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Uterine Fibroids in the Setting of Infertility: When to Treat, How to Treat?

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Abstract
Purpose of Review We aim to provide insight on the treatment of fibroids in the infertile patient. Specifically, we discuss which fibroids, based on size and location within the uterine wall, have the most impact on fertility outcomes. In addition, we demonstrate which methods are best for treatment of fibroids in the infertile patient, focusing on minimally invasive techniques.
Recent Findings Current research demonstrates that, in addition to submucosal fibroids, also intramural fibroids can have a negative impact on fertility via molecular and mechanical disruption of the endometrium and of normal uterine peristalsis. Certain intramural fibroids should be considered for removal or treatment in the infertile patient, depending on size and patient history. We also provide a large body of evidence demonstrating the safety and clinical advantages of minimally invasive techniques, such as hysteroscopy, laparoscopy, and robot-assisted laparoscopy in the treatment of uterine fibroids.
Summary All submucosal and many intramural fibroids interfere with uterine function. In the evaluation of the infertile patient, accurate fibroid mapping within the uterus is essential to identify those submucosal and intramural fibroids that are likely to have the most impact of fertility outcomes. The mainstay of treatment is surgery for those fibroids with the most detrimental impact. Nonsurgical alternatives such as magnetic resonance-guided focused ultrasound (MRgFUS) and radiofrequency volumetric thermal ablation (RFVTA) need further validation before their widespread adoption in infertile patients.

Keywords Fibroids · Leiomyoma · Infertility · Myomectomy · Intramural fibroids · Submucosal fibroids

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Introduction

The contributory role of uterine fibroids in the etiopathogenesis of infertility has long been debated. Their presence among reproductive age women is particularly common, with an estimated 20–40 % women harboring one or more of these benign solid tumors [1]. By age 40, approximately 50 % of women have fibroids, and by menopause, almost 70 % of white women and 80 % of African American incur this pathology [2•, 3]. Literature from the 1980s estimated that fibroids existed in 5–10 % of infertile women by physical examination, but only 2–3 % of subfertility could be attributed to their presence [4]. In the last 30 years, we have advanced our diagnostic ability through ultrasonography and magnetic resonance imaging (MRI), with more recent literature estimating 12.6 % of women undergoing IVF treatment and over 25 % of older women receiving donated oocytes have fibroids [5]. The impact of fibroids on fertility is becoming increasingly relevant given that since 2007, the largest increase in birth rates (15 %) is seen in women aged 40–44 years and is at its highest rate since 1966 [6]. This is a fundamental concept in modern gynecological care: we now diagnose more fibroids in more women who have not yet completed childbearing. The conundrum of when, and to what extent, to intervene to remove this pathology has become one of the most common in our practice. Patient counseling is complex, and it must be based on updated clinical and scientific knowledge. Indeed, even if conservative surgery for uterine fibroids is generally considered to be one of the most complex in gynecology, it is correct patient counseling that is the hardest to provide.

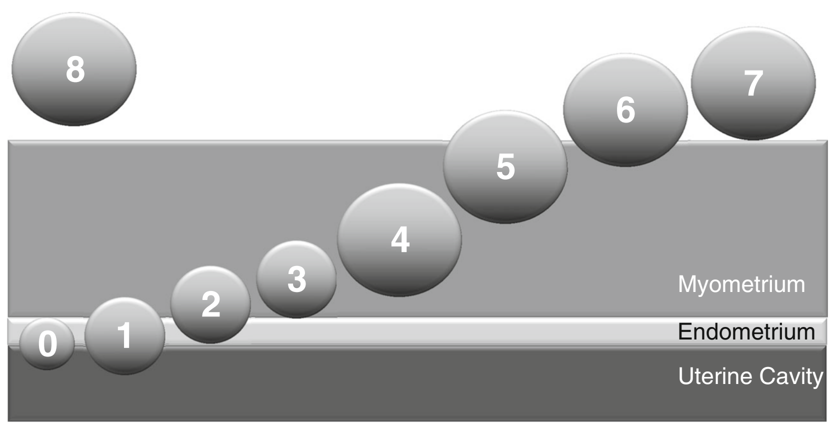
With our advances in the diagnosis of fibroids through imaging, we have expanded our understanding of how fibroids may affect fertility through molecular and genetic mechanisms and physiologic changes. Most importantly, we have elucidated which fibroids have the most impact on reproductive outcomes by evaluating their specific location within the uterine wall and size. With the advent of the International Federation of Gynecology and Obstetrics (FIGO) classification system, we are able to better study and delineate different subtypes of fibroids (Fig. 1) [7•]. Along with updates on the above topics, we describe in this review the most effective treatment of fibroids for reproductive outcomes, emphasizing minimally invasive approaches. In this advancing field, we have still not answered all the questions regarding fibroids and infertility with finality but have improved upon our ability to know when to treat and how to treat.

Mechanisms of Action: Molecular and Physiologic Effects of Fibroids

The explanation for the detrimental effect of uterine fibroids on fertility and pregnancy outcome has long remained elusive, until molecular research began describing specific changes in the endometrium of women with fibroids. The homeobox-containing transcription factor essential for embryonic uterine development and endometrial receptivity, *Hoxa10*, has been found to be critical for implantation and is expressed throughout the menstrual cycle in humans. In *Hoxa10* deficient mice, embryos are produced and can implant in wild-type surrogates, but these same embryos are unable to obtain successful implantation in *Hoxa10* deficient mouse uteri [8]. In 2010, Rackow et al. described substantially decreased *Hoxa10* mRNA in endometrial biopsies from women with submucosal fibroids compared to women without fibroids in the proliferative stage of the menstrual cycle. Endometrial tissue from women with intramural fibroids showed a trend towards less *Hoxa10* mRNA, which was not statistically significant [9]. A more recent study in 2016 by Makker et al. analyzed biopsies from mid-secretory endometrium in women with a single intramural fibroid (mean size 5.57 ± 0.37 cm) alongside fertile controls, looking at *Hoxa10* and *Hoxa11*, which have both been described as endometrial receptivity markers. Those participants with an intramural fibroid had a significant decrease in *Hoxa10* mRNA [10]. Three months after myomectomy for intramural fibroids, Hoxa10 and Hoxa11 mRNA expression in endometrial tissue has also been shown to increase 12.8- and 9.0-fold, respectively [11].

Other studies have investigated bone morphogenetic protein 2 (BMP-2), a growth factor regulating cell proliferation and differentiation found to be critical to endometrial decidualization. Endometrial stromal cells (ESC) isolated from 12 women with either submucosal or intramural fibroids were found to secrete threefold less BMP-2 than ESC from healthy controls [12]. These recent studies demonstrate that both submucosal and intramural fibroids alter the molecular make-up of the endometrium, largely decreasing the production of endometrial factors important for implantation. One important factor to consider when looking at these studies is that FIGO type 3 myomata, which touch the endometrium but not enter the

Fig. 1 FIGO classification of uterine fibroids



Submucosal: Type 0 (peduculated), Type 1 (≥50% intracavitary), Type 2 (≤50% intracavitary)
Intramural: Type 3 (contacts endometrium), Type 4 (intramural), Type 5 (subserosal, ≥50% intramural), Type 6 (subserosal, ≤50% intramural)
Subserosal: Type 7 (subserosalpedunculated)
Other: Type 8 (specify: e.g. cervical, parasitic, etc.)

Redrawn from Munro, MG et al. IntJ GynecolObstet2011 endometrial cavity, are usually considered as part of the intramural myoma population but are probably a different condition altogether. They are likely more similar to FIGO types 0, 1, and 2 under the standpoint of the molecular impact on the overlying endometrium. Future studies will have to focus on FIGO type 3 myomata as a unique and separate entity.

Another theory to explain the deleterious effect of fibroids on reproductive outcomes focuses on the altered contractility and mechanics of the uterus. Specifically, alterations in blood flow, lower resistance index (RI), and pulsatile index (PI) have been found in women with fibroids distorting the cavity on day of embryo transfer. This alteration was also correlated with decreased clinical pregnancy rate compared to women with non-cavity-distorting fibroids [13]. Along with vascular changes, abnormal peristalsis of the uterine wall has been detected in uteri with fibroids, not just cavity-distorting fibroids. In the normal nonpregnant uterus, peristaltic waves run from the fundus to the cervix to clean out the cavity in the early follicular phase. In the late follicular phase and periovulatory phase, peristalsis occurs in the opposite direction, from the cervix to the uterus, likely for transport of sperm to the fallopian tube. Finally, in the mid-luteal phase, the uterus appears to slow down peristaltic movements to facilitate embryo implantation [14]. Two studies have utilized ultra-fast MRI to compare fibroid uteri with normal uteri and have found abnormal peristaltic patterns. Specifically, uterine peristalsis was significantly decreased in women with fibroids, supporting the theory that fibroids prevent "subtle wave conduction" in myometrial muscle [15]. In addition, uterine peristalsis was noted during the mid-luteal phase or "implantation window" in women with fibroids whereas was absent in controls [16]. Yoshino et al. found that women with fibroids who exhibited high levels of uterine peristalsis during the implantation window (luteal phase days 5–9) and who subsequently underwent myomectomy ceased to have abnormal peristalsis. These previously infertile women (n = 15) who had a myomectomy and resumed normal uterine peristalsis attempted conception after surgery with a 40 % success rate [17]. Current research suggests that fibroids, including intramural fibroids, alter the physical environment of the uterus, making it much more difficult for implantation to occur due to abnormal vascular flow and peristaltic movement.

Fibroids and Infertility: Location Matters

The location of the fibroid within the uterine wall has been a critical part of deciding whether or not to treat in the setting of infertility. Several studies have tried to elucidate which fibroids need treatment in the setting of infertility, but their findings are often disparate, largely due to methodologic flaws such as small sample size and inconsistent diagnostic imaging and evaluation of the uterine cavity [18•]. Another factor in the often contradictory literature regarding which fibroids should be treated stems from the fact that infertility is often multifactorial, and fibroids might be just one of many variables impeding conception in a given couple. Utilizing the FIGO classification for myomas [Fig. 1], we are making steps to advance our understanding which fibroids have the most effect on implantation and are getting closer to outlining a more definitive treatment algorithm for fibroids in the setting of infertility.

Submucosal Fibroids (FIGO 0–2)

The most definitive research involves the effect of submucosal (FIGO 0–2) fibroids on infertility. Three systemic reviews in the last decade have all demonstrated that submucosal fibroids are associated with infertility [5, 18•, 19]. Klatsky et al. in 2008 showed that submucosal fibroids had the strongest association with lower ongoing pregnancy rates, compared to other types of fibroids, with an odds ratio (OR) of 0.5 and 95 % confidence interval (CI) of 0.3–0.8. Specifically, implantation rates decreased from 11.5 to 3.0 % and ongoing pregnancy rates decreased from 30 to 14 % in women with submucosal fibroids. Miscarriage rates for this group were also increased from 22 to 47 % [5]. In the largest systematic review to date, Pritts et al. in 2009 confirmed that clinical pregnancy rate, implantation rate, and ongoing pregnancy/live birth rate were all significantly decreased by submucous fibroids, while spontaneous abortion rate was increased [18•]. Lastly, Somigliana et al. in 2011 showed that submucosal lesions appear to strongly interfere with the chance of pregnancy with the OR (95 % CI) for conception and delivery at 0.3 (0.1–0.7) and 0.3 (0.1–0.8), respectively. What is lacking in these studies is the separate analysis of FIGO type 3 fibroids (abutting but not entering the endometrial cavity) [19]. Given the new molecular data implicating both submucosal and intramural fibroids having deleterious effects on the endometrium, no doubt these FIGO type 3 fibroids would also negatively impact implantation.

Unfortunately, the one randomized matched control trial evaluating removal of submucous myomas on pregnancy rates was published in 2010 but retracted in 2011 [20]. We have yet to see other prospective randomized trials published in this area, but given the strong and consistent data from retrospective and observational studies in the last decade, we recommend removal of submucosal fibroids in the setting of infertility or recurrent pregnancy loss.

Intramural (FIGO 3–5) and Subserosal Fibroids (FIGO 6–7)

Early literature from the 1990s repeatedly found that intramural fibroids did not affect clinical pregnancy rates. In fact, a meta-analysis in 2001 by Pritts et al. failed to find an adverse effect on pregnancy rates in women with fibroids not encroaching on the endometrial cavity [21]. When Pritts et al. reanalyzed this subgroup in a 2009 systematic review of 23 studies, intramural fibroids did in fact negatively affect implantation rate, ongoing pregnancy/live birth rate, and increased spontaneous abortion rate [18•]. Subserosal fibroids have never been linked to infertility, with a systematic review of 11 trials in 2007 evaluating the effect of subserosal tumors, demonstrated no effect on clinical pregnancy rates or delivery rates [22]. Sunkara et al. in a 2010 systematic review focused on 19 observational studies focusing on intramural fibroids and found a significant decrease in the live birth (RR = 0.79, 95 % CI 0.70–0.88) and clinical pregnancy rate (RR = 0.85, 95 % CI 0.77–0.94) in women with these fibroids [23]. In conclusion, more recent literature has affirmed that intramural fibroids do have an adverse effect on fertility.

The debate still remains regarding the tumor size at which intramural fibroids have the most negative effect on fertility. In 2004, Oliveira et al. compared 245 women with intramural fibroids to healthy controls undergoing IVF-ICSI and found that when fibroids were >4 cm, there were significantly lower pregnancy rates [24]. Guven et al. in 2013 in a similar study found that intramural fibroids negatively affected implantation, with the mean fibroid diameter in his study population at 4.96 ± 1.3 cm [25]. Most recently, Yan et al. in 2014 found that when the largest diameter of the fibroid was >2.85 cm, clinical pregnancy rate was not affected but delivery rate was [26]. Somigliana et al. in 2011 published that small intramural fibroids (mean diameter in his study was 2.2 ± 1.0 cm) did not impact clinical pregnancy rate or delivery rate [19]. Previous literature had found that fibroids >5 cm also affect birth outcomes, causing increased risk of prematurity, fetal malpresentation, and labor dystocia [27]. Given the convincing data regarding intramural fibroids, we recommend removal of these fibroids when they are >4 cm in the setting of infertility or failed ART cycles. Although data is less convincing, it might not be unreasonable to remove intramural fibroids >2.85 cm in the setting of recurrent pregnancy loss or multiple failed cycles with transfer of high-quality or euploid embryos.

Surgical Treatment of Fibroids

Myomectomy is the mainstay of fibroid treatment in symptomatic women wishing to preserve their fertility. It is also the chosen treatment if fibroids are thought to be affecting a woman's fertility. Although evidence is mounting that both submucosal and intramural fibroids affect fertility, we lack definitive studies to indicate myomectomy improves a woman's ability to conceive. This is largely due to the heterogeneity of studies and nonrandomized nature of the literature at the present time. In 2012, a Cochrane review examined the surgical treatment of fibroids for subfertility found there was, "currently insufficient evidence from randomized controlled trials to evaluate the role of myomectomy to improve fertility" [28]. More recently, a Cochrane review in 2015 examining the effect of hysteroscopy in treating subfertility for uterine cavity anomalies concluded that a large clinical benefit cannot be excluded given that if 21 % of women with fibroids achieve a clinical pregnancy having timed intercourse only, with evidence suggesting that 39 % of women will achieve pregnancy after hysteroscopic fibroid removal [29]. The only well-controlled prospective (though nonrandomized) trial by Buletti et al. in 1999 suggests a beneficial role of laparoscopic surgery in fibroid removal. Women with 1–5 intramural fibroids (with at least one >5 cm) who underwent myomectomy had clinical pregnancy rates of 33 %, compared to 15 % in women who did not have surgical intervention [30].

Although multiple reviews on fibroids and infertility agree that submucosal fibroids should be removed, they caution against the removal of intramural fibroids purely for infertility purposes, citing lack of evidence [31, 32]. We recommend that each case be evaluated individually. A recent study from Japan found that the beneficial effect on fertility with conservative treatment of submucosal and intramural fibroids plateaued at 1 year [33]. Given that reproductive age is still the most important determinant of successful live birth, we recommend myomectomy be performed sooner rather than later in women with intratumoral fibroids >4 cm with decreased ovarian reserve or advanced maternal age. At the same time, decision making regarding when to operate should only be done after thorough preoperative evaluation, and it is often dictated by the clinical presentation. All data and controversies aside, we must be intellectually honest and agree that basically every gynecologist in the world will look at the same exact 5-cm intramural myoma as an "innocent bystander" in a 28-year-old woman with a year of unsuccessful attempts at conception but as a "likely contributor to implantation failure" in a 38-year-old who failed two euploid embryo transfers: same tumor, same species, different clinical scenarios. This should bring all of us to pause and drop our personal biases when faced with these clinical scenarios. In the age of patient-centered, personalized, medicine, the decision is the patient's. And the patient needs solid, simplified, data to make the decision. Communication of data in simple fashion is not easy, nor fast, and requires adequate imaging, for a start. We have long been strong advocates of high-quality pelvic imaging to assist in our surgical strategy: MRI is the imaging of choice for uterine fibroids, followed by high-quality 3D ultrasonography and sonohysterography, limited to smaller pathology [34•, 35] (Fig. 2). We make extensive use of MRI imaging in our counseling sessions, given their operator independent nature, which allows every person with basic knowledge of human anatomy to actually understand the relative size and location and tissue distortion caused by their tumors.

The decision whether to perform a hysteroscopic myomectomy versus a laparoscopic or robot-assisted laparoscopic

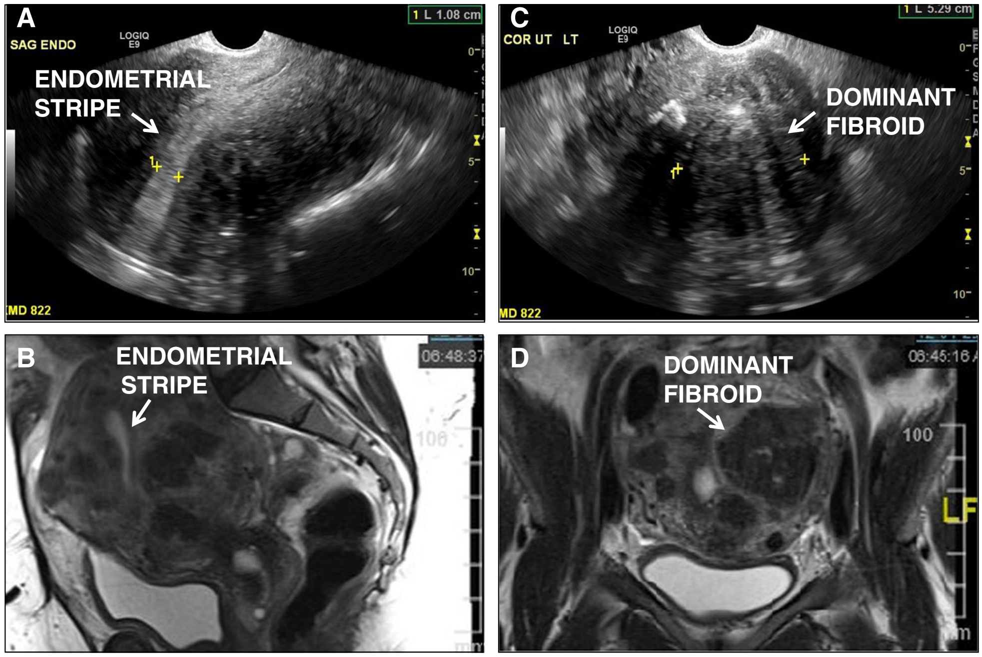


Fig. 2 Comparison of ultrasound and MRI in the diagnosis of fibroids in the same patient. **a** Ultrasound with depiction of endometrial strip. **b** MRI with depiction of the endometrial stripe and surrounding fibroids. **c** Ultrasound image of dominant fibroid. **d** Coronal view of MRI showing clear delineation of dominant fibroid as well as multiple other fibroids

myomectomy depends on thorough imaging. Transvaginal ultrasound (TVUS) is our first-line imaging modality, best done cycle days 5–9, for a detailed evaluation of the uterus [36]. TVUS has its limitations in that it cannot capture multiple large fibroids in the same plane (Fig. 2). We recommend utilizing ultrasound for imaging of relatively small uteri (contained within the bony pelvis) with four or fewer fibroids. Saline sonohysterograms and office hysteroscopy are particularly helpful in delineating intrauterine pathology [37]. With regard to when to operate with intramural fibroids, MRI has proven to be the most sensitive in detecting submucosal fibroids [38]. In addition, MRI is more reproducible compared to TVUS, which is provider dependent [39]. MRI allows for adequate fibroid mapping, enabling surgeons to plan the route of fibroid removal, and excludes non-fibroid pathology such as adenomyosis. The decision to proceed with surgery for infertility purposes should also be done with generous counseling reviewing the risks and limitations of undergoing surgery, with the knowledge that it might not improve fertility (or ART outcome) in some cases.

Hysteroscopic Myomectomy

Fibroids with the FIGO classification 0, 1, or 2 have the optimal pathology for hysteroscopic resection. Limits of fibroid size depend on the comfort and experience of the operator, with most sources recommending the limit for hysteroscopic resection at 5 cm [40•]. Given hysteroscopic fluid limits, there might need to be an interval resection of the fibroid (i.e., a second operation) if it cannot be safely removed in one sitting [40•]. When comparing the instrumentation of hysteroscopic fibroid removal, one recent meta-analysis compared hysteroscopic intrauterine morcellator (first described in 2005) versus the more traditional hysteroscopic resectoscope which has been used since the 1970s [41]. Shazly et al. found that hysteroscopic morcellation was associated with less incomplete removal of the fibroid and shorter operating times, although studies were small and meta-analysis was limited by heterogeneity [42]. At this time, we recommend that gynecologic surgeons employ the hysteroscopic device they have the most comfort with, until more concrete data demonstrates superior efficacy for one method versus the other.

Hysteroscopic myomectomy (HM) has the potential to cause further uterine cavity distortion with the formation of intrauterine adhesions (IUA). The patients with the highest risk of forming IUA are those that have hysteroscopic resection of two submucosal myomas that are opposing one another. One small study found that out of nine patients with two or more apposing submucous myomas undergoing diagnostic office hysteroscopy after surgery, seven (78 %) had IUA [43]. Another study found that IUA were found in 31.3 % of patients after removal of a solitary fibroid and in 45.5 % of patients after removal of a multiple intracavitary fibroids [44]. Meanwhile cold resection, without thermal energy, for small fibroids has been reported as having a 4 % rate of postsurgical adhesions [45]. If the size of the fibroid and/or bleeding during the surgery necessitates use of thermal energy, we recommend to use the least amount possible, with the goal to maintain as much normal endometrium as possible. In addition, an early postoperative look with office hysteroscopy, 2–4 weeks after myomectomy surgery, has been shown to be a preventative as well a therapeutic strategy to prevent long-lasting intrauterine adhesions [46]. We recommend this be a prerequisite before commencing infertility treatments.

Minimally Invasive Myomectomy: Laparoscopic Versus Robot-Assisted Laparoscopic Myomectomy (RALM)

For those fibroids inoperable by hysteroscopy, namely FIGO types 3–5, and FIGO type 2 with minimal free myometrial margin, minimally invasive surgery is recommended over open abdominal surgery. A large number of studies have detailed the improved surgical outcomes seen in laparoscopic myomectomy compared to abdominal myomectomies [47]. In addition, Palomba et al. in 2007 described improved reproductive outcomes with a minimally invasive approach. Those women undergoing laparoscopic versus minilaparotomic myomectomy were found to have higher cumulative pregnancy rates in the laparoscopic group (52.9 %) versus the mini-laparotomy group (38.2 %) [48•]. Similarly, a 2006 retrospective study looked at obstetric and delivery outcomes after laparoscopic myomectomies reported 158 pregnancies and no uterine ruptures during deliveries [49]. The risk of uterine rupture with laparoscopic myomectomies has been reported as quite low, with only one reported rupture in 2000 cases over 6 years [50]. Furthermore, analysis of cases of uterine rupture has been attributed to overuse of electrocautery and inadequate closure of the myometrial defect [40•, 51]. It appears that laparoscopic myomectomies may improve fertility over abdominal myomectomies, and there is no evidence that they have a negative impact on obstetric outcomes.

Laparoscopic surgery has made advances in terms of surgical and reproductive outcomes but is ergonomically challenging and technically difficult—and has yet to become widely adopted [52]. The introduction of RALM has enabled more surgeons to provide minimally invasive myomectomies to patients given its relatively fast learning curve [53]. Reproductive outcomes have consistently demonstrated the importance of incorporating RALM in the armamentarium of fibroid removal techniques in the setting of infertility. In women who underwent RALM for deep, symptomatic fibroids and unexplained infertility, the pregnancy rate after recovery was reported to be as high as 68 % [54]. In a 3-year follow-up after RALM surgery for the purpose of infertility, the pregnancy rate was 80 % in symptom-free patients [55]. RALM may also allow for a finer dissection of the fibroid tumor, with preservation of its pseudocapsule. A true intracapsular myomectomy has been shown to be critical for myometrial healing [56•]. Regardless of whether conventional or robot-assisted laparoscopy are utilized, we recommend attempting fibroid removal with a minimally invasive approach whenever safely feasible, to maximize reproductive outcomes and patient recovery.

Medical Therapy: Presurgical Treatment

Preoperative treatment with gonadotropin releasing hormone agonists (GnRH-a) and selective progesterone receptor modulators (SPRMs) has been proposed to shrink the size of the fibroid prior to HM. Studies utilizing pretreatment with GnRH-a 2 or 3 months prior to surgery report operating times were reduced, and there was decreased hysteroscopic fluid resorption [57, 58]. SPRMs have also been used prior to HM and have demonstrated reduction in size of fibroids and decreased vaginal bleeding preoperatively [59]. When SPRMs (ulipristal acetate) and GnRH-a were compared head to head, there was no difference in operative time, amount of resection completed, or fluid deficit in hysteroscopic procedures [60].

In laparoscopic myomectomies, GnRH-a and SPRMs have also demonstrated utility in presurgical treatment. Most recently, a 3-month pretreatment with ulipristal acetate decreased intraoperative blood loss, hemoglobin drop, need for postoperative blood transfusion, and length of surgery compared the no pretreatment arm [61]. Similarly, Chang et al. found that pretreatment with GnRH-a analogue reduced intraoperative blood loss, operating time, formation of pelvic hematomas, and need for blood transfusion [62]. More studies are needed to confirm these findings and pharmacologic doses, but these medications have a potential to make surgeries less challenging and safer for patients.

Alternatives to Surgical Treatment

Uterine Artery Embolization

Since the 1990s, uterine artery embolization (UAE), whereby the fibroids shrink due to blockage of arterial blood flow and its resulting necrosis, has been touted as a surgical alternative to myomectomy. The procedure utilizes fluoroscopic guidance to pass a catheter from the femoral vessels to the uterine arteries where embolizing agents are then released. This therapy leads to shrinkage of the dominant fibroid by about −40 %, and about 80 % of women have relief of symptoms such as menorrhagia, dysmenorrhea, and bulk symptoms by 11 months post-procedure [63]. When comparing surgery versus UAE, a Cochrane meta-analysis from 2014 found that there were no differences in major complications between the two procedures; however, UAE had a higher likelihood of having minor complications and requiring surgery in 2–5 years from the procedure [64]. For women of reproductive age, perhaps, most concerning is the documentation of impairment of fertility after UAE. Although there are documented pregnancies after UAE [65], other studies have found very low pregnancy rates, with only 1 documented pregnancy out of 31 women with severe symptomatic fibroids, which ultimately failed to result in a live birth [66]. A randomized controlled trial comparing surgery versus UAE found that 2 years out from either procedure patients who had myomectomies had higher pregnancy rates (78 vs 50 %) and lower miscarriage rates (23 vs 64 %) [67]. Given the data indicating decreased fertility after UAE, the first-line treatment for fibroids in women desiring to conceive is myomectomy. Patients of reproductive age who desire UAE need to be counseled extensively about the risks of decreased fecundity and poor obstetric outcomes [68].

Magnetic Resonance-Guided Focused Ultrasound

Other noninvasive fibroid-removing techniques include the magnetic resonance-guided focused ultrasound (MRgFUS) fibroid treatment. In 2004, the ExAblate® 2000 device (InSightec, Haifa, Israel) received U.S. FDA approval for fibroid treatment. Focused ultrasound therapy causes thermal injury of the fibroid tissue by absorption of sound wave energy, vibratory effects, and cavitation through generation of microbubbles [2•]. A T1-unenhanced and gadolinium-enhanced MR imaging study is performed to calculate the degree of ablation or "nonperfused volume." There is a lower likelihood of needing further treatments if the "nonperfused volume" is >50–60 %. With just >30 % "nonperfused volume" achieved, patients report improved symptom control and greater reduction in fibroid volume [69]. Although study patients report improved symptom control, the maximal reduction in fibroid size at 12 months is only approximately 25 % [70]. The effects on pregnancy and fertility are still being studied but there appears to be successful reproductive outcomes after MRgFUS. A prospective registry of all known pregnancies after MRgFUS treatment for conservative treatment of clinically significant fibroids maintained by the manufacturer revealed 54 pregnancies in 51 women with live births in 41 % of pregnancies and a 28 % miscarriage rate. Fifty-seven percent of the pregnancies had no neonatal or maternal complications [71]. Although further research still needs to be done to verify the safety of MRgFUS in reproductive age women, the results appear promising for nonsurgical treatment of fibroids.

Laparoscopic Radiofrequency Volumetric Thermal Ablation

The newest noninvasive treatment of fibroids is laparoscopic radiofrequency volumetric thermal ablation (RFVTA) which was approved in 2012 for patients who desired conservative treatment and quick recovery (Acessa procedure; Halt Medical, Inc., Brentwood, CA, USA) [72]. The procedure occurs under laparoscopic guidance where an ultrasound probe delineates fibroids and real-time imaging monitors insertion of the electrodes into the fibroids, resulting in fibroid ablation [72]. Outcomes of initial studies report sustained relief from fibroid symptoms and improvement in quality of life during the 36 months after ablation. In addition, only 11 % of patients at 36 months needed repeat intervention [73]. In a randomized controlled trial, outcomes of laparoscopic myomectomy to RFVTA improvements in the severity of symptoms were shown to be significantly improved in both groups [74]. Despite the requirement that women enrolled in early premarket RFVTA studies were to have completed childbearing, nine women were between ages 31 and 40 years of age. Six subjects became pregnant within 15 months of treatment, with five having successful live births and one miscarrying [75]. Larger studies are needed to confirm the efficacy and safety of this fibroid treatment, but initial studies are promising for the treatment of fibroids in the setting of infertility.

Conclusion

Our understanding of how and why fibroids contribute to infertility and adverse pregnancy outcome has vastly grown. We have clearly identified submucosal fibroids as having the most direct and negative effect on implantation. While our data on the impact of intramural fibroids on fertility is more recent, there is now no doubt that they too can affect the endometrium at a molecular level and physically disrupt uterine peristalsis. Moreover, through the compilation of studies, we have determined that certain intramural fibroids above 4 cm are very likely to be detrimental to fertility. Treatment modalities for fibroids have vastly improved as well. Hysteroscopic myomectomy, a routine surgery in general gynecology, has proven to enhance pregnancy rates when cavity-distorting fibroids are removed. Advances in minimally invasive surgery, employing RALM, have demonstrated successful reproductive outcomes and are poised to be adopted more widely than laparoscopy myomectomy, due to their ergonomic advantages. Employment of GnRH-a analogues and SPRMs has improved surgical outcomes by allowing reliable shrinkage of fibroid tumors, making both hysteroscopic and laparoscopic operations more often feasible. New technologies such as MRgFUS and RFVTA have emerged as possibilities in the nonsurgical treatment of fibroids, although their safety in the reproductive age patient has yet to be confirmed and is needed before their widespread adoption. The most recent evidence allows us to give clearer guidelines on when to treat and how to treat fibroids. For now, surgery remains the gold standard for fibroid removal for infertility treatment.

Compliance with Ethical Standards

Conflict of Interest Erin I. Lewis declares no conflicts of interest.

Antonio R. Gargiulo is a consultant for Medicaroid, which builds robotic equipment for medical use, and a consultant for OmniGuide Holdings, which builds laser and ferromagnetic energy tools for medical use.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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