrink leiomyoma size with minimal side effects.

This consequently will be discussed.

3.1. Vitamin D (VitD). Data from our laboratory demonstrate that Vitamin D (VitD) is an antifibrotic factor and inhibits growth and induces apoptosis in cultured human leiomyoma cells through the downregulation of PCNA, CDK1, and BCL-2 and suppresses COMT expression and activity in human leiomyoma cells [16–18]. We have also recently demonstrated similar effects in the Eker rat model of uterine fibroids [19]. Another group in Finland demonstrated that Vitamin D inhibits growth of both myometrial and leiomyoma cells in vitro [20]. The growth inhibition was concentration dependent and the level of inhibition was statistically significant with the concentration of 1000 nM.

Table 2: Diagnosis of uterine leiomyoma.

(i) Pelvic examination: enlarged, irregular, firm, nontender uterus
(ii) Ultrasound: transvaginal ultrasound, hypoechoic, heterogenous masses
(iii) Saline sonohysterography: for submucous fibroids or polypi
(iv) MRI: best method for exact mapping, numbering of fibroids
(v) Hysteroscopy: diagnosis of submucous fibroids

In a separate study from our group, the correlation between low serum levels of VitD and the increased risk of having symptomatic uterine fibroids were evaluated [21, 22]. We measured both the biologically active 1, 25 dihydroxyvitamin D3 and the precursor 25-hydroxyvitamin D3 in the serum from African American and white women with fibroids as well as normal healthy controls. Interestingly, then observed that 1, 25 dihydroxyvitamin D3 is significantly lower in women with fibroids compared to normal healthy controls; additionally, there have been detected lower levels of total serum 25-hydroxyvitamin D3 in women with fibroids compared to healthy controls. These findings were observed both in African American women and in Caucasian women.

The aim of the study was to determine whether serum levels of VitD correlated with disease severity in women with symptomatic uterine fibroids. The study population consisted of 67 patients who had detailed repeated pelvic ultrasound evaluations over a 2-year period with specific measurements of the total uterine volume and the volume of the individual leiomyoma lesions. The patients also had detailed laboratory analysis including serum 25 hydroxy Vit D3 levels. As shown in (Figure 1), a statistically significant negative correlation between the low serum VitD levels and the total uterine leiomyoma volume ($P < .05$) as well as the number of leiomyoma lesions/uterus ($P < .05$) was detected [23]. Taken together, our preliminary results suggest a strong dose-response correlation between lower serum VitD levels and increased severity of uterine fibroids. This presents an opportunity for the potential use of VitD or its potent analogues as novel treatment options or for the prevention of uterine fibroids.

To date no randomized controlled trials had been implemented to prospectively assess the efficacy of VitD in the management of uterine fibroids.

4. Epigallocatechin Gallate (EGCG): Green Tea Extract

Tea is one of the most widely consumed beverages all over the world. Both the green tea and the black tea are derived from

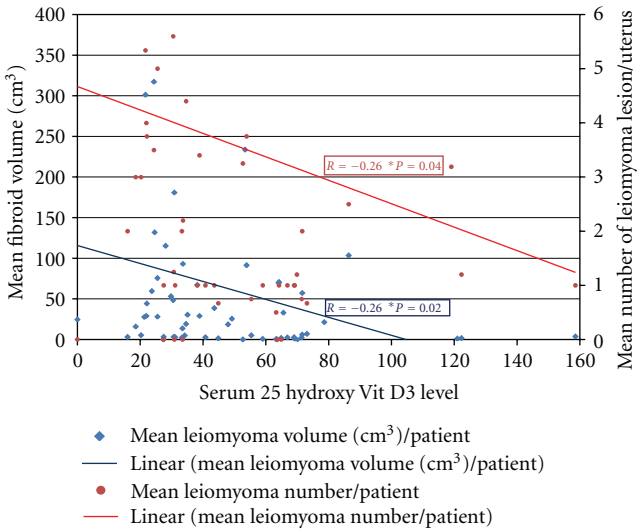

Figure 1: Serum Vitamin D3 level (nmol/L) inversely correlates with both mean volume and number of uterine fibroids.

the leaves of the plant "Camellia sinensis", the most signficant components of which are phytochemicals, of which Green tea is thoroughly studied for its health benefits.

A typical green tea beverage, prepared in a proportion of 1 g leaf to 100 mL water in a 3-min, brew, usually contains 250–350 mg tea solids, and catechins account for 30–42% of the dry weight of the solids [24]. It has been demonstrated that tea constituents exhibit various biological and pharmacological properties such as anticarcinogenic, antioxidative, antiallergic, antivirus, antihypertensive, antiatherosclerosis, anticardiovascular disease and antihypercholesterolemic activities [25, 26].

The major green tea catechins are epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin. Catechins are a group of bioflavonoids that exhibit antioxidant and anti-inflammatory capacity. Chemically, catechins are polyhydroxylated with water-soluble characteristics [27]. Epigallocatechin gallate (EGCG), which is the principal catechin, comprises >40% of the total polyphenolic mixture of green tea catechins [28]. Grapes also contain polyphenols and catechins such as EGCG [29]. Epigallocatechin gallate exhibits various biological activities including potent antioxidant and anti-inflammation capacity [30].

EGCG appears to block each stage of tumorgenesis by modulating signaling pathways involved in cell proliferation, transformation, inflammation, and oxidative stress, which are clearly involved in pathogenesis of various tumors including uterine fibroids [31]. In our laboratory, the effect and potential mechanisms of EGCG action on human leiomyoma (HuLM) cells [32] were studied: cell proliferation and apoptosis were assayed; the protein levels of PCNA, CDK4, BCL2, and BAX were examined by Western blot analysis, and it was found that EGCG inhibits the proliferation of HuLM cells and induces apoptosis. These results suggest that EGCG may be a potential anti-uterine fibroid agent acting through multiple signal transduction pathways [33].

Additional validation of these findings was achieved using orally administered EGCG to shrink preexisting subcutaneous leiomyoma lesions in immune-compromised mice [32]. Previous studies have shown that EGCG inhibited the growth of various human cancer cells, such as epidermoid carcinoma cells [34], hepatoma cells [35], prostate carcinoma cells [36], and breast cancer cells [37]. Those findings motivated us to initiate a currently ongoing double-blind placebo-controlled clinical trial (phase II trial) to evaluate the promising clinical role of EGCG in women with symptomatic uterine fibroids.

5. GnRH Antagonists

The 3rd-generation GnRH antagonists display a more tolerable side effect profile compared to the first-generation GnRH antagonists (histamine release and severe allergic reactions) and the second generation GnRH antagonists (allergy and gel formation); some of the GnRH antagonists approved for clinical use by the US FDA include cetrorelix (Cetrotide; Serono) and ganirelix (Antagon; Organon International). These agents are usually used as injectables. GnRH antagonists exert their action through the direct competitive inhibition of GnRH by occupying the pituitary GnRH receptors and therefore blocking the access of the endogenous GnRH and exogenously administered agonists to their receptor sites [38, 39]. These agents may induce a deep suppression of gonadotropins and the sex steroids, while avoiding any "flare up" phenomena, which may lead to a reduction in uterine fibroids size of up to 50% [40]. One of the major limitations to the wide use of the GnRH antagonists in leiomyoma treatment is the short half-life of these agents and the non-availability of the Depot formulation, thus require repetitive dosing (daily for most of the antagonists) [41].

5.1. Promising GnRH Antagonist (Elagolix). Elagolix is a second-generation new nonpeptide (GnRH) antagonist, highly potent antagonist orally active and rapidly bioavailable after administration that is being developed by Abbott Laboratories (Abbott) in collaboration with Neurocrine Biosciences [42, 43]. It is finalizing the Phase III for endometriosis and finalizing Phase II for uterine leiomyoma with opportunity to be its first and only approved oral treatment for uterine leiomyoma [44]. This promising compound inhibits gonadotropin releasing hormone (GnRH) receptors in the pituitary gland leading to a dose-dependent suppression of LH, FSH, and estradiol. Consequently, suppression of E2 is more prolonged at higher doses [45]. Pituitary suppression is maintained for only a portion of the day, and baseline gonadotropin levels return by 24 hours [46].

These properties suggest that Elagolix may enable dose-related pituitary and gonadal suppression in premenopausal women as part of treatment strategies for reproductive hormone-dependent disease states [46]. To date, Elagolix has been studied in 18 clinical trials totaling more than 1,000 subjects.

Elagolix seems to be well tolerated for multipledoses up to 200; rapidly absorbed after oral administration, with

median time of maximum plasma concentration (Tmax) values ranging from 0.5 to 1 h, the primary metabolite (NBI-61962) appears in the serum rapidly after administration [46].

The therapeutic window of E2 levels for suppression of endometriosis is attainable at a dose of 100–150 mg/day with serum estradiol remained between 20 and 50 pg/mL [45]. This is supported by Barberi RL findings which showed that E2 levels between 30 and 50 pg/mL are effective in inducing endometrial atrophy [47]. The Elagolix therapeutic dose for management of uterine fibroid is yet to be determined.

6. Selective Estrogen Receptor Modulator (SERMs)

Selective estrogen receptor modulators (SERMs) are nonsteroidal estrogen receptor ligands that display tissue-specific agonist-antagonist estrogenic actions. They are used frequently in the treatment and prevention of estrogen receptor-positive carcinoma of the breast in addition to their use as ovulation induction agents [48, 49]. Tamoxifen is one of the oldest known SERMs, but it may potentially cause endometrial carcinoma due to its partial agonistic effect on the endometrium [50]. There are no randomized controlled trials that have investigated the potential role of Tamoxifen in the treatment of uterine fibroids; however, a few case reports have suggested that it actually increases leiomyoma growth [48, 51]. Raloxifene is another SERM that can be theoretically considered to be a candidate therapeutic option for uterine fibroids. Raloxifene only slightly affected collagen biosynthesis in control myometrium cells; however, it significantly inhibited collagen biosynthesis in leiomyoma cells [52] and exerted its action at the transcriptional level [53]. A newly developed SERM, "Lasofoxifene", is currently awaiting FDA approval. However, the results of early trials suggest that there were no significant benefits compared to raloxifene for the skeleton, breast, heart, or reproductive tract [54, 55].

6.1. Mechanism of Action. The most probable hypothesis that explains SERMs' mechanism of action is that they induce changes in estrogen receptors, which result in differential expression of specific estrogen-regulated genes in different tissues [56]. Every member of the SERM family has its own individual characteristics, which depend on its structure, the type of estrogen receptor they bind to, and the set of molecules that interact with its estrogen receptor/SERM complex in affected cells, and these characteristics result in either agonistic or antagonistic activity [57]. SERMs could potentially provide therapeutic benefits by having antagonistic effects at uterine myometrial level and by preventing ovarian stimulation which has been achieved in rat studies. The difference in activity of SERMs is based on the structure activity relationships (SARs) [58].

6.2. SERMs and Treatment of Uterine Fibroids. All SERMs, with their estrogen blocking activity, would be theoretically expected to exert at least some therapeutic effect on uterine fibroids. Raloxifene has been shown to enhance the shrinkage of uterine fibroids in postmenopausal women [59, 60]. However, a recent report from Italy that addressed the effect of raloxifene on uterine leiomyoma showed that the leiomyoma size in premenopausal women who were administered daily 60 mg doses of raloxifene over a 2-year period exhibited no change in leiomyoma size [61].

6.3. Adverse Events. Tamoxifen is not recommended for women with a prior history of deep venous thrombosis, pulmonary embolus, stroke, or transient ischemic attack because it increases the risk of ischemic stroke, particularly in women who are 50 years of age or older. Additionally, the risk of uterine/endometrial cancer was approximately doubled with tamoxifen use [62], and the risk of superficial thrombophlebitis was three times higher [41, 50]. Some of these side effects could be explained by the inhibition of cellular glutamine uptake, oxidative stress, and the induction of apoptosis [63]. SERMs are seldom used for the treatment of uterine fibroids [52].

7. Aromatase Inhibitors

Aromatase inhibitors (AIs) significantly block both ovarian and peripheral estrogen production within 1 day of treatment [64]. Letrozole suppressed the production of estrogens, particularly estrone and estradiol, by 76–79% compared to their baseline levels [65]. The underlying mechanism is the inhibition of the aromatase enzyme, which is the enzyme that catalyzes the conversion of androgenic substances into estrogens [66]. Recent reports have suggested that aromatase is expressed to a greater extent in uterine leiomyoma tissues of African-American women compared to Caucasian women, which may contribute to the higher incidence of ULMs in African American women [67]. Aromatase inhibitors have been shown to be effective against fibroids in limited short term studies with dosing regimens that included 2.5 mg per day of letrozole and 1 mg per day of anastrozole [68]. One of the major concerns with the use of aromatase inhibitors is the reported bone loss with prolonged use, which necessitates the concomitant use of oral contraceptive pills or progesterone [69]. A recently published RCT compared the effects of three months of aromatase inhibitor (letrozole) to that of three months of gonadotropin-releasing hormone agonist (triptorelin) on uterine leiomyoma volume and hormonal status [70]. The results showed an advantage of the rapid onset of action of AIs in addition to the avoidance of the flare ups that initially occurs with GnRHa. Both treatment options induced significant shrinkage of the uterine fibroids and improvement in leiomyoma-associated symptoms [70]. The mean reduction of leiomyoma volume with 3-month use of anastrozole is 55.7% [71]. The authors suggested that aromatase inhibitors should be considered in women with fibroids on a short-term basis or in women who want to avoid surgical intervention to preserve their potential fertility [72]. Another concern with the use of AIs as a treatment option for uterine leiomyoma is its off-label use, which mandates a thorough review with patients prior to the initiation of the therapy [69]. Several RCTs are underway that would

hopefully add to our understanding of the potential promising role of AIs in the treatment of uterine leiomyomas [62].

8. Antiprogesterones

Estrogen has traditionally been considered to be the most important stimulus for leiomyoma growth and numerous studies that included cell culture and animal models supported this concept [73]. Surprisingly, recent findings suggest that volume maintenance and growth of human ULMs are also heavily progesterone dependent, and hence antiprogesterone could reverse leiomyoma growth effects [74, 75]. One potential link between the effects of the two key steroid hormones on ULMs is that estradiol induced the expression of the progesterone receptor and supported progesterone action on leiomyoma tissue [73]. Clinical findings also support these laboratory observations; studies have involved the evaluation of mifepristone (RU 486) [76–78], azoprisnil [68, 75], and, more recently, CDB-2914 and CDB-4124 (CDB: Contraceptive Development Branch) [79].

8.1. Mifepristone. Mifepristone (RU486), a well-known oral antiprogesterone compound, has been used for more than 20 years for multiple clinical indications [70, 80–82]. It has recently been evaluated as a potential therapeutic agent for uterine fibroids with a dose that ranges from 5 mg to 50 mg over a 3-month period [83–85]. Mifepristone reduced leiomyoma size (26% to 74%) and improved leiomyoma related symptoms (63% to 100% induction of amenorrhea). Reported side effects included transient elevations in transaminases, which occurred in 4% of cases as well as endometrial hyperplasia and was detected in 28% of the women who were screened with endometrial biopsies [86]. However, these studies were mostly preliminary with limited numbers of subjects, and therefore, larger randomized well-controlled trials that include thorough monitoring of liver function and endometrial histology are required to conclusively determine the safety and efficacy of this treatment modality.

8.2. Asoprisnil. Asoprisnil (J867, BAY86-5294) is an investigational selective progesterone receptor modulator (SPRM) that was developed for the treatment of progesterone-sensitive myomata. It induces unique morphological changes and is associated with inhibited proliferation of the endometrium and leiomyomata. These changes may lead to amenorrhea, which is usually encountered with its use [68, 87, 88]. Asoprisnil is a tissue selective molecule that binds to the progesterone receptors with a threefold greater affinity than endogenous progesterone [83]. It reduces the uterine and leiomyoma volumes in a dose-dependent manner while achieving remarkable decreases in menorrhagia scores in women with menorrhagia [89]. Amenorrhea rates also increased as the dose of asoprisnil was increased [84, 87]. When asoprisnil was administered daily for longer than 3-4 months, significant endometrial thickening and unusual histological appearance of the endometrial glands occurred [85].

8.3. Telapristone Acetate/CDB-4124 (Proposed Trade Names, Proellex, Progenta). CDB-4124 is another SPRM, but it is a relatively pure progesterone antagonist. It was studied in recent years for the treatment of uterine fibroids and is still being evaluated to address its safety and dose parameters in premenopausal women [90]. Limited information or publications are currently available on the various clinical trials that have investigated CDB-4124; these studies have either been completed or were terminated due to adverse liver-related events according to the http://www.clinicaltrials.gov/ website. New clinical trials using lower doses of CDB-4124 have recently been approved by the FDA.

8.4. Ulipristal/CDB-2914 (VA 2914, EllaOne, Ella). Ulipristal is an FDA-approved selective progesterone receptor modulator (SPRM) that is indicated for emergency contraception. It is structurally similar to mifepristone and seems to be effective in the treatment of uterine fibroids. It is associated with a reduction in pain, bleeding, and leiomyoma size between 17 and 24% [91], as well as an improvement in quality of life [92]. However, data on long-term treatment are lacking, and similar to other SPRMs, ulipristal may be associated with endometrial thickening and endometrial hyperplasia [85, 93, 94]. Large randomized well-controlled clinical trials are needed to evaluate the utility of ulipristal for potential clinical treatment of uterine fibroids [93].

9. Somatostatin Analogues

Increasing evidence has demonstrated a role for growth factors, such as insulin growth factor I (IGF-I) and IGF-II, in the initiation and progression of uterine fibroids [95–98]. Leiomyoma tissue expresses higher levels of IGF-I/IGF-II receptors compared to normal adjacent myometrium [89, 97]. Additionally, these tissues secrete their own IGF-1, probably for autocrine and paracrine use [98]. From a clinical perspective, it has been recently reported that patients with high levels of growth hormone (acromegalic patients) have a higher prevalence of uterine fibroids than the general population [99]. Lanreotide, which is a long-acting somatostatin analogue that has been shown to reduce growth hormone secretion, has also recently been evaluated in seven women with uterine fibroids in Italy [100]. Interestingly, lanreotide induced a 42% mean myoma volume reduction within a 3-month period. These results show that somatostatin analogues may potentially be a new therapy for uterine fibroids [101]. The treatment with somatostatin analogues for diseases other than leiomyoma appears to be safe and is usually well tolerated with some reports of gallstone formation [102, 103]. However, the lacking of clinical trials which test the long-term use of somatostatin analogues along with the severe and adverse health implications such as decreased life expectancy due to accelerated heart disease observed in adults with growth hormone deficiency may hinder its future use for leiomyoma treatment.

10. Cabergoline

Carbergoline is a well-known dopamine agonist that is effectively used in the treatment of prolactinoma and for

the inhibition of lactation. A recent study [104] evaluated carbergoline as a therapeutic option for uterine fibroids. The rational for such an approach lies in its effect as an inhibitory agent on GnRH release. A group in Iran published a preliminary study in 2007 [104] that favored the use of carbergoline as a medical treatment of uterine fibroids on which they reported a volume reduction of about 50% with 6-week use [92]. The same group performed a subsequent study that compared carbergoline with diphereline, which is a gonadotropin-releasing hormone agonist [105]. They reported comparable results in terms of the shrinkage of the fibroids and the improvement in the sonographic, clinical, and intraoperative outcomes [105]. These findings warrant future larger controlled trials to clearly assess the potential use of carbergoline in the treatment of uterine fibroids.

11. Danazol

Danazol is a synthetic steroid that inhibits steroidogenesis through multienzymatic actions in addition to its suppressor effect on sex hormone binding globulin [106]. It reportedly induced a significant 24% volume reduction [107, 108]. However, a recent Cochrane study failed to identify any randomized controlled trials that compared danazol to placebo or any other medical therapy in women with uterine fibroids [109].

12. Gestrinone

Gestrinone is a steroid that possesses antiestrogen receptor and antiprogesterone receptor properties in various tissues, including the endometrium [110]. A recent report from Italy evaluated the use of Gestrinone in the treatment of premenopausal women with uterine fibroids at a dose of 2.5 mg twice per week over a 6-month period [110]. The authors reported a 32% ± 10% reduction in uterine volume [110]. A subsequent study reported up to 60% leiomyoma shrinkage in size [111]. Gestrinone is a contraceptive agent and also exhibits several unfavorable side effects, such as mild androgenicity, weight gain, seborrhea, acne, hirsutism, and occasional hoarseness.

Disclosure

Dr. A. Al-Hendy was a site principal investigator in phase III clinical trials of "Azoprisnil" and "Pro-ellex". Dr. Mohamed Sabry has nothing to disclose.

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Review Article

Counselling Patients with Uterine Fibroids: A Review of the Management and Complications

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Fibroids are very common in Afro-Caribbean women. They can cause severe complications. The treatment modalities are not without risk and should be weighed against the complications of the fibroids.

1. Introduction

Leiomyomata uteri (uterine fibroids) are benign tumours of the smooth muscle of the uterus. These tumours have prevalence ranging from 20 to 50% of women depending on the age, ethnicity, parity, and methods use to assess their presence. In one series, they were said to be present in 77% of postmortem specimens where detailed examination of the uterus was done looking for theses fibroids. In that series, over 50% of the women were asymptomatic [1].

Uterine fibroids grow under the influence of the hormone oestrogen and are most often seen after the menarche, and tend to shrink after the menopause. Typically the patient is nulliparous or of low parity and they are more commonly seen in women of African ancestry.

Common complications of uterine fibroids include menorrhagia with symptoms of anaemia, dysmenorrhoea, pressure symptoms, abdominal distension, and infertility. Infertility appears to be an incidental finding rather than a consequence of the fibroid, except in cases of submucosal fibroids [2, 3]. Other complications include degeneration, torsion, prolapse of a submucous fibroid, ureteric obstruction, venous thromboembolism, intestinal obstruction, and malignant transformation.

2. Menorrhagia

Menorrhagia is defined as regular, cyclic menstrual flow with excessive volume and durations. Clinically, menorrhagia is defined as total blood loss exceeding 80 mL per cycle or menses lasting longer than 7 days [4]. In practice, measuring menstrual blood loss is difficult. Thus, the diagnosis is usually based upon the patient's history. These patients will complain of flooding, overflow, and passage of large clots. In many cases women will notice that they have an increased need for sanitary napkins compared to those obtained in the past.

Menorrhagia must be distinguished clinically from other common gynecologic diagnoses. These include metrorrhagia (flow at irregular intervals), metromenorrhagia (frequent, excessive flow), and polymenorrhea (bleeding at intervals <21 d).

The mechanism by which fibroids cause menorrhagia is not well understood. The blood supply to the fibroid is different compared to the surrounding endometrium and is thought to function independently. This blood supply is greater than the endometrial supply and may have impeded venous return, causing pooling in the areas of the fibroid. Heavy pooling is thought to weaken the endometrium in that area, and breakthrough bleeding ensues.

Fibroids located within the uterine wall may inhibit muscle contracture, thereby preventing normal uterine attempts at haemostasis. In many cases the fibroids increase the size and volume of the uterus and uterine lining with increased bleeding [5].

2.1. Intermenstrual Bleeding. Submucosal fibroids may also present with intermenstrual bleeding. This is especially prevalent with prolapsed submucous fibroids. Any woman with

fibroids and intermenstrual bleeding must, however, have a pelvic examination and pap smear to make sure an obvious cervical cancer is ruled out.

2.2. Haematological Disorders. This is most commonly iron deficiency anaemia secondary to uterine haemorrhage. However women with fibroids sometimes have polycythemia [6] due to increased production of erythropoietin and also thrombocytosis in response to excess bleeding [7]. These two hematological complications are well known to be associated with venous thromboembolism and are one mechanism by which this occurs in patients with fibroids.

2.3. Pressure Effects. These are usually manifest on the urinary tract (distorting the bladder producing urinary frequency or paradoxically acute retention), ureters (causing hydroureters and hydronephrosis), rectum (causing tenesmus), and veins (principally the left common iliac vein causing varicosities, venous thromboembolism [8, 9], and leg oedema. These problems are more likely with large fibroids and renal and venous obstruction are potentially life threatening. Women diagnosed with these problems need to have the fibroids removed to prevent permanent kidney damage of pulmonary embolism.

2.4. Pain. Women with uterine fibroids typically have spasmodic dysmenorrhoea [10], with the uterus going into spasms as it tries to expel the large clots and excess blood. The pain typically starts with the bleeding and ends abruptly with the end of the bleeding. This must be differentiated from congestive dysmenorrhoea which occurs with conditions such as endometriosis where the pain starts before any bleeding and continues for several days after the end of bleeding. Many women have both conditions so women who have clinically palpable fibroids but have congestive-type dysmenorrhoea quite often have endometriosis at surgery.

Infarction in fibroids (spontaneous infarction, torsion causing infarction) can cause quite severe acute pain. Pedunculated subserosal or submucosal fibroids can undergo torsion. Extrusion of a submucosal fibroid polyp may be associated with "labour-like" pains.

Fibroids may enlarge to the point that they outgrow their blood supply and undergo necrosis (red degeneration). This also causes a great deal of pain for patients. This most commonly seen in pregnant women with fibroids and is a common problem in these women.

2.5. Degeneration in Fibroids. There are several types of degeneration in a fibroid [11]. *Hyaline* changes is the commonest; it is present in two-thirds of fibroids and consists of deposition of mucopolysaccharide around the muscle fibres. *Calcification* is also common, especially after the menopause. These calcifications have been known to result in intestinal obstruction in postmenopausal women [12]. *Fatty changes* are uncommon and usually asymptomatic. *Red degeneration* (infarction of fibroid) is commoner in pregnancy.

2.6. Infection. Infection with pyometra may also be associated with submucosal fibroids. It is most likely to occur in the puerperium during uterine involution and when the cavity is colonized by microorganisms. Pyomyoma is a rare condition which is seen in pregnant women and perimenopausal women with vascular disease [8, 9]. In these women the fibroid becomes necrosed and becomes infected. The triad of (1) bacteremia or sepsis (2) leiomyoma uteri; and (3) no other apparent source of infection should suggest the diagnosis of pyomyoma [13].

2.7. Complication in Pregnancy. Red degeneration is the most common problem with fibroids in pregnancy and usually causes severe pain. These women should be treated conservatively as any surgical procedure during the pregnancy can result in preterm delivery and foetal loss. Although myomectomy in early pregnancy has been successfully done, it is not recommended because of the risk of maternal haemorrhage and foetal loss. Other associated problems include placenta praevia and intrauterine growth restriction [14], fetal obstruction with malpresentation or obstructed labour, postpartum haemorrhage, and puerperal infection. Women with fibroids who get pregnant should be allowed to continue pregnancy and all efforts made to make sure they have a normal haemoglobin at delivery. Delivery should be planned to ensure the correct route is chosen. Vaginal delivery is preferred if feasible. Caesarean section is done when needed and usually a lower segment procedure is better. If small fibroids are in the lower segment then these can be removed at the same time. If the lower segment has very large fibroids then a classical incision may be the better option. Caesarean myomectomy is a feasible option but with caution. The baby must be removed before myomectomy is done. If there is much bleeding during delivery the baby and the placenta, myomectomy must be postponed. An oxytocic agent must be used to prevent haemorrhage at myomectomy, and the use of vasopressin is a valuable adjunct [15]. Newer drugs such as carbetocin may be also very valuable here as the oxytocic effect lasts much longer than oxytocin [16]. In some women who have very large fibroids and have completed their family a subtotal hysterectomy at caesarean section may be of value to avoid an interval procedure.

2.8. Malignant Transformation. One of the most feared complications of fibroids by patients is if the fibroids can become cancerous.

The answer to this is that this is possible; however, these events are very rare occurring in less than 1% of patients with fibroids. Patients who have fibroids who have sudden rapid growth in size or women who notice other symptoms such as shortness of breath or increased abdominal discomfort need evaluation. CT scans and MRI can show atypical myomata and surgery may be recommended. However, the only definitive way to diagnose leiomyosarcomatous change is by histological examination.

Other rare histological types have been found such as intravascular leiomyomatosis and even the more rare intravascular leiomyosarcomatosis first described by Coard and Fletcher [17].

Perimenopausal and postmenopausal women who have large fibroids should be monitored for increased symptoms

and have hysterectomy in the event that there is a suspicion of malignancy.

2.9. Infertility. Several studies have shown that submucous fibroids are associated with infertility, probably as a result of decreased implantation [14]. Some studies have also shown that submucous fibroids are associated with recurrent spontaneous abortions. However, in many cases the infertility preceded the fibroids and the fibroids have grown because of incessant ovulation. In many of these women the cause of the infertility is tubal occlusion or endometriosis. There may also be abnormalities of tubal motility or tubal obstruction based on the location of the fibroid. Otherwise fibroid is not a significant cause of infertility. Women who have infertility and fibroids should be properly evaluated with hysterosalpingograms and laparoscopy. Submucous fibroids if found should be removed by hysteroscopy [18]. Tubal surgery and myomectomy are notoriously inefficient in treating infertility as adhesion formation is inevitable. Fertility after one myomectomy is about 50% and after two myomectomies is only 15% [19]. The use of adhesion barriers may be beneficial but many of these have not had the benefit of randomized placebo-controlled trials.

3. Management

Management of a patient with uterine fibroids is highly dependent on the presentation and patient wishes. Other causes of abnormal bleeding need to be ruled out. In many cases the management of the fibroids is also risky and in some women the fibroids are best left alone.

Fibroids are very common and women with small fibroids who are asymptomatic are best left untreated. Women with symptoms who have small fibroids but are close to the menopause or who are trying to conceive should be treated conservatively with analgesics and hematinics. Women who have severe symptoms or very large fibroids usually need surgical intervention. This may be conservative with myomectomy done by laparotomy (all fibroids), laparoscopy (subserous fibroids), or hysteroscopy (submucous fibroids). All women going for myomectomy must also be consented for hysterectomy as haemorrhage is the main complication and hysterectomy may be life saving when done early enough.

Prior to any treatment women need proper evaluation with history and examination. This usually will give an idea of the severity of the condition. Women must also have proper laboratory investigation to confirm the severity of their condition.

A general history must be done to rule out other causes of bleeding since fibroids are so common. Some women may in fact be discovered to have a bleeding condition for the first time based on history. They must be asked about social habits such as excess alcohol intake leading to liver disease. They should also be asked about other factors suggesting bleeding diatheses such as bleeding from other orifices and also presence of purpura and eccymoses.

May women will have other complaints such as pica or shortness of breath suggesting anaemia. However, if this is an acute problem remember to rule out pulmonary embolism.

The examination findings must also be general before targeting the abdomen. Pallor abdominal swelling and pedal oedema are common findings. Unilateral swelling of the legs is a very suspicious complaint and DVT must be ruled out.

3.1. Laboratory Studies. A complete blood count (CBC) may be used as a baseline for hemoglobin and hematocrit or to rule out anemia polycythemia or thrombocytosis. The platelet count in conjunction with a peripheral smear may indicate thrombocytopenia, confirming a bleeding disorder in some cases.

Iron Studies. Total iron-binding capacity (TIBC) ferritin levels are used to assess iron stores when iron deficiency is found. This is not always needed and is done when there is any doubt about the type of microcytic anemia found.

When bleeding disorders are suspected, studies are used to rule out von Willebrand's disease, platelet disorders, and factor II, V, VII, or IX deficiency. These tests should be ordered sparingly because they are expensive tests for rare disorders usually done based on level of suspicion from the history and examination.

Pregnancy remains the most common cause of abnormal uterine bleeding in patients of reproductive age. Bleeding usually denotes threatened abortion, incomplete abortion, or ectopic pregnancy. A pregnancy test may be of value in cases where pregnancy is suspected as a possible cause of bleeding or pain.

Hormonal tests such as follicle stimulating hormone, luteinizing hormone, progesterone, thyroid function tests and prolactin level are tests done to rule out conditions that can cause ovarian dysfunction leading to possible menorrhagia.

Liver function and/or renal function tests are done when liver disease is suspected, such as in persons with alcoholism or hepatitis. It is very important to rule this out as a cause of bleeding prior to attempting surgery.

Urea and creatinine tests assess renal function especially if obstruction has been found on imaging.

3.2. Imaging Studies. Pelvic ultrasound is the best noninvasive imaging study to assess uterine shape, size, and contour; endometrial thickness; adnexal areas. It is also useful to evaluate the urinary system. Hydroureters and hydronephrosis are common findings in patients with fibroids an indication that surgical intervention is needed

Sonohysterography (saline-infusion sonography) where fluid infused into the endometrial cavity enhances intrauterine evaluation. One advantage is the ability to differentiate polyps from submucous fibroids.

3.3. Surgical Evaluation. Evaluation of the patient may require hysteroscopy in some cases and laparoscopy in others. In one series from Jamaica fibroids were found in 30% of patients who had hysteroscopy for abnormal uterine bleeding [20].

4. Treatment

4.1. Medical Care. Care should be tailored to the individual. Factors taken into consideration when selecting the appropriate treatment include the patient's age, coexisting medical diseases, family history, and desire for fertility. Medication cost and adverse effects are also considered because they may play a direct role in patient compliance.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line medical therapy in ovulatory menorrhagia. These drugs have been found to be better than placebo in reducing menstrual blood flow [21].

NSAIDs reduce prostaglandin levels by inhibiting cyclooxygenase and increasing the ratio of prostacyclin to thromboxane. NSAIDs are ingested for only 5 days of the entire cycle, limiting their most common adverse effect of stomach upset and the risk of stomach ulceration.

Oral contraceptive pills (OCPs) are a popular first-line therapy for women who desire contraception.

Menstrual blood loss is reduced as effectively as NSAID's secondary to endometrial atrophy [22].

OCPs suppress pituitary gonadotropin release, preventing ovulation. Common adverse effects include breast tenderness, breakthrough bleeding, nausea, and, possibly, related weight gain in some individuals. Care should be taken in use of OCPs in women with fibroids as these increase the risk of venous thromboembolism [23].

Gonadotropin-releasing hormone agonists are used on a short-term basis due to high costs and severe adverse effects. The agonists are effective in reducing menstrual blood flow. They inhibit pituitary release of FSH and LH, resulting in hypogonadism. A prolonged hypoestrogenic state leads to bone demineralization and reduction of high-density lipoprotein (HDL) cholesterol.

Progestin therapy is the most frequently prescribed medicine for menorrhagia. Therapy with progestin results in a significant reduction in menstrual blood flow when used alone.

Progestin works as an antiestrogen by minimizing the effects of estrogen on target cells, thereby maintaining the endometrium in a state of downregulation.

Common adverse effects include weight gain, headaches, edema, and depression.

Levonorgestrel intrauterine system (LIS) reduces menstrual blood loss by as much as 97% [24]. This is comparable to transcervical resection of the endometrium for reduction of menstrual bleeding [25].

The United States FDA approved a new indication for the levonorgestrel intrauterine system, for the treatment of menorrhagia in women who use intrauterine conception. Approval was granted subsequent to a randomized, open-label, active-control (medroxyprogesterone) clinical trial of women ($n = 160$) with established heavy menstrual bleeding. The results demonstrated that LIS reduced menstrual blood loss significantly compared with medroxyprogesterone ($P < 0.001$) [26]. Adverse effects of LIS include uterine bleeding or spotting, headache, ovarian cysts, vaginitis, dysmenorrhea, and breast tenderness.

Depo-medroxyprogesterone acetate (DMPA) which is inexpensive has been found in our unit to be very valuable, reducing menstrual bleeding and allowing women to improve their haemoglobin prior to surgery [27]. However like GnRh, DMPA is also antiestrogen and can decrease bone density when used for a long time [28].

Danazol competes with androgen and progesterone at the receptor level, causing amenorrhea in 4–6 weeks. Androgenic effects cause acne, decreasing breast size, and, rarely, lower voice.

Tranexamic acid was the first nonhormonal product approved by the US FDA (in November of 2009) [29] for the treatment of heavy menstrual bleeding. Tranexamic acid is a synthetic derivative of lysine that uses antifibrinolytic effects by inhibiting the activation of plasminogen to plasmin.

The mechanism of action in treating heavy menstrual bleeding is by prevention of fibrinolysis and the breakdown of clots via inhibiting endometrial plasminogen activator.

In a recent, double-blind, placebo-controlled study, women taking 3.9 g/d of tranexamic acid showed a significant reduction in menstrual blood loss and an increase in their health-related quality of life compared with those taking placebo [30]. Common adverse effects include menstrual discomfort, headache, and back pain.

4.2. Surgical Care. Surgical management has been the standard of treatment for fibroids especially when medical therapy fails to alleviate symptoms. Surgical treatment ranges from a simple D&C to a full hysterectomy.

4.3. Dilatation and Curettage. A D&C should be used for diagnostic purposes. It is best done in women who are perimenopausal or any woman found with an excessively thickened endometrium on ultrasonography. It is not used for treatment because it provides only short-term relief, typically 1-2 months.

This procedure is used best in conjunction with hysteroscopy to evaluate the endometrial cavity for pathology.

It is contraindicated in patients with known or suspected pelvic infection. Risks include haemorrhage uterine perforation, infection, and Asherman syndrome.

4.4. Resectoscopic Endometrial Ablation Techniques. Transcervical resection of the endometrium (TCRE) has been considered the criterion standard cure for menorrhagia for many years [31]. This procedure requires the use of a resectoscope (i.e., hysteroscope with a heated wire loop), and it requires time and skill. The primary risk is uterine perforation.

Roller-ball endometrial ablation essentially is the same as (TCRE), except that a heated roller ball is used to destroy the endometrium (instead of the wire loop).

It has the same requirements, risks, and outcome success as TCRE. Satisfaction rates are also equal to those of TCRE [32].

Endometrial laser ablation requires Nd : YAG equipment and optical fiber delivery system.

The laser is inserted into the uterus through the hysteroscope while transmitting energy through the distending media to warm and eventually coagulate the endometrial tissue.

Disadvantages include the high expense of the equipment, the protracted time required to do the procedure, and the risk of excessive fluid uptake from the distending media infusion and irrigating fluid.

This technique has largely been replaced by the nonresectoscopic systems (discussed below).

Radiofrequency electricity is a detailed microprocessor-based unit with a bipolar gold mesh electrode array. It contains a system for determining uterine integrity based upon the injection of CO_2.

The device is placed transcervically, the array is opened, and electrical energy is applied for 80 to 90 seconds, desiccating the endometrium.

Balloon thermohydrotubation is similar to the other procedures above as the aim is to destroy the endometrial lining. Heated fluid is instilled into the uterine cavity via a balloon. This coagulates the endometrium and this invariably stops the menorrhagia. The procedure appears to be simpler than many of the others mentioned with less side effect and similar efficacy.

5. Surgical Techniques

5.1. Myomectomy. Myomectomy can be useful in women who wish to retain their uterus and/or fertility.

Since myomectomy can be associated with significant blood loss, this procedure is often reserved for cases of a single or few myomas. In skilled hands many fibroids can be removed with the use of a hemostatic agent. The procedure of choice is the use on vasopressin injected perivascularly around the uterine and ovarian vessels. This occludes both arms of the anastamosis and hence this has been found to be superior to older methods such as tourniquets which occlude only the uterine vessels.

The use of vasopressin is relatively new and still evolving. The drug is usually diluted to 1 : 19 or 1 : 49 mls normal saline if there are many fibroids. Both sides of the broad ligament are injected to form a bleb around the vessels. Great care must be taken to avoid intravascular injection as this can cause systemic vasoconstriction with cardiac ischemia, right-side cardiac venous return overload, and left-side arterial constriction with acute hypertension and left hear failure.

Myomectomy is usually achieved with lowered blood loss; however, the cavities must be closed off securely to avoid secondary haemorrhage [33].

Great care must be taken in handling the tissue and placement of as few incisions as possible to avoid tubal occlusion form direct damage or postoperative adhesions.

The use of postoperative adhesion barriers in this era is mandatory but this needs further study.

5.2. Hysterectomy. Hysterectomy provides definitive cure for fibroids.

This procedure is more expensive and results in greater morbidity than ablative procedures.

A study by Roberts et al. [34] reviewed the cost effectiveness of first-generation and second-generation endometrial ablative techniques, hysterectomy, and the levonorgestrel-releasing intrauterine system (Mirena) for the treatment of heavy menstrual bleeding [34]. Although the authors did not define "heavy menstrual bleeding," their analysis concluded that the most cost-effective initial treatment for menorrhagia that yielded the best quality of life was hysterectomy.

Other Techniques. Hysterectomy has been found to be safer than myomectomy as there is less bleeding; however, this is a definitive procedure removing any further reproductive desires for most women. Hysterectomy is also associated with other complications such as bladder or ureteric injury and also bowel injury. The risk of posthysterectomy vault prolapsed is a well-known entity, and this has resulted in many gynaecologists especially in Europe doing subtotal hysterectomies in order to avoid damaging the supports of the vagina. Others claim that removal of the cervix is more risky with more likelihood of damage to the urinary tract. However, in countries where cancer of the cervix is more common it is recommended that the cervix be removed since post hysterectomy cancer of the cervix is more difficult to treat.

Reattaching the cardinal ligaments to the vaginal vault after total hysterectomy seems to work well in our setting as vaginal vault prolapsed is not as common in our patients with this procedure.

5.3. Uterine Artery Embolisation. Uterine artery embolization (UAE) is a procedure where an interventional radiologist uses a catheter to deliver small particles that block the blood supply to the uterine body. The blood supply to the fibroids is said to be more tenuous than the uterus so the end result is that the fibroids become necrosed and shrink. The procedure works well in many women who do not want surgery. However, it can sometimes diminish fertility as the endometrium and myometrium can also be necrosed. Its effects on future fertility need further evaluation in large studies [35].

6. Summary

Uterine fibroids are very common in all ethnicities. They are especially problematic in women of Afro-Caribbean ancestry. Many women need no intervention for their fibroids. Many women only need conservative treatment. This can be medical treatment or surgical. The management of uterine fibroids requires the balance of the complications of the fibroids versus the risks of the treatment options.

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Review Article

Intrauterine Adhesions following Conservative Treatment of Uterine Fibroids

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Uterine fibroids are common in women of reproductive age and various conservative treatments are available. In order to achieve a successful conservative treatment of fibroids, functional integrity of the uterus is as important as tumor removal or symptoms relief. In this context, intrauterine adhesions must be recognized as a possible complication of conservative management of uterine fibroids, but diagnostic pitfalls might justify an underestimation of their incidence. Hysteroscopic myomectomy can cause adhesions as a result of surgical trauma to the endometrium. The average reported incidence is around 10% at second-look hysteroscopy, but it is higher in certain conditions, such as the case of multiple, apposing fibroids. Transmural myomectomies also have the potential for adhesion, especially when combined with uterine ischemia. Uterine arteries embolization also carries a risk of intracavitary adhesions. Prevention strategies including bipolar resection, barrier gel or postoperative estradiol, might be useful, but stronger evidence is needed. In view of current knowledge, we would recommend a prevention strategy based on a combination of surgical trauma minimization and identification of high-risk cases. Early hysteroscopic diagnosis and lysis possibly represents the best means of secondary prevention and treatment of postoperative intrauterine adhesions.

1. Introduction

Uterine fibroids are an extremely common finding in women of reproductive age, and various conservative treatment approaches are available.

Indications to conservative treatment might be represented by the patient's wish to avoid a hysterectomy or to preserve or enhance her reproductive potential.

In the latter case, functional integrity of the uterus is as important as the complete removal of the fibroid tumors or symptoms relief, in terms of surgical outcomes and success.

Women, undergoing major gynaecological surgery, have a high risk of developing postoperative adhesions of some extent [1]. This circumstance, although commonly considered inevitable, represents a short-/long-term complication of surgery, with important repercussions on patients' health and quality of life, as well as relevant direct and indirect costs for the healthcare systems [2].

Adhesions in gynecology have a particular relevance, because of the potential impact on reproductive function, on top of the known consequences, such as abdominal/pelvic pain or bowel obstruction. Therefore, medical literature of the last decades has dedicated great attention to the topic of adhesion prevention after "gynaecological surgery" by focusing on peritoneal adhesion, but not on intracavitary adhesions [3]. Nevertheless, intrauterine adhesions are a possible complication of therapeutic procedures on the uterus and, although often silent, can interfere with fertility and always hide the potential of becoming symptomatic, for example, the Asherman's syndrome.

This paper focuses on intrauterine adhesions that might occur as a result of conservative management of uterine fibroids.

2. Intrauterine Adhesions following Treatment of Submucous Fibroids

Hysteroscopic myomectomy is currently the gold standard for the surgical treatment of submucosal fibroids, having

replaced traditional surgical approaches such as hysterectomy and abdominal myomectomy. It was first described in 1976 by Neuwirth and Amin, who used an urologic resectoscope [4], while the first report of a gynaecological instrument came by Hallez in 1987 [5]. Resectoscopic myomectomy is safe and effective in removing fibroids and treating related symptoms [6], and a wide range of instruments is now available [7].

As any other intrauterine operation, hysteroscopic myomectomy can cause adhesions as a result of surgical trauma to the endometrium. Hysteroscopic surgery is commonly considered as a minor risk when compared with the interventions with the highest adhesiogenic potential, such as dilatation and curettage (D and C) following delivery or miscarriage [8]. Nevertheless, pitfalls in the diagnosis of postoperative intrauterine adhesions might cause an underestimation of the problem, and a second-look hysteroscopy would be needed to calculate the real incidence (Table 1).

In a prospective study by Taskin et al., a second-look diagnostic hysteroscopy showed mild intrauterine adhesions in the 37.5% of patients after monopolar resection of a single fibroid, and in the 45% after resection of multiple fibroids [9]. Interestingly, a lower incidence of adhesions was reported by the same study following the resection of polyps (3.6%) or uterine septa (6.5%), and no differences were found between patients who were pretreated with danazol and untreated ones. The incidence of adhesions reported by Taskin et al. is definitely high but could be justified by the short interval between primary surgery and hysteroscopic followup. As a matter of fact, the latter was conducted between 14 and 30 days after the fibroid resection, and the same Authors reported doubts whether the adhesions were "de novo", or part of the normal healing process.

In contrast with those findings, Yang et al. report a low rate of 1.5% of adhesions at 1-to-3-month hysteroscopic second look following the removal of a single submucous fibroid, while, in their experience, adhesion rate after resection of apposing fibroids reaches the 78%, in spite of the insertion of an intrauterine device (IUD) postoperatively [10]. Interestingly, a subgroup of seven patients, who were operated for multiple apposing fibroids and did not receive an IUD, underwent an early lysis of adhesions at 1-2 weeks from the primary surgery, and none of them presented with adhesions at the scheduled 1–3-month second look.

In the setting of a larger, randomized study on the prevention of adhesions with auto-cross-linked hyaluronic acid gel following resectoscopic surgery, Guida et al. diagnosed postoperative adhesions in one fourth of patients submitted to fibroid resection [11]. However, the rate of adhesions, detected at a 3-month hysteroscopic second look, was significantly lower when auto-crossed hyaluronic acid gel was used following fibroid resection (16% cases versus 33.33% controls), although larger, and adequately powered, trials would be needed to confirm this finding. In this study, the fibroid resections were accomplished with bipolar resectoscopes. These instruments are currently replacing the older generation of monopolar instruments because of the invaluable advantage of using an electrolyte-containing isotonic distension medium such as normal saline. The reduction of the risks of electrolyte imbalance related to fluid overload [12] increases the safety profile of this kind of surgery.

A role of bipolar resectoscopes in reducing the risk of postoperative intrauterine adhesions has been suggested by Touboul et al. [13]. These Authors reported the findings of systematic second-look hysteroscopy following bipolar hysteroscopic myomectomy, demonstrating synechiae only in 4 out of a group of 53 infertile patients (7.5%). The latter evidence is anyway weak and not supported by comparative studies. Moreover, low rates of intrauterine adhesions have also been reported following monopolar resection of fibroids.

Roy et al., for instance, retrospectively analyzed the two-month second-look hysteroscopy in 186 patients with infertility and recurrent abortions submitted to myomectomy with monopolar resectoscope, showing adhesions in only 2 patients (1.07%) [14]. However, all the patients in this study had received intra and postoperative antibiotic prophylaxis, as well as a course of estradiol valerate, 2 mg per day, during 30 days.

Finally, in a series of five patients with diffuse uterine leiomiomatosis who underwent selective hysteroscopic resection, published by Yen et al. in 2007, postoperative intracavitary adhesions were found in 2 cases [15]. Interestingly, one out of those two patients had developed hypomenorrhea and had repeat hysteroscopic adhesiolysis, but also conceived spontaneously at 4 months following the last surgery, and eventually delivered an healthy infant (cesarean section for breech presentation) after an uneventful pregnancy.

3. Intrauterine Adhesions following Treatment of Intramural Fibroids

The potential role of hysteroscopic fibroid surgery in inducing intrauterine synechiae is obvious. Nonetheless, also other conservative treatments of uterine fibroids might lead to intracavitary adhesions.

Myomectomy, both abdominally and laparoscopically, is a common and safe conservative surgical procedure for intramural fibroids, especially in women of reproductive age [16]. The medical literature proves its role in symptom relief and fertility preservation, although it is still debated as a purely fertility-enhancing procedure in infertile patients.

The occurrence of abdominal and pelvic adhesions as a complication of open or laparoscopic fibroid enucleation is well documented [17]. On the contrary, intrauterine synechiae are not commonly addressed as a potential risk of myomectomy. Indeed, reasonable evidence exists on the development of adhesions following transmural surgery, such as caesarean sections or abdominal myomectomy [18, 19].

The overall risk following myomectomy is considered low (1.3%) [20], but the heterogeneity of this kind of surgery (e.g., not all the fibroids are transmural, and not all the abdominal myomectomies require the opening of the endometrial cavity) makes it difficult to study the association between myomectomies and risk of synechiae.

Table 1: Intrauterine synechiae following resectoscopic myomectomy. Second-look hysteroscopy.

Author	Instrument	Second-look interval	Fibroids	Additional treatment	Adhesions/second-look hysteroscopies	Adhesion rate
Taskin et al. 2000 [9]	monopolar	14–30 days	single	no/placebo	8/22	36.36%
				Danazol	7/20	35%
			multiple	no/placebo	6/13	46.15%
				Danazol	6/14	42.85%
Guida et al. 2004 [11]	bipolar	3 months	single*	no/placebo	8/24	33.33%
				a–c hyaluronic acid gel	4/25	16%
Yang et al. 2008 [10]	monopolar*	1–3 months	single	No	2/132	1.5%
			2, nonapposing	IUD, 1 month	0/5	0%
			≥2 apposing	IUD, 1 month	7/9	78%
			≥2 apposing	early lysis 1-2 weeks	0/7	0%
Touboul et al. 2009 [13]	bipolar	2 months	single*	No	4/53	7.5%
Roy et al. 2010 [14]	monopolar	6 weeks	single	estradiol valerate (6 weeks) antibiotics (5 days)	2/186	1.07%
Total					54/510	10.58%

* Extrapolated, but not clearly stated on the original paper.

Moreover, synechiae can be seen at hysterosalpingography [18] and hysteroscopy [19], but those diagnostic procedures are not routinely used postoperatively. In addition, we need to be aware of certain groups of patients, or procedures, that might increase the risk of adhesions.

Several approaches have been studied and proposed to facilitate myomectomy or reduce feared complications such as hemorrhage, and the related risk for hysterectomy, although their potential effect on the uterine cavity has seldom been assessed. Tixier et al. studied the effect of preoperative uterine arteries embolization (UAE) and uterine arteries surgical ligation on the outcomes of laparoscopic or open myomectomy [21]. The patients wishing to conceive after myomectomy were submitted to diagnostic hysteroscopy 3 months after surgery. The authors reported an incidence of 18% (4/22) of synechiae in women whose myomectomy had been preceded by a temporary uterine artery embolization. On the contrary, no intrauterine adhesions were found among the cases where the uterine arteries were ligated intraoperatively by mono- or bilateral reabsorbable clips. The same measure was 14.8% (4/27) for patients who had not received any preparation prior myomectomy.

The same research group also reported on retrospective findings of hysteroscopic evaluation 3 months following myomectomy with previous UAE, in patients wishing to conceive [22]. In that case, three out of the ten patients presented intrauterine synechiae (30%).

Uterine artery embolization under X-ray guidance is also the main nonsurgical alternative to myomectomy [23]. It was initially described in 1995 [24], and it is an effective treatment in reducing symptoms such as bleeding or pelvic pain and also induces shrinkage of the tumors [20]. It is contraindicated in case of intracavitary fibroids, because of a risk of spontaneous expulsion [25]. UAE is controversial for fertility wishing patients since long-term effects on ovarian function and fertility are not known, and complicated obstetrical outcomes have been reported [26, 27].

In a study by Mara et al. on women of fertile age undergoing UAE for symptomatic uterine fibroids, hysteroscopy performed at 3 to 9 months from the embolization showed a high prevalence of pathological or abnormal findings, among which 14% of intrauterine or cervical adhesions (7 out of 51 patients) [28]. These findings demonstrate that surgical trauma is not essential for the development of synechiae and support the doubts existing on the suitability of UAE for fertility wishing patients, in spite of the evidence of successful pregnancies published in recent years [29].

4. Discussion

While the mechanism of adhesion formation is still largely unknown, and multiple predisposing and causal factors are probably implicated, trauma to the endometrium is commonly considered the major factor in the genesis of uterine synechiae.

The endometrium is composed of two layers, a functional layer and an underlying basal layer. The latter is needed for regenerating the functional layer, which is lost with the menstruation. Trauma to the basal layer can lead to the development of intrauterine scars resulting in adhesions, which can obliterate the cavity to varying degrees. A peculiarity of intrauterine trauma is that it often occurs simultaneously on apposing surfaces, because of the limited volume of the cavity. This is quite evident in case of blind procedures, such as a dilatation and curettage. The association between trauma, synechiae, and specific symptoms is what had already been identified by Joseph Asherman in the first half of last century (*amenorrhoea traumatica*) [30].

As a consequence of trauma, a tissue healing process is started, and it can progress by two different modalities: regeneration or repair. Regeneration occurs cyclically after the menstruation, when the lost tissue is replaced by a new functional layer, originating by a healthy basal layer. A repair mechanism, instead, replaces the missing normal tissue with an extracellular matrix (e.g., fibronectin and collagen), leading to scar formation. As such scarring could be considered a failure of tissue regeneration.

Postsurgical adhesions develop in a similar fashion as scars, that is, within the repair healing process. Initially, the injury is covered and sealed by fibrin (filmy, "fibrinous" adhesions). Most commonly, physiologic fibrinolysis is able to limit the extent of those filmy adhesions and dissolve them. Factors such as a persistent or extended tissue trauma might disrupt the process of fibrinolysis. When that occurs, collagen and other matrix substances are produced by repair cells such as fibroblasts or macrophages, resulting into permanent fibrous adhesions [31].

Tissue hypoxia is thought to be a factor that potentiates the initial tissue injury and triggers a cascade of responses that leads to the creation of adhesions [32, 33]. Hypoxia negatively affects fibrinolysis [34], and in vitro studies demonstrate that it also induces irreversible phenotypic changes in fibroblasts [35].

The current knowledge of the mechanism of adhesion formation is certainly not exhaustive but justifies the clinical findings of higher rate of synechiae following removal of multiple, apposing fibroids (extended trauma) or UAE (hypoxia).

Nevertheless, some patients develop adhesions regardless of the extent of the trauma or other plausible risk factors. Moreover, the diagnosis of silent intrauterine adhesions is not straightforward, and we believe that their incidence might be underestimated. As a matter of fact, the main diagnostic tool used in gynaecology, ultrasonography, does not seem to be accurate in diagnosing synechiae, and hysteroscopy should be considered the gold standard. For instance, systematic pre-IVF outpatient hysteroscopy in patients with normal findings at HSG shows 4.1% of adhesions, whereas ultrasound could not detect any [36]. Moreover, hysteroscopy identifies intrauterine adhesions in 11% of patients with repeated failure of IVF-ET, none of them suspected at standard TV ultrasound [37]. It is still a matter of debate whether infertile patients should undergo systematically a diagnostic hysteroscopy [38], but we believe that those at a higher risk of synechiae, such as following a multiple resection of fibroids, should be offered an endoscopic assessment of their uterine cavity, which is a method with high compliance, that can be performed in an outpatient setting without any need for anesthesia [39].

Prevention of synechiae has not been exhaustively studied in medical literature. Proposed strategies mostly focus on etiopathology. For instance, IUDs have been advocated, in order to avoid apposing surfaces postoperatively but have not been proven effective [10]. Some authors have also proposed intrauterine balloons, such as foley catheters, but the benefits of these intrauterine devices are not clearly higher than, for instance, the risk of postoperative infections [40].

Reabsorbable barriers such as auto-cross-linked hyaluronic acid gel have been shown to significantly reduce adhesions' reformation and severity after hysteroscopic adhesiolysis [41] and might be effective after resectoscopic myomectomy because of high sensitivity and prolonged intracavitary residency time [11, 40].

Postoperative treatment with oral estrogens has been used, in order to stimulate endometrial regeneration [14]. Although the potential effect of an estrogenic stimulus on the endometrium appears logical, available evidence supporting its use is not strong, and, therefore, they cannot be recommended routinely. On the contrary, it seems reasonable to avoid, when possible, any iatrogenic hypoestrogenic status, such as that induced by preoperative GnRH agonists, whose role in facilitating surgery has been suggested but is still controversial [3, 42, 43].

Finally, although it has been proposed that infection might cause adhesions, no evidence supports the prophylactic use of antibiotics for primary hysteroscopic surgery or synechiolysis [40, 44].

Surgical strategies might also offer ways to prevent synechiae. For instance, resection of apposing fibroids could be avoided, by the adoption of two-step procedures. Minimizing tissue trauma by reducing thermal injury and preferring mechanical instruments is possible during resectoscopic myomectomy [45]. The use of bipolar resectoscopes is recommendable because of overall advantages, but we lack comparative studies to prove their superiority on monopolar counterparts in terms of postoperative synechiae. Reducing the size of the instruments could also potentially play a role, but it is limited by the volume of the fibroids [46, 47].

In case of myomectomies for intramural fibroids, intraoperative techniques to reduce bleeding, such as those by endoscopic loops or ligations [48–50], might be preferable over preoperative UAE [22]. Identification and separate suturing of different layers, especially in case of opening of the endometrial cavity, is recommendable.

Finally, performing a second-look or control hysteroscopy as a followup of the primary surgery, especially in high risk cases, seems to be a feasible and effective way to diagnose and treat synechiae, often at their early, fibrinous stage [10].

5. Conclusions

The conservative treatment of fibroids on women of reproductive age is also necessarily a functional treatment. Both the anatomy and the functionality of the uterus need to be respected, preserved, and in some cases improved. In this context, postoperative intrauterine synechiae, although considered uncommon, must be considered as potentially serious complications of fibroids' treatment.

Hysteroscopic resection of fibroids might cause synechiae, especially in the case of multiple, apposing fibroids. Transmural myomectomies also have adhesiogenic potential, especially when combined with uterine ischemia. Uterine arteries embolization cannot be considered a first choice for

patients with fibroids who wish to conceive, also because it carries a risk of intracavitary adhesions.

The real occurrence of intrauterine adhesions following myomectomy might be underestimated because of diagnostic pitfalls and low awareness [51].

Various strategies have been suggested for the prevention of postoperative uterine synechiae, but we are lacking well-powered and designed studies to assess their value after myomectomy or, for instance, UAE.

In view of current knowledge, we recommend a prevention strategy based on a combination of good surgical practice and awareness of high-risk cases and procedures.

Surgery should minimize the damage to healthy tissue and avoid simultaneous trauma on apposing endometrial surfaces. Identification of high-risk patients, followed by early hysteroscopic diagnosis and lysis of postsurgical synechiae, possibly represents the best means of secondary prevention and treatment of intrauterine adhesions.

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Research Article

Surgical Management of Uterine Fibroids at Aminu Kano Teaching Hospital

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Objective. To determine the influence of age and parity on the surgical management of uterine fibroids, clinical presentation, presence of pelvic adhesions, cadre of surgeons, and postoperative complications at the Aminu Kano Teaching Hospital, Kano, Nigeria. *Methods*. A retrospective analysis of 105 cases of uterine fibroids that were managed between 1st January 2003 and 31st December 2007. *Results*. The period prevalence of uterine fibroids was 24.7% of all major gynecological operations. The mean age was 35.8 ± 7.6 and mean parity 4.7 ± 2.8. Abdominal hysterectomy accounted for 58.1% of the cases and myomectomy 41.9%. The odd of using abdominal hysterectomy was about twice that of myomectomy. Pelvic adhesions were found in 67.6% of the cases. Menorrhagia (86.7%) was the commonest symptom, while post operative anemia and pyrexia showed significant association with myomectomy. There was no maternal mortality. *Conclusion*. Surgical operations for uterine fibroids are safe and common kind of gynecological operations at the Aminu Kano Teaching Hospital. Uterine fibroid is associated more with high parity and dominance of abdominal hysterectomy over myomectomy, because early girl marriage is common in our community.

1. Introduction

Uterine fibroids are the most common pelvic tumour and the most common noncancerous tumors in women of childbearing age [1]. As many as 1 in 5 women may have fibroids during their childbearing years, and it usually affect women over the age of 30 years [1, 2]. It is estimated that 20 to 30% of women above the age of 30 years harbor uterine fibroids, which account for 3.2–7.6% of new gynaecological cases and 68.1% of hysterectomies [3–5].

An incidence of 17.9%–26% has been found at laparoscopy in some Nigerian studies [6, 7], which is much higher than 11% reported from Europe and the USA [8]. Overexpression of estrogen receptor (ER) alpha genotype and aromatase, which has been found to correlate with incidence and size of uterine fibroids, is particularly pronounced in Afro-American women [9, 10] and may explain why African American women are at three to five times greater risk for fibroids than white women and Negros 3–9 times than Caucasians [10]. Aromatase inhibitors are currently being considered for prevention and treatment of uterine fibroids [11].

The cause of uterine fibroids is not known, but there are several risk factors [1, 2]. Known risk factors are Afro-American descent, nulliparity, obesity, polycystic ovary syndrome, diabetes, and hypertension [12, 13]. Current working hypothesis is that gene predisposition, prenatal hormone exposure, and effects of hormones, growth factors, and xenoestrogens cause fibroid growth [12].

Genetic and hereditary causes are being considered [14, 15]. First degree relatives have 2–5-fold risk, and nearly 6-fold risk when considering only early onset cases [14]. A positive family history suggests genetic factors, and a gene encoding for fibroid development has been suggested [15].

Fibroid growth is strongly dependent on estrogen and progesterone, which are regarded as growth promoting [16, 17]. Paradoxically, fibroids will rarely grow during pregnancy despite very high steroid hormone levels, and pregnancy appears to exact a protective effect. The mechanism(s) by

which pregnancy exerts its protective effects is unclear, but may be mediated by an interaction of estrogen, prostaglandins, and oxytocin [18, 19]. This is said to explain why the incidence of uterine fibroids is decreased with increasing number of term pregnancies [18], although studies from Nigeria [5] did not agree with this.

Uterine fibroids, although asymptomatic in many women, are often detected in women undergoing infertility evaluation in many black communities [6, 7]. They tend to give symptoms from the age of 30 years to the end of the reproductive life [12, 13]. They grow very slowly, but their rate of growth varies from patient to patient or under differing circumstances, with 90% of them ceasing to grow or even regressing after the menopause [2], probably because the ER-beta, ER-alpha, and progesterone receptors are overexpressed in premenopausal fibroids [14, 20–23].

Hysterectomy which is a major procedure that removes the uterus is the definitive treatment for uterine fibroid [2, 9, 24]. Myomectomy which removes only the fibroids and leaves the healthy areas of the uterus in place is usually reserved for women under the age of 40 years, who are of low parity and desire to maintain their fertility, when the procedure is surgically feasible and there is a reasonably good chance of subsequent pregnancy [9, 25–27]. The rates of hysterectomy for fibroids vary between 32% and 70.4% [4, 5, 9] and myomectomy between 15.8% and 86% [3–5].

Newer techniques include the use of laser vaporization, ultrasonic diathermy coagulation to burn the fibroid nodules, and laparoscopic myomectomy for abdominal myomectomy [2]. The use of gonadotrophic releasing hormone analogs and uterine artery embolization (UAE), which reduce the blood supply to the uterus and fibroids, making them shrink [1, 2], are procedures that would be extremely popular in developing countries, where the culture often makes women resent undergoing major surgery or losing their uterus [9]. However, the expensive equipments and cost of the procedures make them often out of the reach of most developing countries [9].

It is evident that the determining factors in the management of uterine fibroids and the outcome of treatment vary widely in different communities. It is therefore the purpose of this study to determine the factors that influence the management of uterine fibroids in our community, the presentation and outcome.

2. Material and Methods

A retrospective analysis of 105 cases of uterine fibroids that were managed at the Aminu Kano Teaching Hospital, Kano, Nigeria, between the 1st January 2003 and 31st December 2007. The patients' identification data were retrieved from the gynecological ward admission and discharge record books and theatre's operation register. Their case notes were retrieved from the Medical Records Department and analyzed for incidence, age, parity, clinical presentation, presence of pelvic adhesions, type of surgical treatment, and postoperative complications.

During the study period, myomectomy was done using the tourniquet method, in which a tourniquet was applied around the lower uterine segment and below the fibroids, to achieve mechanical vasoconstriction on the ascending uterine artery bilaterally [28, 29]. A tourniquet time was kept, and the tourniquet was released after 30 minutes and reapplied after 5 minutes to reestablish blood flow and prevent irreversible damage to the uterine muscle cells [28, 29].

Postoperatively, a packed cell volume of less than 30% was considered as anemia, a temperature of 38°C or more on two consecutive days after the first post operative day was considered as pyrexia, dysuria and/or frequency of micturtion with positive urine microbiology culture was taken as urinary tract infection (UTI), and local erythema or suppuration was considered as wound infection.

The data obtained were recorded using tables. Statistical analysis was done with Chi-square test using a commercial statistical package (SPSS/PC version 11.0, SPSS Inc., Chicago, Ill, USA).

The odds ratio (OR) and 95% confidence interval (CI) were determined where appropriate. A P value of less than 0.05 was considered significant.

3. Results

During the study period, surgical operations for uterine fibroids were carried out in 115 cases out of 465 major gynecological operations that were performed, giving a period prevalence of 24.7% of major gynecological operations for uterine fibroids. Only 105 case notes were retrieved from the Medical Records Department giving a retrieval rate of 91.3%. Abdominal hysterectomy was performed in 58.1% of the cases, while 41.9% had abdominal myomectomy, the odd of using abdominal hysterectomy was about twice that of myomectomy (OR = 1.92. CI = 1.07–3.46, $P < 0.05$). There was no case of vaginal hysterectomy or endoscopic surgery, and all the hysterectomies were total abdominal hysterectomy. Pelvic adhesions were found in 67.6% of the cases, while 32.4% had clean pelvic cavity. All the surgeries were done with consultant gynecologists participating.

The age range among the patients was 26–55 years, with a mean age of 35.8 ± 7.6. The highest frequency (65.7%) was in the 30–34-year age group, while the least (6.7%) was among the 25–29-year age group. The odd of having hysterectomy was highest among 35–39-year age group (OR = 5.72, CI = 1.43–26.52, $P < 0.05$), while there was no statistically significant difference in the odd of having hysterectomy or myomectomy among the 30–34-year age group (OR = 0.40, CI = 0.15–1.02, $P > 0.05$). All the patients in the 20–29-year age group had myomectomy, while the only nulliparous patients among the 40-year-or-more age group had hysterectomy Table 1.

The parity range was from 0 to 12, with a mean parity of 4.7 ± 2.8. Among the patients, 6.7% were nulliparous, while 93.3% were of parous, with at least one living child. Among them, 33 women (31.4%) were grand multiparae, which accounted for the highest frequency among the patients, while the least frequency was among the nulliparae. The use of hysterectomy was significantly higher among Para 4 and Para ≥5, while myomectomy was significantly higher

Table 1: Age and type of operation performed.

Age (years)	Hysterectomy	Myomectomy	OR	CI	*P* Value
25–29	—	6	—	—	Significant**
25–29	35	34	0.40	0.15–1.02	>0.05 (NS)
35–39	17	3	5.80	1.32–24.59	<0.05*
≥40	9	1	7.44	0.90–163.00	<0.05*
Total	**61 (58.1)**	**44 (41.9)**	**1.92**	**1.07–3.46**	**<0.05***

* Statistically significant for hysterectomy
** Statistically significant for myomectomy
NS: Not statistically significant.

Table 2: Parity and type of operation performed on the patient.

Parity	Hysterectomy	Myomectomy	OR	CI	*P* value
O	2	5	0.26	0.03–1.65	<0.05**
1	3	8	0.23	0.05–1.06	<0.05**
2	3	10	0.18	0.04– 0.76	<0.05**
3	12	18	0.35	0.13–0.92	< 0.05**
4	13	2	5.69	1.12–38.84	<0.05*
≥5	28	1	36.48	4.85–757.27	<0.05*
Total	**61 (58.1)**	**44 (41.9)**	**1.92**	**1.07–3.46**	**<0.05***

* Statistically significant for hysterectomy
** Statistically significant for myomectomy.

Table 3: Clinical presentation of patients.

Presentation	Frequency *n* (%)
(i) Menstrual abnormalities	91 (86.7)
(ii) Abdominal swelling	64 (61.0)
(iii) Lower abdominal pain	58 (55.2)
(iv) Dysmenorrhoea	40 (38.1)
(v) Infertility	25 (23.8)
Primary	5 (20.0)
Secondary	20 (80.0)

among Para 0–2. There was no significant difference in the use of hysterectomy or myomectomy among Para 3. Two nulliparous women in the 30–34-year age group had hysterectomy, because of huge fibroid and technical difficulties that were encountered during myomectomy. Table 2.

Menorrhagia (86.7%) was the commonest symptom, followed by abdominal swelling (61.0%), lower abdominal pain (55.2%), and dysmenorrhoea (38.1%). Infertility (23.8%) accounted for the least frequency, with majority of them (80.0%) having secondary infertility Table 3.

Postoperative anemia (41.0%) was the most common complication, followed by post operative pyrexia (33.3%), UTI (8.6%), and wound infection (15.2%). Postoperative anemia (OR = 5.37, CI = 2.13–13.77, $P < 0.05$), and pyrexia (OR = 4.47, CI = 1.74–11.70, $P < 0.05$), showed statistically significant association with myomectomy. Postoperative anemia occurred 5 times more, while postoperative pyrexia occurred 4 times more among patients who had myomectomy compared to hysterectomy. There was no statistically significant difference ($P > 0.05$) in the frequency of urinary tract infection (UTI) and wound infection in the two groups Table 4. There was no maternal mortality.

4. Discussion

The period prevalence of 24.7% of major gynaecological operations for uterine fibroids in this study is similar to the findings in other studies from Nigeria [27], but lower than reports from Europe [8], probably because uterine fibroid is more common among the black race [9].

In this study, uterine fibroids occurred most often in the third decade of life, which agrees with the findings of other studies [27, 30, 31], which may probably be because uterine fibroids is uncommon before the age of 30 years and after menopause [9].

Majority of the patients were of high parity because of early girl marriage and childbearing in our community, and uterine fibroid was associated more with secondary infertility in this study, which does not agree with the findings in the study from Ilorin [27] in north-Central Nigeria, Enugu [31], and Abakaliki [32] in-south-eastern Nigeria, and Addis Ababa in Ethiopia [30], where women delay marriage, and uterine fibroid is associated more with low parity and primary infertility [27, 32]. This may be because prolonged periods of voluntary infertility from delayed age of marriage are usually associated with development of uterine fibroids and primary infertility [1, 2]. This may also explain why the overall hysterectomy rate was twice as much as that of myomectomy in this study, while myomectomy was used more than hysterectomy in the study from Ilorin [27], Enugu [31] and Abakaliki [32] in Nigeria and Addis Ababa in Ethiopia [30]. A Study from Gombe [33] in-north-eastern Nigeria, which is also predominantly Islamic communities

Table 4: Postoperative Complications.

Complication	Frequency n (%)		OR	CI	P-value
	Myomectomy $n = 44$	Hysterectomy $n = 61$			
Anaemia	28	15	5.37	2.13–13.77	<0.05*
Fever	23	12	4.47	1.74–11.70	<0.05*
UTI	4	5	1.12	0.23–5.22	>0.05
Wound infection	9	7	1.98	0.60–6.61	>0.05

* Statistically significant.

like ours, where early girl marriage is common, recorded low frequency of nulliparity among their hysterectomy patients, majority of whom had uterine fibroids, compared to similar study from Ibadan [34] in-south-west Nigeria where women delay marriage, in which uterine fibroids was also the commonest indication.

Majority of the women had pelvic adhesions, which agree with other studies from Nigeria [7, 26, 27]. The high association of uterine fibroids with pelvic adhesions has been attributed to the high prevalence of pelvic inflammatory disease (PID), previous caesarean section, and laparotomy in developing countries [26, 33], which may cause tubal disease and contribute to the significant association with infertility [1, 2]. Early girl marriage and childbearing in our community before the age when uterine fibroids are common may explain why menorrhagia was the commonest clinical presentation and infertility the least in this study, while infertility (mainly primary) was the commonest clinical presentation in the study from Ilorin [27] and Abakaliki [32] in Nigeria, where women delay marriage and childbearing.

The high association of uterine fibroids with pelvic inflammatory disease and pelvic adhesions, and the large size of most fibroids in developing countries [9] has been found to be the reason why vaginal hysterectomy is not commonly employed in the management of uterine fibroids, because of the technical difficulties that may be involved [9]. This may explain why vaginal hysterectomy was not employed in the management of uterine fibroids in this study. With the advent of laparoscopic-assisted vaginal hysterectomy in our hospital, smaller fibroids may be removed per vaginam.

There was no case of hysterectomy carried out among women who were less than 30 years, probably because hysterectomy among women in that age group is not done for emotional reasons [9]. Two nulliparous women had hysterectomy, because of huge uterine fibroids and technical difficulties at surgery. Huge uterine fibroid as a result of delay in presentation is a common occurrence in developing countries like Nigeria and has been reported to be a cause of emergency hysterectomy as a result of technical difficulties encountered during myomectomy [34], which further emphasizes the need to obtain consent for hysterectomy in addition, before embarking on myomectomy.

Most of the women aged ≥40 years had hysterectomy, because they were parous, and also because of the low probability of further pregnancies at that age compared to future complications [9], which advised in favour of hysterectomy, in order to give them good quality of life. The only case of myomectomy among the 40-year-and-above age group, was the only case of primary infertility in that group, so as to enable her to benefit from in vitro fertilization and embryo transfer, which she can afford and agreed to during preoperative counseling. Myomectomy and recourse to IVF-ET is a possibility that is currently being explored in the management of uterine fibroids in older women with primary infertility [27].

Postoperative anaemia and pyrexia were the commonest postoperative morbidity, which agrees with other studies [1, 2]. Postoperative anaemia and pyrexia occurred more with myomectomy than hysterectomy, which may probably be due to bleeding into the fibroid cavities and peritoneum, with resultant reactionary pyrexia following myomectomy [2], so effort must be made to obliterate all dead spaces at surgery [1, 2].

The higher frequency of complications with myomectomy compared to hysterectomy in this study agree with other studies [2]. This can be reduced by using endoscopic methods like da Vinci Myomectomy, which is a new category of minimally invasive myomectomy, and the latest evolution in robotics technology, which combines the best of open and laparoscopic surgery [35]. With minimally invasive myomectomy using endoscopic methods, surgeons can remove uterine fibroids through small incisions with unmatched precision and control, and carry out comprehensive reconstruction of the uterine wall, regardless of the size or location of the fibroids. Among the potential benefits of minimally invasive myomectomy using endoscopic methods as compared to traditional open abdominal surgery are better opportunity for future pregnancy, significantly less pain, less blood loss, fewer complications with less scarring and possibility of uterine rupture during future pregnancies, a shorter hospital stay, and a faster return to normal daily activities [35]. We advocate the introduction of minimally invasive myomectomy using endoscopic methods in health facilities that perform myomectomy.

Wound infection and urinary tract infection which did not show statistically significant difference between myomectomy and hysterectomy cases may be a result of poor environmental and personal hygiene in our community in a developing country, and urethral catheterization, which has been known to predispose postoperative patients to urinary tract infection [9].

The uterine tourniquet which was applied round the lower uterine segment and below the fibroids during myomectomy in this study, is a mechanical vaso-occlusive technique

to achieve mechanical vasoconstriction on the ascending uterine artery bilaterally [28, 29]. It has been found to be associated with low risk of haemorrhage and difficulty with securing haemostasis, as well as postoperative morbidity, shorter mean duration of operation and hospital stay [28, 29]. This may explain why only two cases of myomectomy were abandoned for hysterectomy, because of difficulty during the operation in this study.

There was no maternal mortality, probably because of meticulous care and the surgeries were done with consultant gynecologists participating. This calls for consultant's participation in surgeries for uterine fibroids.

5. Conclusion and Recommendations

Surgical operations for uterine fibroids are common gynaecological operations at the Aminu Kano Teaching Hospital. Myomectomy and hysterectomy which are the only modalities of management of uterine fibroids that are presently available are safe and effective, the choice of which should be individualized among the patients. Communities where early girl marriage and childbearing is practiced should expect uterine fibroids to be associated more with high parity, and dominance of abdominal hysterectomy over myomectomy.

Introduction of minimally invasive myomectomy using endoscopic methods may reduce the higher frequency of complications that are associated with myomectomy, and laparoscopic-assisted vaginal hysterectomy may make smaller fibroids to be removed per vaginam.

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Review Article

Radiofrequency Ablation for Treatment of Symptomatic Uterine Fibroids

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The use of thermal energy-based systems to treat uterine fibroids has resulted in a plethora of devices that are less invasive and potentially as effective in reducing symptoms as traditional options such as myomectomy. Most thermal ablation devices involve hyperthermia (heating of tissue), which entails the conversion of an external electromagnetic or ultrasound waves into intracellular mechanical energy, generating heat. What has emerged from two decades of peer-reviewed research is the concept that hyperthermic fibroid ablation, regardless of the thermal energy source, can create large areas of necrosis within fibroids resulting in reductions in fibroid volume, associated symptoms and the need for reintervention. When a greater percentage of a fibroid's volume is ablated, symptomatic relief is more pronounced, quality of life increases, and it is more likely that such improvements will be durable. We review radiofrequency ablation (RFA), one modality of hyperthermic fibroid ablation.

1. Introduction

Uterine fibroids (leiomyomata uteri) are benign solid tumors that are present in the majority of women in the USA by the age of 50 [1]. While often asymptomatic, fibroids can result in abnormal uterine bleeding, pelvic pressure, pain, subfertility, dyspareunia, and other symptoms. Submucous and intramural fibroids are most associated with heavy menstrual bleeding (HMB) [2–5]; subserosal fibroids are more often innocuous unless sufficiently large so as to contribute to bulk symptoms. Many fibroids contain elements of more than one fibroid type; that is, fibroids may have submucous and subserosal components and may be transmural.

Fibroids are the most common benign female reproductive system tumor and remain the leading benign indication for hysterectomy in the USA [6, 7]. Between the years 1990 and 1997, the presence of symptomatic leiomyomata uteri was the primary diagnosis in 40.2% of all hysterectomies in the USA [6]. In the UK, fibroids are the second most common indication for hysterectomy, as approximately 30% of 42,500 annual hysterectomies are performed for fibroids [8, 9].

Fibroids have been reported to occur at a rate of 2.0–9.2 per 1,000 woman-years, and the incidence increases with age until menopause [7]. Women of African ancestry are at increased risk for the development of uterine fibroids, with a reported fibroid incidence of 34.4 per 1,000 woman-years in this population [7]. By the age of 50, approximately 70% of white women in the USA will have developed at least one fibroid, whereas the cumulative incidence was over 80% in one large study of black women [1].

When symptomatic, uterine fibroids are associated with a significant reduction in health-related quality of life (HRQOL) as determined by The uterine fibroid symptom and quality of life questionnaire (UFS-QOL), a validated fibroid-specific survey tool [10]. Fibroids also result in a significantly greater degree of health care utilization, including office and clinic visits. For every woman with fibroids, the average annual medical cost is $5,989 USD. This is greater than the $1,846 annual health care cost per woman without fibroids. If one includes indirect costs, such as the costs of excess absenteeism and disability claims, the total per-woman cost of fibroids amounts to $8,192 each year, which is 2.6 times the annual total health care cost for women without

fibroids [11]. It has been estimated that the total annual direct cost of fibroids in the USA amounts to $2 billion [12].

Classic treatment options for symptomatic fibroids include hysterectomy and myomectomy. More recently, uterine artery embolization (UAE) has been demonstrated to be safe and effective, but the impact of this treatment modality upon fertility remains to be determined [13]. Despite the availability of suitable management choices for fibroids, there remain unmet needs. Hysterectomy does not preserve the uterus and fertility, and represents major surgery with the risk of significant complications. Uterine artery embolization is not currently recommended for women who desire future fertility, and fibroid recurrence is a possibility, with approximately 20% of patients subsequently requiring hysterectomy [14]. Myomectomy, which may be performed via laparotomy, laparoscopy, hysteroscopy, or occasionally the vaginal route preserves the uterus and fertility, but like UAE is not definitive therapy for many women.

There has been considerable interest in the use of various forms of energy to heat and ablate uterine fibroids, including radiofrequency energy, focused ultrasound and microwaves. Unlike uterine artery embolization, which results in tissue infarction with disruption of cell membranes and spillage of intracellular contents, hyperthermic ablation results in thermal fixation, which preserves cellular architecture, as well as, coagulative necrosis [15].

Magnetic resonance-guided focused ultrasound (MRgFUS) utilizes focused ultrasound waves to heat and ablate fibroids, leading to fibroid shrinkage and improvement in fibroid symptoms and quality of life [13, 16–21]. However, the durability of MRgFUS beyond two years remains to be established and the availability of the procedure is currently limited. It is apparent that the clinical results of MRgFUS have greater significance and durability if higher percentages of the targeted fibroids are ablated [20].

Radiofrequency ablation (RFA) has been extensively researched as a treatment option for uterine fibroids. Medical devices utilizing radiofrequency energy are widely available and familiar to physicians. There is an established history of treating hepatocellular carcinomata and other soft tissue malignancies with radiofrequency ablation [22–31]. In the case of uterine fibroids, the presence of coagulative necrosis after treatment with RF energy can result in volume reduction of the myoma and symptomatic relief [15, 32–40].

It has become clear from more than two decades of clinical evidence that hyperthermic fibroid ablation, regardless of the thermal energy source, can create large areas of necrosis within fibroids that result in improved quality of life and reductions in fibroid volume, associated symptoms, and the need for reintervention. It is therefore neither necessary to perform hysterectomy nor to remove myomata in order to enhance the health and well-being of women with symptomatic fibroids. The larger the volume destroyed within a targeted fibroid, the higher the probability that treatment will be durable over the long term. While the threshold ablation volume for treatment durability remains to be established, it is apparent that when only a small portion of the fibroid is destroyed through hyperthermic ablation, the surviving fraction of the fibroid can continue to grow and symptoms can persist [20].

In this paper, we review the use of radiofrequency ablation in the management of uterine fibroids. All of the current RF devices have the same impact on fibroids. What differs among them are their electrode designs (bipolar versus monopolar, single tine versus multiple tines), how they are deployed (transabdominally, transcervically, transvaginally), the technique used for real-time visualization (laparoscopy, sonography), and the hardware and software that regulates energy delivery to tissue.

Despite differences in treatment modalities, it is evident that hyperthermic energy-based systems can improve a woman's quality of life. Nonetheless, there remains an unmet need for a minimally invasive fibroid treatment that is amenable to an outpatient setting, involves a short treatment time and may be performed without the risks of general anesthesia.

2. Early Approaches to Hyperthermic Fibroid Ablation

The concept of ablating fibroids with hyperthermic energy, initially referred to as myoma coagulation or myolysis, was initially performed using a neodymium-doped yttrium aluminum garnet (Nd : YAG) laser to deliver energy to fibroids via laparoscopy or hysteroscopy, resulting in destruction of the local vascular supply and subsequent fibroid necrosis [41–43].

The development of bipolar RF needle electrodes paved the way for electrosurgical ablation of fibroids via laparoscopy. This was initially reported by Gallinat and Lueken in 1993 using their own device that was suitable for small fibroids [43]. Goldfarb developed two versions of his own bipolar needle electrode device, one of which was intended for coagulation of posterior myomata [44, 45].

In 1995, Goldfarb reported on his experience with RF ablation in a study of 150 women [45]. Of note, patients received neoadjuvant GnRH-analogues (GnRH-a) for at least three months to shrink fibroids at least 25% before ablation; patients who did not respond to GnRH-a treatment were offered myomectomy or hysterectomy. An average of 30–50 needle insertions were made into a fibroid, and Goldfarb reported that a 7 cm fibroid (reduced from 10 cm after the use of GnRH-a) could be treated in 20–30 minutes. It should be noted that concomitant with RF ablation, 30% of the subjects underwent a hysteroscopic endometrial ablation, 20% were treated with hysteroscopic resection of submucosal fibroids, and 37% had endometrial ablation combined with hysteroscopic myomectomy. These adjuvant procedures, along with the use of preoperative GnRH-a, confound the ability to evaluate the impact of myoma ablation on bleeding outcomes. That said, Goldfarb reported additional reductions in fibroid size at six months (as much as 50%), above what had been accomplished temporarily with GnRH-a treatment. No fibroids increased in size after treatment, and there were few complications. Two women were readmitted, one for a pelvic abscess requiring hysterectomy and the other for parenteral antibiotics due to bacteremia. Of the

150 patients, only six had pain symptoms suggestive of fibroid degeneration, and these women were managed expectantly. Three women underwent second-look laparoscopy, and all of these had mild pelvic adhesions that were managed with adhesiolysis; it was felt that there were fewer adhesions than after Nd : YAG laser ablation. One woman had been diagnosed preoperatively with a leiomyosarcoma suggested by the massive growth of a fibroid during GnRH-a treatment. It was noted that 100% of the 150 women treated with RF ablation (with or without concomitant endometrial ablation and/or hysteroscopic myomectomy) responded to these early attempts at RFA treatment of uterine myomata, with significant reductions in fibroid size at six months; all subjects were asymptomatic after treatment.

3. Risks and Concerns Associated with Early Methods of Hyperthermic Fibroid Ablation

Despite good reported efficacy, laser ablation and the early RF bipolar needle electrodes were not widely utilized. The transserosal use of bipolar needle electrodes and Nd : YAG laser energy was associated with serosal injury and abdominopelvic adhesions, likely due to the multiple passes through the serosa necessary to adequately treat a single fibroid with a bipolar array in the absence of real-time uterine imaging. Goldfarb suggested that, compared to the use of the Nd : YAG laser, the use of bipolar needle electrodes was associated with a decreased risk of adhesions based on small case series and one personal communication [45].

There have also been concerns expressed about uterine rupture during future pregnancies after these original methods of performing RF ablation of fibroids, albeit based solely on anecdote. Arcangeli and Pasquarett reported a single case of uterine rupture at 26 weeks' gestation in which the neonate subsequently died from prematurity and anemia [46]. Phillips and colleagues published their experience with 167 women who underwent either Nd : YAG laser or bipolar needle hyperthermic ablation of fibroids, with or without concomitant endomyometrial resection or hysteroscopic myomectomy; some women also received neoadjuvant GnRH agonist therapy [47]. Phillips and colleagues recommended that, because of the potential for injury to the surrounding myometrium, hyperthermic fibroid ablation should be considered only on an individualized basis in women who desire future childbearing. It is interesting to note, however, that two women in their study conceived and underwent uncomplicated, full-term vaginal deliveries. Their warning about hyperthermic fibroid ablation (i.e., the older technique of multiple transserosal punctures without concomitant imaging) is based on the case report of Arcangeli and Pasquarett, a personal communication involving two women who experienced uterine rupture at 32 weeks' gestation and at term, respectively, and case reports of uterine rupture after laparoscopic myomectomy in which electrosurgery was employed and 3–0 and 4–0 polyglactin sutures were used for uterine closure. Phillips and colleagues suggested "the use of these sutures rather than ones with stronger tensile strength such as 1 or 0 polyglactin may have been responsible for or have contributed in part to the uterine rupture."

Vilos and his colleagues published a report of three women who conceived against medical advice after laparoscopic RFA with bipolar needles [48]. One of the three women successfully delivered at term via Cesarean section. The two other women experienced uterine rupture at 32 weeks' and 39 weeks' gestation, respectively; the premature fetus did not survive. Vilos also took note of a report by Wood and colleagues, in which a catastrophic gravid uterine rupture at 26 weeks' gestation took place three months after bipolar RF needle ablation of a fundal fibroid; after repair, a uteroperitoneal fistula resulted [49].

Even with this very limited literature base, the possibility of uterine rupture and its attendant consequences remain a potential concern with the earlier methods of Nd : YAG laser ablation and bipolar RF needle ablation, performed without imaging guidance.

4. Volumetric Hyperthermic Fibroid Ablation

One of the limitations of the initial attempts at hyperthermic fibroid ablation was the inability to determine the extent of the ablation during surgery. The creation of multiple ablation sites within a given fibroid is one way to maximize the ablation volume, which in turn increases the likelihood that the fibroid will undergo sufficient volume reduction as to prevent symptoms and regrowth in the long term. However, as performed with a bipolar needle electrode system passed through the serosa, this is time consuming and adhesiogenic, due to the electrode geometry and the multiple violations of the serosal tissue. And as mentioned, repetitive, multiple unguided ablations of uterine fibroids may raise the possibility of myometrial weakening and future uterine rupture during pregnancy.

Recent RF energy delivery systems have obviated the need for multiple repetitive insertions of needle electrodes through a targeted fibroid in order to achieve an optimal ablation. Real-time sonography can provide confirmation of accurate targeting during the procedure, and the ablation volume can be tailored to an individual fibroid, minimizing the need to create more than one or two ablations in that fibroid. This is a volumetric approach to ablation, in which generally one or two ablations of predictable volume are created to destroy a desired volume of the targeted fibroid. The successful application of RF ablation to solid tumors of the liver and other organs has affirmed the validity of this approach [50, 51].

Image-guided, volumetric hyperthermic fibroid ablation thus obviates the use of multiple ablations within a fibroid in the absence of concurrent imaging with the potential for unintended and unrecognized ablation of surrounding myometrium. This creates a new level of safety and predictability of fibroid ablation with RF devices, and increases the probability that targeted RFA of uterine fibroids is not associated with uterine rupture and other effects on future pregnancy.

5. Clinical Studies of Volumetric Radiofrequency Ablation of Uterine Fibroids

The feasibility of percutaneous RF ablation under ultrasound guidance was demonstrated by Recaldini and colleagues [40]. They treated six women who had up to three symptomatic submucosal or intramural fibroids 4–6 cm in diameter using a LeVeen coaxial needle electrode. The needle electrode was placed percutaneously under ultrasound guidance. Outcome measures included the uterine fibroid symptom and quality of life questionnaire (UFS-QOL) and fibroid volume reduction as assessed by contrast-enhanced sonography. Mean followup was nine months, and median fibroid diameter and volume were significantly reduced from 4.8 cm (range, 4.4–5.2) and 58.57 cm^3 (range, 44.58–73.58) to 2.3 cm (range, 1.2–3.2) and 8.97 cm^3 (range, 0.90–18.81), respectively. The median symptom score on the UFS-QOL fell from 47.2 (range, 31.8–67.3) to 5.15 (range, 0–26) and the median quality of life score increased from 63.92 (range, 37.2–86.0) to 96.2 (range, 86.3–100.0). Four of the six patients were free of symptoms.

A followup to the study of Recaldini and colleagues was published in 2009 by Carrafiello and colleagues [36]. This medium-term follow-up report involved eleven women (six from their previous report) with 1–3 symptomatic fibroids up to 8 cm in diameter. The patients underwent percutaneous, transabdominal radiofrequency ablation, again using a LeVeen needle electrode (Boston Scientific) under contrast-enhanced transabdominal sonographic guidance. Outcome measures were the UFS-QOL and fibroid volume reduction. The mean baseline symptom score was 50.30 (range 31.8–67.30), and the mean baseline quality of life score was 62 (range 37.20–86.00). The average baseline diameter of the treated fibroids was 5.5 cm (range 4.4 cm–8 cm) and their mean volume was 101.5 cm^3 (range 44.58 cm^3–278 cm^3). For fibroids over six centimeters in diameter (two patients), two ablations were performed to maximize the volume of necrosis. Of the eleven women, one woman had two fibroids, only one of which was treated; the remainder had a single fibroid. After treatment, contrast-enhanced sonography indicated complete ablation of all fibroids, as evidenced by hypovascular necrosis. Mean followup was nine months (range 3–12 months), during which time the mean symptom score fell to 13.38 (range 0–67.1) and the mean quality of life score rose to 90.4 (range 43.8–100). At the last evaluation, the posttreatment mean fibroid diameter was 3.0 cm (range 1.20 cm–4.5 cm) and the mean volume was 18 cm^3 (range 0.90 cm^3–47.6 cm^3). Of note, in the two subjects with fibroids over 6 cm in diameter, the reported volume reduction was 90% and this was stable at 12 months. Nine of eleven patients (81%) experienced volume reduction over 65% at six months after treatment. At the last checkup, six of eleven patients (54%) were asymptomatic, while symptoms had decreased for another four patients (36%). Thus, symptom and quality of life scores improved in 10 of 11 patients (91%). One patient, despite volumetric reduction, did not experience symptomatic improvement and underwent hysterectomy. At the time of hysterectomy, there were no adhesions noted and there were two necrotic adjacent nodules in the endometrial surface from the previous ablation. There were no complications noted and no patient required retreatment. The authors concluded that this larger cohort with longer followup confirmed previous papers from their group on the feasibility and effectiveness of this approach. The feasibility of multiple electrode deployments and ablations was also highlighted, as these were not associated with complications.

Bergamini and colleagues used a multitine RF needle electrode placed laparoscopically to ablate fibroids in 18 women with fibroids 5–8.6 cm in diameter and 14.8–332.8 cm^3 in volume [35]. As opposed to a single needle electrode system, this multitine device was able to produce a spherical, as opposed to cylindrical, volume of ablated tissue. A single insertion was used for fibroids up to 5 cm in diameter. Outcome measures included fibroid volume reduction (as determined sonographically) and UFS-QOL score; median followup was 10 months (range 3–12). By month six, the median fibroid volume decreased by 77% ($P < 0.01$). No additional significant volume reductions were detected after that time point. Nine women were followed out to 12 months and there was no evidence of new growth. Seven of the nine subjects (77.8%) were symptom free at 12 months after treatment. At six months, median symptom scores fell from 43.7 (range 12.5–90.6) at baseline to 9.7 (range 1.1–52.8; $P < 0.01$). Median quality of life scores rose from 66.7 (range 35.0–93.9) at baseline to 100.0 (range 98.2–100; $P < 0.01$) at six months.

Ghezzi and colleagues provided data on the first 25 women treated in their center with a multitine needle electrode device [38]. All 25 women were assessed at six months, 24 through one year, 18 through two years, and 9 through three years; median followup was 24 months. Fibroid measurements were performed with sonography. Mean fibroid volumes were reduced by 65.6%, 77.9%, 78.6%, and 83.9% at 6, 12, 24, and 36 months, respectively. Mean UFS-QOL symptom severity scores went from a baseline of 43.7 to 4.7 at six months and 0 by 12 months; mean symptom scores remained at zero through 36 months of followup. Health-related quality of life (HRQOL) on the same UFS-QOL questionnaire rose from a median baseline score of 63.1 to 99.1 at six months and then to 100 at 12 months, which persisted through 36 months. There were no long-term complications reported. One woman underwent hysterectomy for recurrent fibroid symptoms at 12 months after treatment despite a significant reduction in fibroid volume.

Cho et al. have employed a single, straight 25 cm 18-gauge radiofrequency ablation needle electrode to manage symptomatic uterine fibroids [37]. The needle electrode was generally placed transcervically; the posterior cul-de-sac or anterior vesicouterine fold was also utilized in selected subjects. Targeting of selected fibroids was carried out using either transabdominal or transrectal sonography. Experience with this system has been reported for 153 women, 14 of who were excluded due to lack of followup. Mean pretreatment dominant fibroid volume, as determined by sonography, was 65.12 cm^3; multiple ablations were performed to treat fibroids larger than 5 cm in diameter. By 18 months, the mean dominant fibroid volume was 19.3 cm^3 (73% reduction).

The vast majority of the reduction in dominant fibroid volume occurred within the first 12 months. For fibroids with a pretreatment volume of 75 cm^3 or less, mean UFS-QOL symptom severity scores went from 46.9 to 4.2 at 18 months ($P < 0.05$). Mean health-related quality of life scores rose from 66.9 to 97.7 at 18 months ($P < 0.05$). Six women (4.3%) underwent reintervention during this period, and women with fibroids with a volume >75 cc (5.3 cm in diameter) were more likely to require reintervention and have lower satisfaction scores. It should be noted that of the six women who were retreated, five had reintervention prior to the 12-month followup and the single reintervention at 16 months was due to a *de novo* fibroid that was asymptomatic but had a more rapid growth rate. Long-term complications by 18 months were also uncommon and minor, consisting of spotting up to 8 weeks after ablation in 9.6% of women. There were no major complications, such as injury to the bowel or bladder.

Szydłowska and Starczewski published their experience with performing radiofrequency ablation of uterine fibroids in 46 women with a monopolar needle electrode delivered laparoscopically [34]. Their procedure involved making a single puncture for fibroids with diameters ≤3 cm and two punctures through the serosa for fibroids > 3 cm in diameter, with three 10-second ablations per puncture. Followup at six months, which included Doppler velocimetry, produced striking results. In 73.3% of women who had fibroids with volumes less than 5 cm^3 (roughly corresponding to diameters of 2 cm and less), their fibroids were undetectable on sonographic imaging at six months. In the remaining 26.7% of women with initial fibroid volumes of 5 cm^3 or less, their fibroids were reduced in mean volume by 83.5% ($P < 0.001$). For women with initial fibroid volumes over 5 cm^3, 41.9% of subjects had undetectable fibroids at six months, with 75% mean shrinkage noted in the remaining cohort ($P < 0.001$). Fibroid volume reduction correlated with increases in the pulsatility index (PI) and resistance index (RI) in both uterine arteries at six months, signifying a reduction in blood flow to treated fibroids. There was symptomatic relief of HMB and/or pelvic pain in 88% of patients by six months. One subject was refractory to the effects of fibroid ablation, with no diminution in size of her fibroid and the appearance of two new fibroids; she was managed with open myomectomy, and no adhesions were noted at the time of laparotomy.

Recently, Kim and colleagues have reported results of RF ablation in 69 women with fibroids up to 12.5 cm in diameter, some of who desired fertility [39]. They used a single RF needle electrode that was saline cooled, to prevent carbonization, and inserted it transvaginally under conscious sedation with transvaginal ultrasound guidance. In the 10.1% of women who desired future fertility, the needle electrode was purposely placed so as to avoid the endometrium. Outcomes were assessed at 1, 3, 6, and 12 months after ablation. Fibroid volumes were measured by transvaginal sonography, and HMB was evaluated by a tabulation of the number of soaked normal-sized sanitary products in a menstrual cycle; overall symptoms were assessed with the UFS-QOL symptom severity score (SSS) questionnaire. There were significant improvements in heavy menstrual bleeding noted at each assessment (1, 3, 6, and 12 months; all $P < 0.001$ versus baseline). Overall symptoms, as measured with the UFS-QOL SSS, were also significantly reduced at all assessments. Finally, there were three reported uncomplicated pregnancies; two normal spontaneous vaginal deliveries and one Cesarean section. This paper by Kim and colleagues is particularly important as it represents the first bleeding study of any hyperthermic ablation technique, and also provides pregnancy data (albeit with a very small population). Given the small number of patients who became pregnant, it remains unproven if current RF ablation methods would avoid the occasional cases of uterine rupture reported after the earlier work with both Nd : YAG laser and bipolar needle myolysis. That said, the early evidence is promising. Unlike the earlier methods of myoma coagulation that involved multiple ablations of fibroids without imaging guidance, today's volumetric, image-guided ablation permits the operator to ablate a fibroid with a single ablation in most cases, and often in a fashion that confines the ablation to the myoma and spares the surrounding myometrium and endometrium. For additional support, there have been more than 50 reported cases of pregnancy after MRI-guided focused ultrasound, another form of hyperthermic ablation, with generally good outcomes and no reports of uterine rupture [52–55].

Finally, intrauterine ultrasound-guided radiofrequency ablation of fibroids is a procedure that has been reported to be safe and reliable in a cohort of 19 women [56]. This technique involves the use of the VizAblate System, which combines RF ablation for treatment with intrauterine sonography for imaging in a single device that is inserted transcervically. There were no complications when the device was used to ablate 20 fibroids in the 19 subjects. After either immediate or delayed (16-17 days after ablation) total abdominal hysterectomy, the extirpated uteri were stained with triphenyltetrazolium chloride (a vital stain to discriminate between viable and nonviable tissue). This vital staining indicated that in these patients, 67.2% ± 27.0% of the fibroid volume was successfully ablated (range 15–100%; median 75%). As noted previously, it is not necessary to completely ablate fibroids in order to provide symptomatic relief. An efficacy study involving the VizAblate System is currently in progress in Europe and Mexico.

There has been no reported experience with preoperative use of GnRH agonists in the setting of RF ablation, outside of the early experience with what had been termed "myolysis." Some recent studies of RF ablation in uterine fibroids specifically excluded women who had received GnRH agonist therapy [37, 38]. That said, there is no obvious reason why pretreatment with GnRH agonists would not be helpful when considering large fibroids for treatment with RF ablation. Large fibroids may pose a challenge for both ablative and embolizational therapies. It is unclear what precisely qualifies a fibroid as "large." Regardless, it is thought that increased tissue impedence and vascularity may limit the ability of hyperthermic ablation therapies to destroy large fibroids, even when multiple, overlapping ablations are created in a single fibroid [37]. Thus, preoperative use of

GnRH agonists may enable the wider use of RF ablation with large fibroids.

Reintervention rates, which are perhaps more clinically meaningful than fibroid volume reduction, have been reported to be under 10% in several studies from 3–36 months. [36–38] While additional study is necessary to clarify the recurrence and reintervention rates after RF ablation of uterine fibroids, the initial evidence base is favorable.

6. Conclusion

The use of radiofrequency energy has a demonstrable ability to successfully and safely ablate a range of fibroid volumes. Earlier management with RF ablation has been limited by the lack of concurrent imaging and the need for multiple fibroid punctures resulting in serosal injury, adhesions, and potential myometrial disruption during pregnancy. More recent volumetric techniques, in concert with sonography, minimize the need for multiple punctures through fibroids; in the case of transcervical or transvaginal RF ablation, the serosa is entirely avoided.

Hyperthermic fibroid ablation results in thermal fixation and coagulative necrosis within the fibroid. When a sufficient percentage of a fibroid has been ablated, a reduction in fibroid volume and associated symptoms can be realized. Such symptomatic relief appears to be durable, but additional, longer studies are required to more fully ascertain the reintervention rate after RF ablation of uterine fibroids. The emerging clinical literature base indicates that patients will reliably experience significant reductions in fibroid volumes and symptoms as a result of radiofrequency ablation.

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