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Review Article

Uterine Fibroids in Association with Infertility

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Abstract

Background: In recent years, health researchers have shifted their focus on examining the contribution of uterine fibroids to infertility. The incidence and prevalence of these benign tumors have been established to increase with age, which becomes highly rampant as more women embrace delaying childbearing.

Aim: The following literature review aims to critically analyze the pathophysiology, etiology, epidemiology, alongside treatment and management of uterine fibroids and infertility using current evidence.

Conclusion: Treatment and management of fibroids depends largely on the location of the fibroids alongside the size. Among some of the most utilized interventions used in the treatment of fibroids, include laparoscopic, and surgery using magnetic resonance guided ultrasound. Even though there is consensus on the treatment of submucosal fibroids, it is worth noting that the management of intramural fibroids among infertile patients remains largely controversial.

Keywords: *Uterine Fibroids; Infertility; Leiomyoma; Myomectomy*

Introduction

Uterine fibroids are one of the most prevalent benign tumors affecting women with the reproductive age group. According to estimates by the Center for Disease Control and Prevention, the prevalence rate of uterine fibroids ranges between 20 - 50%. Uterine fibroids are the underlying cause for an estimated 40% of the hysterectomies performed globally [1]. Additionally, multiple evidence has also shown that fibroids are 5 - 9 times more common among women of African descent than in Caucasians thereby strongly suggesting an associa-

tion between ethnicity and race. The condition is also highly prevalent among nulliparous or those with infertility and are linked with elevated incidence of miscarriages [2]. The clinical manifestation of fibroids is variable and this is largely influenced by the size alongside the location of the fibroids in the uterus. However, a significant proportion are incidental findings during clinical examination, and as such, asymptomatic.

A significant proportion of symptomatic patients usually present with abdominal inflammation and discomfort, uterine bleeding, infertility alongside pressure symptoms. A large percentage of patients with fibroids usually present infertility component [3]. Symptomatic fibroids with infertility usually possess challenges in treatment and management. Management interventions are usually tailored based on the presenting symptoms other than challenges in conceiving, the size and location of the tumors, age of the patient, and socioeconomic position of the patient. The following paper critically analyzes the epidemiology, etiology, pathophysiology, diagnosis, treatment and management of uterine fibroids.

Pathophysiology and etiology of uterine fibroids

Although the underlying pathophysiology of uterine fibroids is unknown, fibroids are an outcome of the unusual growth of myometrium [4]. Evidence suggests that the commencing event for fibroid development usually starts with a single smooth muscle cell, which is afterwards followed by nonconformities from the normal signaling pathways of cellular divisions. Furthermore, fibroids are perceived to be dependent on estrogen due to the fact that leiomyoma tends to over-manifest specific receptors of estrogen and progesterone when contrasted to the normal surrounding myometrium [5]. The underlying rationale behind this aspect stems from the fact that estrogen and progesterone typically stimulate uterine lining development during each cycle in preparation for fertilization. Besides, multiple evidence has also shown that fibroids usually shrink during menopausal transition due to a reduction in the production of estrogen and progesterone hormones [5,6].

Clinical experience has also demonstrated that genetic changes is also another major cause of uterine fibroids. It is worth mentioning that most fibroids are accompanied by changes in genetic structure that substantially differ from those in normal uterine muscles. Ultimately, research has also pointed extracellular matrix as one of the major etiology of fibroids. The extracellular matrix is the substance that integrates cells together and usually contain growth factors that biologically alter the cells thereby exposing women to fibroids [7]. Regarding the potential influence of uterine fibroids on fertility, that there is a myriad of various mechanisms through which fibroids adversely affects fertility [8]. One influence that has been mentioned by the authors pertains to the size alongside the location of the tumor. The author goes ahead to assert that fibroids may acts as a barrier in the transportation of sperms, eggs and their implantation. Besides, the presence of submucosal fibroids also negatively influences glycodelin. Notably, these cytokines usually support implantation as well as early embryonic development. However, the progression of fibroids usually inhibits this fundamental role.

Epidemiology of uterine fibroids

Uterine fibroids are seen in 45 - 60% of women, with the percentage increasing to 70% once they attain 50 years [9]. Out of this proportion, 30% of the cases usually result in morbidity as a result of pelvic pressure alongside unusual uterine bleeding. Epidemiological statistics by the organization further indicate that women with African-descent are at a significant risk of being affected by the condition, specifically at an earlier age as compared to their Caucasian counterparts [10]. Furthermore, the organization also acknowledges that uterine fibroids may occur at any instance between menarche and menopause but are prevalent among women between the ages of 35 - 49 years of age. Uterine fibroids are present in an estimated 5 - 10% of women presenting with infertility [11].

Diagnosis

Uterine fibroids evaluation is primarily based on the patient's clinical manifestation including abnormal menstrual cycle, pelvic pain, bulk symptoms, alongside suggestive anemia. Uterine fibroids are in certain instances diagnosed in asymptomatic women during routine

pelvic assessment or imaging [12]. There are numerous approaches used in the identification and characterization of uterine fibroids, including ultrasound, CT and MRI scans, and hysterosalpingography, and sonohysterogram. The author's note that of significance importance is each modality capacity to distinguish uterine cavity's involvement. Hysterosalpingogram has relatively low specificity and sensitivity for the evaluation of the involvement of the uterine cavity. Regarding transvaginal ultrasound, has been widely considered as being accurate in the assessment of submucous fibroids, with older studies indicating a sensitivity of 100% and specificity index of 95%. However, a study contrasting transvaginal ultrasound with MRI, reported a specificity and sensitivity index of 80% and 65% accordingly [13]. The same study further reports a specificity and sensitivity index of 91% and 100% accordingly for MRI, which current evidence consider it as the most effective imaging modality when it comes to the diagnosis and characterization of submucous and intramural fibroids. Some of the differential diagnosis associated with uterine fibroids include adenomyosis, ectopic pregnancy, endometrial carcinoma and uterine carcinosarcoma.

It is generally challenging to establish risk aspects associated with fibroids largely because for a study to have rational scientific evidence, it would require a lot of participants [14]. Nevertheless, a cohort study, for a group of participants that were followed up for 10 years to establish whether or not they developed the condition. The authors further established that there are four risk factors associated with uterine fibroids, including age, parity, African ancestry and early age menarche. These risk factors all relate to already mentioned exposure to reproductive hormones alongside the duration of exposure [4]. However, the cohort study failed to explain why some women with same risk factors that are not common developed the condition while others did not. Furthermore, observational studies have shown that there is no link between smoking as well as that there was no link between contraceptive pills and fibroids not unless used prior to the age of 17 years [12]. Other findings from the study, include no associated between body mass index with the development of fibroids and that alcohol as well as caffeine intake was linked with the development of fibroids.

One clinical manifestation that providers usually look out for that could potentially diagnose uterine fibroids relates to the increase in size as well as the number of tumors. Tumors that rapidly develop after menopausal transition are less likely to be fibroids [12]. However, towards post-menopausal, fibroids may grow as a result of increased amount of cycles without ovulation as well as the secretion of high levels of estrogen in the body. Other clinical manifestations that potentially indicate presence of uterine fibroids, include menorrhagia i.e. prolonged and heavy bleeding within usual menstrual cycle, subfertility, bladder and bowel pressure associated with pressure, alongside symptoms associated with pregnancy such as abdominal pain, recurrent and spontaneous abortion, as well as post-partum bleeding. Some of the less symptoms associated uterine fibroids include malignant change into leiomyosarcoma in an estimated 0.15 - .305 of the cases [14]. The authors further note that the most common reported symptom by patients is menorrhagia. They attribute this to the expanded surface of the endometrial lining in instances whereby the fibroids bulge into the cavity.

During diagnosis, it is paramount that physicians conduct a thorough history to be able to evaluate how long the manifestations associated with the condition have lasted [14]. Some of the critical aspects that ought to be taken into consideration when conducting the history of patients include the age of menarche, the parity, whether or not the patient has a history of miscarriages, infertility, alongside desire to have children, as well as the complaints and the timeline of the symptoms, specifically in relation to the menstrual pattern, pressure sign, and dysmenorrhea. Some of the other equally crucial aspects that should be considered include history of sexually transmitted infection symptoms (STI) previous vaginal, abdominal operations, weight, and height. After the completion of history taking, a comprehensive gynecological work-up plan should be undertaken [12]. The primary aim of the work-up plan is to establish whether or not the patient has the condition, and if evident, whether or not they require an operation. To acquire a substantial amount of information, it is paramount that providers create awareness to the patient on what ought to be done and the rationale behind these actions.

Treatment and management of uterine fibroids

Medical intervention

There are numerous options for medical management of uterine fibroids. One approach that has been extensively proposed by the Food and Drug Administration (FDA) for symptomatic fibroids relates to GnRG analog. GnRG analog also referred to leuprolide acetate has shown high efficacy in reducing the size of fibroids [15]. Besides, hormonal contraceptives have also been established by multiple articles to be highly effective in the management of uterine fibroids. Women that utilize combined oral contraceptives have been shown to report reduced menstrual blood loss after a year [16]. However, the authors further note that Mirena results in substantially greater reduction in menstrual blood loss within a year as compared to oral contraceptives. Furthermore, six randomized controlled trials revealed that expulsion rates of intrauterine devices ranged between 0 to 30% among women suffering from uterine fibroids.

Other than hormonal therapy, non-hormonal anti-fibrinolytic agents such as tranexamic acid have been significantly proven to decrease menstrual blood loss, with a mean reduction of 95 mL per cycle. A nonrandomized study established a greater rate of fibroid necrosis among patients that had received tranexamic acid in contrast to patients that did not receive the intervention i.e. 15% versus 4.2% accordingly [17]. The other medication intervention that has also been established to be effective in the management of uterine fibroids revolves around the use of Nonsteroidal Anti-inflammatory Drugs (NSAIDS). The agents have been proven to reduce blood loss, with a mean reduction rate of 124 mL per cycle and further relieve pain compared to placebo. However, multiple studies have also demonstrated that NSAIDs are less effective in the reduction of menstrual blood cycle when compared to Mirena or tranexamic acid within four months [18].

Surgical intervention

Myomectomy refers to the surgical removal of fibroids from the uterus. The effectiveness of myomectomy has been studied as a potential surgical intervention in several studies [16]. The authors assert that an estimated 50% of women with fibroids and infertility conceived after undergoing the procedure. Regardless of whether it is undertaken through laparotomy or hysteroscopically, myomectomy has resulted in a substantial increase in pregnancy. On a similar note, a systematic literature review established that myomectomy prior to intra-venous fertilization significantly improved the success rate, particularly in uterine fibroids without submucosal component [19]. Due to the varying outcomes in literature. The benefit of myomectomy heavily relies on the size and location of the fibroid [20]. According to the author, there is no beneficiary outcome in relation to subserosal fibroids by virtue that they have minimal effect on a woman's fertility. Regarding submucosal fibroids, a positive implication on pregnancy and live birth rates has been extensively documented. However, for intramural fibroids, the effectiveness of myomectomy remains unclear as there are significant risk post-operative complications that may result in infertility.

Uterine artery embolization (UAE) refers to a minimally invasive procedure used in the elimination of tumors of the uterus. In this procedure, the radiologist utilizes catheter to insert small particulates that inhibit the supply of blood to the fibroids. Uterine embolization usually culminates in ischemia for an estimated 48 hours within the uterus and was initially considered as an intervention for women with fibroids that do not wish to conceive [15]. The authors further affirm that although the ischemic effect is expected to be irreversible in the fibroid, there are concerns that the ovaries are at a significant risk of being irreversibly implicated during the procedure. Patients below the age of 35 years that undergo uterine artery embolization have lower chances of conceiving in contrast to their counterparts that undergo myomectomy [21]. Furthermore, the proportion of live births have also been established to substantially reduce among women undergoing uterine artery embolization (75% in contrast to 19% in myomectomy) thereby indicating the superiority of myomectomy.

Magnetic resonance-guided focused ultrasound (MRgFUS) utilizes micro-beam radiation therapy guided ultrasound beams to heat particular areas of fibroids and precipitate destruction through necrosis. The use of this intervention is only limited to patients that do not aspire to conceive [1]. However, in certain circumstances, the cases of pregnancies have been reported among women that have un-

dergone MRgFUS [22]. The table below depicts the highlighted treatment and management interventions for uterine fibroids including their pharma-kinetics, advantages, disadvantages, and whether or not fertility is preserved [23].

Intervention	Description	Advantages/Disadvantages	Fertility Preserved?
Gonadotropin-releasing agonists	Pre-operative treatment utilized in reducing the size of tumors prior to surgery in women undergoing menopausal transition.	Adv.: Reduces loss of blood, operation duration, recovery duration. Dis: Costly due to long-term treatment, loss of bone density, recurrence risk with myomectomy	Largely relies on the ensuing procedure.
Mirena	Manages unusual uterine bleeding through endometrium stabilization	Adv.: High level of efficacy in reducing blood loss and the volume of fibroids. Dis: Unusual uterine bleeding, elevated risk of expulsion	Potential fertility if the symptoms are resolved
Oral contraceptives	Manages unusual uterine bleeding through endometrium stabilization	Adv.: Decreases loss of bloods from fibroids, allows for easier switch to other alternative interventions. Dis: Does not reduce the volume of the fibroid.	Potential fertility if the symptoms are resolved
Non-steroidal anti-inflammatory drugs	Anti-inflammatory as well as prostaglandin inhibitors	Adv.: Decreases pain and loss of blood from uterine fibroids. Dis: NSAIDs do not reduce the volume of fibroids and is accompanied by gastrointestinal adverse events	Yes
Selective progesterone receptor modulators	Preoperative intervention to reduce tumor size prior to surgery among women undergoing menopausal transition.	Adv.: Reduces loss of blood, operation duration, recovery time. Dis: Breast tenderness, headache endometrial changes, elevated risk of recurrence with myomectomy	Largely relies heavily on ensuing procedure
Tranexamic acid	Anti-fibrinolytic therapy	Adv.: Decreases loss of blood form fibroids as well as ease of conversion to alternative therapy. Dis: Does not reduce the volume of fibroids.	Potential fertility if the symptoms are resolved
Surgical Interventions Hysterectomy	Surgical procedure of the removal of uterine (i.e. through laparoscopically, transvaginal, or transabdominal)	Adv.: Decreases loss of blood form fibroids as well as ease of conversion to alternative therapy. Dis: Does not reduce the volume of fibroids.	Yes
Myomectomy	Endoscopic or surgical removal of tumors	Adv. A non-invasive approach characterized by shorter-recovery duration with significant symptom improvement Dis Recurrence risk of between 20 to 40% depending on the tumor size and extent	Yes
Magnetic resonance-guided focused ultrasound surgery	*In situ* elimination through the use of ultra-sound waves	Adv.: A definitive intervention for women that do not wish to conceive. Reduces pain, loss of blood alongside recovery duration. Dis: Adverse events including pain, fever, blood loss, and recovery duration	No
Uterine artery embolization	Radiologic procedure to occlude uterine arteries	Adv.: Non-invasive and short recovery time Dis: Recurrence rate of above 17% at 35 months	Unknown

Conclusion

In summary, the following literature has critically analyzed the pathophysiology and etiology, epidemiology, alongside treatment and management of uterine fibroids. Regarding pathophysiology, the literature has established commencing event for fibroid development usually starts with a single smooth muscle cell, which is afterwards followed by nonconformities from the normal signaling pathways of cellular divisions. Furthermore, fibroids are perceived to be dependent on estrogen due to the fact that leiomyoma tend to over-manifest specific receptors of estrogen and progesterone when contrasted to the normal surrounding myometrium. The underlying rationale behind this aspect stems from the fact that estrogen and progesterone typically stimulate uterine lining development during each cycle in preparation for fertilization. One influence that has been mentioned is the size alongside the location of the tumor. The author goes ahead to assert that fibroids may acts as a barrier in the transportation of sperms, eggs, and their implantation. Besides, the presence of submucosal fibroids also negatively influences glycodelin. Notably, these cytokines usually support implantation as well as early embryonic development. However, the progression of fibroids usually inhibits this fundamental role.

The paper has further established that during diagnosis, it is paramount that physicians conduct a thorough history to be able to evaluate how long the manifestations associated with the condition have lasted. Some of the other equally crucial aspects that should be considered include history of sexually transmitted infection symptoms (STI) previous vaginal, abdominal operations, weight, and height. One treatment and management option that has been highlighted by the paper is Gonadotropin-releasing agonists. This pre-operative treatment is utilized in reducing the size of tumors prior to surgery in women undergoing menopausal transition. Some of the advantages linked with the intervention, include reduction of blood loss, reduction of operation duration, as well as reduction in recovery duration. However, the procedure is usually costly due to long-term treatment, loss of bone density, and recurrence risk with myomectomy. Besides, uterine artery embolization (UAE) refers to a minimally invasive procedure used in the elimination of tumors of the uterus. In this procedure, the radiologist utilizes catheter to insert small particulates that inhibit the supply of blood to the fibroids. Uterine embolization usually culminates in ischemia for an estimated 48 hours within the uterus and was initially considered as an intervention for women with fibroids that do not wish to conceive. The paper has established that although the ischemic effect is expected to be irreversible in the fibroid, there are concerns that the ovaries are at a significant risk of being irreversibly implicated during the procedure.

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