The Effect of Myoma Uteri on Infertility

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ABSTRACT

Myoma Uteri is the most commonly found tumors in women of reproductive age. Their effects on reproductive function and fertility are unknown. Treatment is dependent on myoma's location and size. While there is medical consensus on the treatment of submucosal myoma, there exists controversy in treatment and management of intramural myoma in infertile patients. Surgical treatments include hysteroscopic, laparoscopic and open myomectomies (laparotomy). Results from endoscopic and open myomectomies are comparable. Endoscopic treatment is generally favored due to lower morbidity, same day treatment, shorter hospitalizations and lower costs. Alternative methods, including medical and radiological intervention, are discussed.

Keywords: Myoma uteri; infertility (Siriraj Med J 2020; 72: 443-450)

INTRODUCTION

Myoma Uteri is the most commonly found tumors in 50-60% of reproductive age women. One quarter of patients seeking reproductive assistance present with myoma. They might be the sole cause of infertility in 1-3% of patients.[1]

Mechanisms of Infertility[1-3]

Myomas vary considerably in size, location and number, and mechanisms by which they may cause infertility. Several theories explain myoma's role in infertility.

Mechanisms involving alteration of local anatomy

Myomas are associated with anatomical distortion of the endometrial cavity and the obstruction of tubal ostia or cervix. They may cause changes in the uterine contour, and impair the movement of eggs, sperm and embryos. Histological observations include elongation and distortion of glands, cystic glandular hyperplasia, polyposis and endometrial venule ectasia.

Mechanisms involving functional change

Increased uterine contractility, chronic endometrial inflammation, endometrial blood supply impairment are all potential complications. Myomas can interfere with sub endometrial arterial blood flow, which depresses implantation rates and in vitro fertilization (IVF) outcomes. Myomas can also lead to impaired physiologic decrease of uterine peristalsis during embryonic implantation. This disrupts typical reproductive processes, resulted in decreased pregnancy rates, especially in submucous or intramural myoma cases. The higher myometrial contractility was postulated to come from too much cytokines in myoma capsule. Neuropeptides, growth factor, enkephalin and oxytocin modulators in myoma capsule may also be involved. Glandular atrophy and ulceration affecting the proximal and distal endometrium are the most frequently observed histological changes.

Endocrine mechanisms

The theory of abnormal local hormonal milieu supports the possibility of an endocrinal mechanism for infertility.

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Paracrine molecular effects on adjacent endometrium

Myoma may induce paracrine molecular effects on adjacent endometrium. The secretion of vasoactive amines and local inflammatory might cause impaired fertility function.

Cytokine factors

Many early pregnancy intrauterine cytokines are instrumental in implantation and initial embryonic development. Glycodelin, a progesterone-regulated glycoprotein, promotes angiogenesis and suppress natural killer (NK) cells. Ben-Nagi and his group reported that interluekin 10 and glycodelin levels were significantly decreased in mid luteal uttering washings submucous myoma's patients.[4]

Endo-myometrial Junctional (EMJ) zone alteration

EMJ, represented a 1/3 of the myometrium abutting the endometrium, produces macrophages and uterine natural killer cells (uNK). Macrophages and uNK cells are instrumental in endometrial decidualization during the window of implantation in mid luteal. Japanese researchers documented a clear reduction of macrophages and uNK cells concentration in EMJ of women with uterine myoma. That corresponded to negative effects on implantation.[5] The presence of intramural and/or submucosal myoma possibly disrupts EMJ. It also affects steroid receptors and cause implantation problem or failure.

Endometrial receptivity[6-7]

Examining myoma's effect on endometrial receptivity illuminates a potential mechanism of how myomas can affect fertility without a mechanical component. Embryonic implantation requires endometrial receptivity, which is moderated by levels of cytokines, hormones, growth factors and other signaling molecules. HOXA10 and HOXA11 genes, as well as leukemia inhibiting factors, are theorized to be necessary components for the implantation process. Reduced gene expression was shown in women with myomas. Lower amount or the absent of uterine endometrium HOXA10 can prohibit implantation, later leading to infertility. Rackow and coworkers reported endometrial HOXA10 and HOXA11 mRNA levels reductions in follicular phase of infertile patients who presented submucosal myoma's (FIGO L0 to L2). The drop of endometrial HOXA10 and HOXA11 mRNA expression were noted for the entire uterine cavity. The presence of intramural myomas seemed to lower endometrial HOXA10 and HOXA11 mRNA levels, but not at a significant levels.[8] By contrast, Matsusaki et al. demonstrated a significant decrease in HOXA10 concentrations during luteal phase in infertile patients with intramural myomas when compared to control groups.[7] Myomectomy of intramural fibroid has been demonstrated to increase HOXA10 and HOXA11 expression in the endometrium.

Effect on sexual function

Myomas are associated with higher incidences of pelvic pain and dyspareunia. Decreased libido or sexual dysfunction might be reported due to bulk effect on the vagina. Orgasm might also be affected. Mass effect on the urinary system may increase urination frequency or incontinence leading to stress and embarrassment. While not directly connected to fertility (Assisted Reproductive Technology is unaffected), these factors may contribute to decreased frequency of sexual intercourse and thus a corresponding reduction in opportunity for natural conception.

Classification of myoma uteri

Myomas are classified by their relative uterine wall placement. Subserosal myomas manifest on the outer surface and grow outwards. Intramural myomas grow inside the uterine wall. Submucosal myomas develop around the endometrium and typically grow inwards towards the cavity. Subserosal and submucosal pedunculated myomas both grow on stalks.

FIGO provides additional guidance for users of the myoma subclassification system. They include tertiary classification of myoma categories, with subcategorization for intramural, subserosal and intramural lesions. Fig 1 shows FIGO myoma subclassification system 2018.[9]

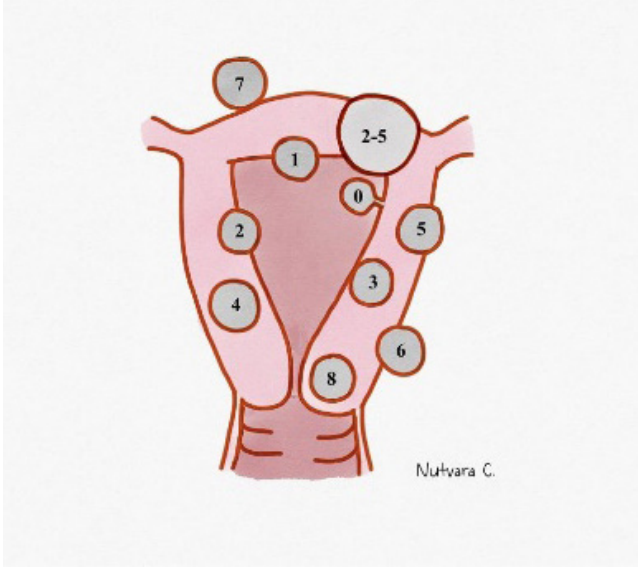

Fig 1. FIGO myoma subclassification system 2018

Submucous type

Type 0: intracavitary lesions are attached to the endometrium by a narrow stalk (< 10% or the mean of three diameter of the myoma).

Type 1: requires a portion of the lesion to be intramural and one diameter <50% of the mean diameter.

Type 2: requires a portion of the lesion to be intramural and at least 50% of the mean diameter.

Type 3: lesions are completely intramural and around the endometrium.

Intramural myoma: transmural lesions are categorized by their relationship to both the endometrium and the serosal surfaces. The endometrial relationship is noted first, followed by the serosal relationship.

Type 4: intramural myomas that are entirely within the myometrium, with no extension to the endometrium surface or the serosa.

Subserous myoma

Type 5: ≥50% intramural

Type 6: <50% intramural

Type 7: attached to the serosa by a stalk that is also < 10% or the mean of three diameters of the myomas.

Other types

Type 8: myomas that do not relate to the myometrium at all, including cervical lesions (demonstrated), those that exist in the round or broad ligament without direct attachment to the uterus, and other 'parasitic' lesions.

Impact of myomas on reproductive function

The effect on fertility depends on the myoma's location

Subserous myoma

The consensus based on clinical experience implies very little causation linking subserosal myomas and infertility. It is not evidence based to perform a myomectomy to remove subserosal myomas to treat infertility.[2]

Submucous myoma

Submucosal myomas that distort the uterine cavity lower implantation rates and increase early pregnancy losses when compared to myoma free patients. Pritts et al. reported a meta-analysis showing submucosal myomas patients with significantly decreased live birth rates/ ongoing pregnancies (RR=0.318, 95% CI: 0.119–0.85, P < 0.001), pregnancy rates (RR=0.363, 95% CI: 0.179-0.737, P = 0.005) and implantation rates (RR=0.283, 95% CI: 0.123-0.649, P= 0.003). This class of myomas is also correlated with increased risk of spontaneous abortion (RR=1.678, 95% CI: 1.373–2.051, P = 0.022).[10] Casini and his group studied a RCT in myomas patients with unexplainable infertility. Patients with clear subserous myomas were excluded. Consented subjects were randomized either to undergo myomectomy or not receiving the procedure. Patients then reported if they could conceive by themselves, and the conception rate was recorded for the following 12 months or longer. Patients who received hysteroscopic or open myomectomy showed increased pregnancy rates. Baseline myoma staging showed no statistical difference. Statistically significant pregnancy rate increases were only observed in patients with submucosal myoma (pregnancy rates between myomectomy/ no myomectomy; submucosal group = 43.3/27.2 %, p < 0.05; intramural with submucosal component = 40/15 %, p < 0.05; all submucosal = 40.4/21.4 %, p < 0.05).[11] To summarize: submucosal myomas demonstrably lower fertility rates, and studies have shown their removal improve both conception and live birth rates.

Intramural myoma

Many hypotheses explain infertility from intramural myomas without uterine cavity involvement. Alterations of uterine peristalsis and vascular flow could disrupt sperm and ovum transportation and embryo implantation. Meta-analysis of Sunkara et al. work showed a significant decrease in clinical pregnancy rate (RR=0.85, 95% CI: 0.77–0.94, P < 0.002) and live birth (RR=0.79, 95% CI: 0.70–0.88, P < 0.0001) in women with non-cavity-distorting intramural myomas compared with those without myomas, following an IVF treatment.[12] Literature review produced a single non-randomized controlled trial investigating pre-IVF myomectomy effects. Patients had one to 5 myomas, with at least one of 5 cm, with no submucosal component. The study revealed many benefits of pre-IVF myomectomy demonstrated by a 25/12 % birth rate in treated/ control group.[13] A Cochrane's review of the RCTs concluded that there was insufficient evidence to recommend myomectomy to improve fertility in cases of asymptomatic intramural myoma.[14] The evidence for using myomectomy to treat infertility in intramural myoma is weak.

Diagnosis[15]

Uterine myomas, can be identified and characterized by the use of transabdominal or transvaginal ultrasounds, sonohysterogram, hysterosalpingogram, MRI and hysteroscopy. Each modality has its own advantage used to characterize the involvement of the uterine cavity.

Ultrasounds are adequate, rapid, safe, and cost-effective in evaluating the size, number, and location

of myomas. Transvaginal ultrasound might be used to identify myomas of up to 5 mm in diameter. Transvaginal ultrasound yielded accurate result in submucous myomas evaluation. Older studies showed a sensitivity of 100% and specificity of 94%.[15] Ultrasound, due to acoustic shadowing, may be suboptimal for multiple myomas as well as endometrial impingement. Additionally, inter-observer variation has been found to be greater with this method compared to MRIs.

Hysterosalpingogram is often performed to assess tubal patency in women with infertility and to exclude intrauterine pathology. However, the sensitivity and positive predictive value of this test for the identification of intrauterine lesions can be as low as 50 and 28.6% respectively. Therefore hysterosalpingography cannot reliably be used to exclude endometrial distortion secondary to submucosal myomas.

Sonohysterography gives similar results to hysteroscopy for submucous myomas diagnosis. Both techniques are superior to transvaginal ultrasound. The 3D sonohysterography is comparable to 2D sonohysterography and hysteroscopy.

MRI has been well studied in the evaluation of uterine myomas, especially for myoma mapping and submucosal penetration. It was shown to be the most reliable evaluation method (100% sensitivity and 91% specificity) compared to transvaginal ultrasound, hysterosonography and hysteroscopy. The gold standard is the pathological examination. The disadvantages of MRI evaluation are the low accessibility and prohibitive cost.

Hysteroscopy provides both diagnostic and therapeutic value. Direct evidence of intrauterine pathology or submucous myoma that distorted the uterine cavity was demonstrated by hysteroscopy. The sensitivity and specificity were 82 and 87 %, respectively.[16]

Treatment[17-18]

Medical management

There is limited data with regards to the medical management of myomas in patients attempting conception. Surgery has associated risks. Not all patients are qualified as candidate for surgery.

Gonadotropin-Releasing Hormone Agonists (GnRH agonist)

These medications work by decreasing estrogen-dependent myoma growth through down regulation of GnRH receptors in the pituitary gland. Follicle-stimulating hormone, luteinizing hormone release and estrogen availability are decreased. By inducing a state of hypoestrogenism and temporary menopause with amenorrhea, GnRH agonists have been used to shrink myomas and restore hemoglobin levels in symptomatic women. Preoperative use of GnRH agonist appears to be relevant and beneficial in patients with submucous myomas. Benefits include resolution of preoperative anemia, decrease in myoma size, reduction of endometrial thickness and vascularization with subsequently improved visibility and reduced fluid absorption.[19] However, GnRH agonists have significant side effects, including medically induced menopause leading to possible hot flashes, vaginal dryness, and osteoporotic effects in bone. When used as a pretreatment to myomectomy, GnRH agonists show no apparent effect on pregnancy rates after surgery, nor is there a difference in the recurrence rate of the myomas.

Selective Progesterone Receptor Modulators (SPRMs)

Oral SPRMs, i.e., ulipristal acetate (UPA) can be used in uterine myoma management. Studies suggested the role of progesterone in the growth of myomas but not in normal myometrial cells. SPRMs could inhibit myoma growth and induce apoptosis selectively.[20] UPA reduces the amount of vascular endothelial growth factor (VEGF) and Bcl-2 expression while increases caspase-3 expression. All events led to impaired vascularization, cell growth, and myoma proliferation.[20] UPA was found to significantly reduce myoma size. Its use could possibly reduce the morbidity rate of the surgery. Or potential patients would no longer require surgery. Adverse effects include headaches, hot flashes, and breast discomfort. Adhesions, uterine rupture, and cesarean rates may be decreased for those patients who could avoid myomectomy or repeat myomectomies by the use of medication. UPA is an alternative preoperative medical treatment prior to myomectomy.

Type 1 myomas - If a myoma is type 1 but >3cm, or if the patient presents with anemia, pre-hysteroscopic medical therapy (SPRMs or GnRH agonist) is indicated. UPA may be given in one or two courses of three months. In a majority of cases, type 1 myomas respond to preoperative therapy and decrease in size, facilitating hysteroscopy conditions. It should be pointed out that in some cases, myomas regress sufficiently that surgery may be avoided.[19,21]

Type 2 myomas - UPA can be proposed. Myomas often respond to this preoperative therapy and regress in size. This reduction also allows a hysteroscopic approach after the first menstrual bleed. In some cases, myomas regress enough that they no longer distort the uterine cavity. Surgery may not be further required.[19]

Type 2 or type 2-5 myomas (single or multiple) distorting the uterine cavity – When multiple myomas (≥2) or myomas of multiple types (type 2–5) are observed, UPA can be administered over two to three month courses. Myoma regression is expected to be very significant (>50% decrease), with no longer distorted uterine cavity. The patient can then attempt natural conception or undergo assisted reproductive techniques.[22-23] If myoma regression is significant (≥25% but <50%), but the uterine cavity remains distorted or if the myoma remains large due to great volume at baseline, a surgery will be indicated. In young patients with symptomatic myomas desiring future fertility, UPA can be administered long term, i.e., in four courses of three months.[22]

SPRMs are beneficial, because long-term intermittent therapy (repeated in case of recurrence during the interval) might help to avoid or postpone surgery until the patient seeks to conceive.[19]

Aromatase Inhibitors (AIs)

The use of AIs in reducing myoma volume has been demonstrated. This medication class works by inhibiting aromatase, a cytochrome p450 enzyme, which blocks the conversion of androgens to estrogens. AIs appear to be as or more effective than GnRH agonists at reducing myoma volume but have significantly fewer adverse effects during short term use.

In one randomized control trial, an AI was shown to decrease the total myoma volume comparatively to GnRH agonists (45.6 versus 33.2%, respectively).[24] Aromatase appears to be prevalent within myoma tissue but not in myometrium, allowing these medications to specifically target myoma. One retrospective study revealed that myomas had triple aromatase amount than in normal myometrium.[25] AIs might work to decrease the complexity of myoma surgery, leading to improved fertility outcomes.[20]

Surgical treatments[3]

When patients' conception difficulties or recurrent miscarriages are attributed to myomas, surgical removal is a recommended option. Removal of submucous myomas was shown to increase clinical pregnancy rates compared to controls where myomas were left in situ. However, myomectomy in cases of intramural myomas is more controversial.

Hysteroscopy

Hysteroscopic myomectomy is a popular surgical method. It is a choice for up to 4-5 cm submucous myomas. It can be performed on type 0, 1 or 2 myomas. But type 2 myomas often require multiple procedures for a complete resection. Uterine perforation, fluid overload, bleeding, and intracavitary adhesion formation are common hysteroscopic myomectomy complications. Several techniques are available for hysteroscopic myomectomy, including electrocautery resection, morcellation, laser ablation and vaporization.

Laparoscopic versus laparotomy

It is known that all myomas FIGO L3 and large L2 are best removed by laparoscopy or laparotomy. Reproductive outcomes appears comparably improved in both methods.

Laparotomy (Open myomectomy)

Laparotomy is a method of choice, especially with multiple complicating intra-abdominal adhesions. All large myomas (i.e., >20 cm in diameter) or any malignant ones require a conventional open approach. The standard risks of open abdominal surgery are increased blood loss and longer recovery times compared to less invasive choices.

Laparoscopy

Laparoscopic myomectomy yields improved visualization, decreased blood loss, faster recovery and reduced postoperative pain compared to laparotomy. Pregnancy outcomes and the risk of myoma recurrence are comparable.[26] Uterine rupture during pregnancy following laparoscopic myomectomy is a great concern, However, the real risk has never been documented. The concern originates from the technical difficulty of performing a multilayer closure. The actual rate of uterine rupture following laparoscopic myomectomy is extremely low.

Robotic-assisted laparoscopy

The Food and Drug Administration (FDA) gave a green light to the da Vinci system for laparoscopic surgery in 2000, and for the use in gynecologic procedures in 2005. Since then, the use of robotic-assisted laparoscopic procedures, including hysterectomy and myomectomy has become increasingly common. The robotic system improves visibility in 3D viewing and intuitive movement of the operating arms. The short-term outcomes are comparable to traditional laparoscopy in terms of blood loss and recovery time. A recent retrospective cohort study displayed pregnancy outcomes following robotic myomectomy to be comparable to traditional laparoscopy. The system incurs higher costs and longer operative time.[27]

Other treatment methods[3]

Uterine artery embolization (UAE) and magnetic resonance focused ultrasound surgery (MRgFUS) are minimally invasive alternative treatments for symptomatic myoma. Pregnancy is possible after these treatments. However, increased obstetrical complications including miscarriage, abnormal placentation and postpartum hemorrhage are reported. The evidence supporting these modalities for patients seeking fertility is limited.

Uterine Artery Embolization (UAE)

UAE was first described in 1995 as an alternative radiological treatment option for women with large myomas no longer seeking to preserve fertility (Fig 2). A transient ischemia is shown by MRI imaging in the body of the uterus and the endometrium lasting for up to 72 hours. This ischemic change is intended to be irreversible only within myoma tissue[15] and temporary within healthy uterine muscle and endometrium. The uterine and ovarian artery has also been shown to anastomose on angiography in at least one side in approximately 46 % of patients.[3]

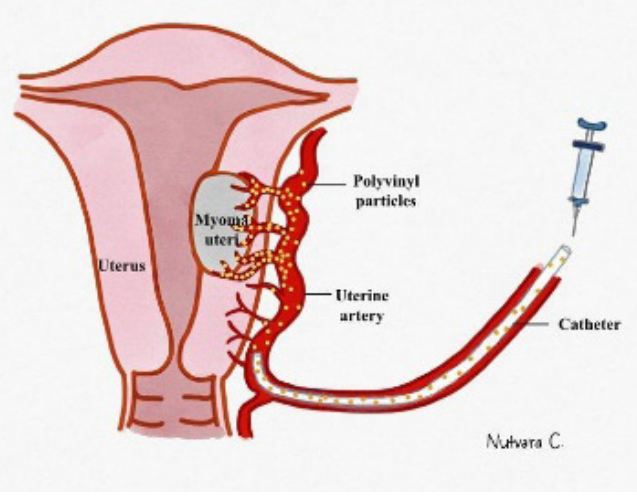

Fig 2. Uterine Artery Embolization

Inadvertent embolization of ovarian tissue may result in ovarian insufficiency and failure, especially in older patients or those with low baseline ovarian reserve. The incidence of amenorrhea is <1% in patients under 40. RCT was conducted for evaluating UAE versus abdominal myomectomy in an infertile population with pregnancy rates of 50 and 78 % respectively.[28] They recruited young patients below age 35 which may explain the high overall conception rates. Time to conception was longer for patients with UAE compared to myomectomy, 18 versus 13 months, respectively. Considering the poor reproductive and obstetric outcomes (increased rate of miscarriage, preterm delivery, abnormal placentation and postpartum hemorrhage), UAE is not a preferred choice for women with infertility or those desire future fertility. It is to be reserved for poor surgical candidates.

Magnetic Resonance-Guided Focused Ultrasound Surgery (MRgFUS)

MRI-directed beams of ultrasound capable of heating an area of myoma tissue to up to 70 °C is used in this method (Fig 3). MRgFUS will cause destruction by coagulative necrosis.[15] Rabinovici et al. reported pregnancies following MRgFUS. Fifty four pregnancies were reported in 51 women. The mean age at MRgFUS was 37.2 years and mean time to conception was 8 months.[29] The miscarriage rate was 28%. The preliminary findings are successful with a high rate of delivered and ongoing pregnancies. There is limited evidence for the use of these methods in patients who later want to get pregnant. It is too early to recommend MRgFUS in the infertile patient desiring conception until further study.

Current practice

When patients seek pregnancy (agnostic to IVF), gynecologists should establish an integrated approach based on the current knowledge by considering patients's age as well as myomas' size, number, and location. The following parameters should be considered before deciding on a surgical treatment: (1) How would the lesion impact patient fertility? (2) What is the efficacy of surgical intervention? (3) What are additional clinical indications associated with the presence of myoma? The current practice for myoma treatment is presented in Table 1.

The recurrent of myoma uteri after treatment[16]

Surgical treatments: Candiani and his group found overall 10-year cumulative new appearance rate at 27 percent. Diagnostic tool in their study was clinical examination with ultrasound confirmation. The new appearance of myomas from both laparoscopic and abdominal approaches were not statistically significant. Malone reported the subsequent surgery rate among single and multiple myomectomy at 11 and 26 percent during an average of 7.6 years follow-up period, respectively.

Other treatment methods: There were limited recurrence rate data among women who initially underwent non-surgical treatment, namely medical and radiological intervention treatments.[16] GnRH agonist, SPRMs and AIs were medical treatments which caused temporary myomas' size reduction. However myoma would return

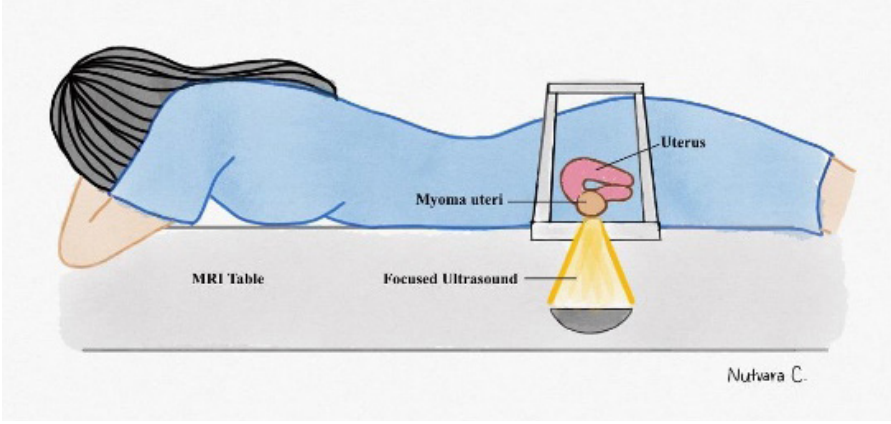

Fig 3. Magnetic Resonance-Guided Focused Ultrasound Surgery (MRgFUS)

TABLE 1. Current recommended practice for the treatment of myomas.

Type	Indication for surgical treatment			Recommendations
	Impact	Effectiveness	Additional	
Submucosal	A	B	AUB	Hysteroscopy
Intramural				
> 4 cm	A	C	PPC, S	Laparoscopy
< 4 cm	D	D	D	Expectant[a]
Subserosal	E	E	PC	Expectant[b]

Impact: Impact on reproductive potential, Effectiveness: effectiveness of surgical intervention, Additional: additional indications, Submucosal: type 0-2, Subserosal: type 5-7, A: significant impairment, B: significant improvement, C: improvement that needed further evidence, D: unclear, E: no significant, AUB: abnormal uterine bleeding, PPC: potential pregnancy complications, S: symptomatic myoma, PC: potential complications, Hysteroscopy: excision via hysteroscopy, Laparoscopy: excision via laparoscopy (preferable), Expectant: expectant management, [a] : Surgery indicated only in cases of multiple IVF failures or poor obstetrical outcome, [b] : Surgery indicated only in the presence of associated symptoms or poor obstetrical outcome.

to its original size when medication was stopped. The use of these agents would be recommended only for preoperative myomectomy but not for any definitive treatment. Radiological intervention treatment was appropriated for women who were not fit for surgery. Radiological hazard made the method not suitable for the women who needed future fertility function. The use of any non-surgical treatment should be under the physician's consideration on a case by case basis.

CONCLUSION

The evidence regarding the effect of myomas on infertility and reproductive outcomes is weak and largely inconclusive. In infertile patients, appropriate evaluation and classification of myomas is important. Submucosal myoma (FIGO L0-L2) should be treated hysteroscopically (or laparoscopic for large L2) to improve conception rates. The management of any intramural myomas should be an individualized case. Subserosal myomas impact on fertility are rather insignificant. Conservative treatment measures (medical, UAE and MRgFUS) should not be routinely offered to women who wish to maintain or improve their fertility due to lack of safety and efficacy data.

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