Published in final edited form as:
Obstet Gynecol Clin North Am. 2012 December ; 39(4): 521–533. doi:10.1016/j.ogc.2012.09.005.

The Impact and Management of Fibroids for Fertility: an evidence-based approach

Xiaoxiao Catherine Guo, B.S. and **James H. Segars, M.D.**
Program in Reproductive and Adult Endocrinology, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, Bethesda, MD, 10 Center Drive, Building 10 CRC 1-3140, MSC 1109, Bethesda, MD 20892-1109, (301) 496-5800

Xiaoxiao Catherine Guo: Catherine.guo@nih.gov

Keywords

Leiomyoma; Infertility; Assisted Reproductive Technology (ART); Myomectomy; Hysteroscopy; Minimally Invasive Gynecologic Surgeries (MIGS); Magnetic Resonance guided Focused Ultrasound (MRgFUS); Uterine Artery Embolization (UAE)

Introduction

Uterine fibroids, or leiomyoma, are benign tumors of the uterus that may cause severe pain, bleeding, and infertility (1). Fibroids affect a woman's quality of life, as well as her fertility and obstetrical outcomes. Fibroids affect approximately 35-77% of reproductive age-women (2-4), although the real prevalence is much higher since many fibroids may be asymptomatic. Nearing age 50, this likelihood may increase to 70-80% depending on the patient's ethnicity (3). Of particular note, Peddada et al. (5) found that fibroid growth rates declined for white women over 35 years old, but did not decline for black women of the same age. Fibroids are a public health concern and have been estimated to cost the U.S. health care system up to $34.4 billion dollars per year (6).

In this review, we examine the medical and surgical therapies that women and their providers may choose to treat uterine fibroids, paying particular attention to pregnancy rates and obstetrical outcomes. When selecting a treatment, individual patient preferences should be taken into account, such as desire for future childbearing. The fibroid location, size, and number are essential considerations.

Aside from traditional surgical therapies such as hysterectomy and myomectomy, minimally invasive gynecologic surgeries (MIGS), Uterine Artery Embolization (UAE), and Magnetic Resonance guided Focused Ultrasound (MRgFUS) are increasing in popularity. The preliminary data using these newer therapies are encouraging. However, patients should be counseled that any uterus-sparing technique has the potential for fibroid recurrence.

Corresponding Author: James H. Segars, M.D., segarsj@mail.nih.gov.

Disclosure: The authors report no conflict of interest.

Reprint Requests: James H. Segars, M.D.; Xiaoxiao Catherine Guo, B.S.

Fibroids and Infertility

Fibroids are present in 5-10% of infertile patients, and may be the sole cause of infertility in 1-2.4% (7, 8). Fibroids may cause infertility by obstructing the fallopian tubes and impairing gamete transport. It is now clear that the critical factor may be distortion of the endometrial cavity, causing abnormal endometrial receptivity, hormonal milieu, and altered endometrial development (14, 15, see below).However, the issue of whether fibroids can be the sole cause of infertility has been poorly understood (7). This is due to the lack of prospective, randomized, and controlled studies separating out other infertility factors (8). A randomized and prospective study evaluating spontaneous conception in infertile women with and without fibroids was conducted by Bulletti et al. in 1999. The authors found a significant discrepancy in pregnancy rate for infertile women (11% with fibroids versus 25% without fibroids). Removing the fibroids increased the pregnancy rate from 25% to 42%. (9) This study supports the fact that fibroids influence infertility.

Effect of Fibroids on Art

The relationship between fibroids and infertility has been elucidated through numerous studies on ART patients, which have been summarized in several meta-analyses and systematic reviews (10-13). Although abnormal gamete transfer and blockage of fallopian tubes are circumvented by assisted reproductive technologies (ART), fibroids may also compromise fertility by altering the endometrial receptivity (14, 15); thus negatively affecting embryo implantation and lowering the chances for pregnancy.

Fibroid location is of critical importance in ART outcomes (4). Submucosal fibroids, in particular, significantly reduce implantation and pregnancy rates of ART. Submucosal fibroids that distort the uterine cavity have been found to carry a relative risk of 0.3 for pregnancy and 0.28 for implantation after ART(10, 11, 16), when compared to infertile women without fibroids. Other authors have also demonstrated reduced success following ART with an odds ratio of 0.3 for conception and 0.3 for delivery in the presence of submucosal fibroids (12). The effect is not as pronounced for intramural fibroids with an odds ratio of 0.62 for implantation rate, and 0.7 for delivery rate per transfer cycle (13). Similarly, Somigliana et al. (12) determined an odds ratio of 0.8 for conception and 0.7 for delivery with intramural fibroids. Subserosal fibroids have negligible impact on fertility with ART (8, 12).

Fibroids and Pregnancy

The reported incidence of fibroids in pregnancy ranges from 0.1-10.7% of all pregnancies (17, 1819). A study by De Vivo et al. (20) reported that 71.4% of fibroids grew during the first and second trimesters, while 66.6% grew between the second and third trimesters. Fibroids during pregnancy are more likely to be encountered in patients who are 35 years of age and older, nulliparous, or African American (12, 18, 21). Although most pregnancies with fibroids are uneventful, fibroids increase the risk of pregnancy complications.

During pregnancy, fibroids may grow quickly, causing intense pain. However, fibroid regression after live birth has been demonstrated in 72% of women, with over a 50% reduction in fibroid volume between early gestation and 3-6 months postpartum (22). Women who had a miscarriage or used progestins after delivery experienced less fibroid regression (22), but this difference was not present in women who delivered by cesarean, used other hormonal contraceptives, or breastfed.

A patient with fibroids who is considering pregnancy should be evaluated with a pelvic exam, as well as an ultrasound to delineate the location and size of any fibroid(s). For

patients pursuing assisted reproduction, a pre-conception saline infusion sonogram can be extremely helpful in such cases to identify submucosal fibroids (4, 7). Alternatively, an office hysteroscopy can be used to assess the endometrial cavity. Once a patient becomes pregnant, determining the fibroid location relative to the placenta and cervical canal may be helpful in assessing the risk of placental irregularities.

Fibroids and Obstetrical Outcomes

Complications occur in approximately 10-40% of pregnancies in the presence of fibroids (23, 24). Fibroids may contribute to miscarriage, cesarean section, premature labor, malpresentation of the fetus, and postpartum hemorrhage (See Table 1). Other uncommon complications include pelvic pain due to red or carneous degeneration of the fibroid, low Apgar scores in the neonate, renal failure, fetal limb anomalies, and hypercalcemia(25). The risk of developing complications during pregnancy increases if the fibroids are over 3 cm in size. However, women with fibroids larger than 10 cm can achieve vaginal delivery approximately 70% of the time (18).

Fibroids clearly increase the risk of pregnancy loss. When compared to women without fibroids, women with fibroids in all locations have a relative risk of spontaneous abortion of 1.678 . Women with fibroids pursuing ART also have a significantly lower ongoing pregnancy/live birth rate, with a relative risk of 0.697 when compared to controls, in part due to miscarriages. Additionally, the risk of pregnancy loss correlated with fibroid location. Specifically, submucosal and intramural fibroids had notably higher rates of spontaneous abortion, and notably lower rates of live births. However, subserosal fibroids had no significant impact.(10) Multiple fibroids may further increase the miscarriage rate (11, 26).

Fibroids have also been associated with malpresentation of the fetus. An odds ratio of 3.98 for breech presentation has been calculated for women with fibroids when compared to women without fibroids (17, 23). Fetal malpresentation may increase the probability of a cesarean section, which subsequently increases the risk of maternal morbidity.

Lastly, fibroids may increase the risk of preterm labor. This is particularly true if the fibroids are large, if there are multiple fibroids, or if placentation occurs next to or overlying a fibroid. Other reports concur that fibroids increase the risk of preterm labor, but do not agree on the increase the risk of preterm birth. A 2009 meta-analysis by Olive and Pritts (10) showed no significant disparity in preterm delivery rates among patients with fibroids in all locations when compared to controls.

Medical Therapies

Current medical treatment of fibroids includes progestins, oral contraceptives (OCPs), nonsteroidal anti-inflammatory drugs (NSAIDs), tranexamic acid, and gonadotropin-releasing hormone agonists (GnRHa). Progesterone receptor agonists (PAs), selective progesterone receptor modulators (SPRMs), and aromatase inhibitors have also been investigated as alternatives to surgery. Some of these medical therapies are limited by undesirable side effects (See Table 2). Progestins, NSAIDs, and OCPs have been used off-label for temporary management of bleeding; however they are unlikely to affect fibroid volume. GnRHa reduced fibroid volume by 35-65% in 3 months (27) and induced amenorrhea, but is typically used pre-operatively to postpone surgery in a severely anemic patient or possibly to reduce uterine volume and to facilitate a vaginal approach to hysterectomy (28). More recently, Parsanezhad et al. reported that letrozole at 2.5 mg/day reduced fibroid size by 45.6% versus triptorelin, a GnRHa, which only reduced fibroid size by 33.2% (29). The anti-progestins mifepristone and ulipristal acetate also effectively induce amenorrhea and reduce fibroid volume. Donnez et al. (30, 31) recently published two studies

of ulipristal acetate as a treatment for fibroids. In one study, uterine bleeding was effectively controlled in 91% and 92% of women taking a 5 mg and 10 mg daily dose of ulipristal acetate, respectively, compared to19% in women taking placebo (31). In the second study, Donnez et al. (30) daily oral doses of ulipristal acetate (at both 5 mg and 10 mg) had comparable clinical outcomes and reduction in fibroid volume when compared to once-monthly injections (3.75 mg) of the GnRHa leuprolide acetate.. Further, this reduction was sustained for 6 months after ulipristal acetate was stopped (30). The SPRM, Asoprisnil, also causes a significant reduction in bleeding and size, and the effect appears to persist for 3 months (32, 33). It should be noted, however, that some of these agents have been associated with altered endometrial pathology. However, the long term significance of the endometrial changes is not clear at present.

An effective long-term medical therapy for uterine fibroids would reduce heavy uterine bleeding as well as fibroid/uterine volume without excessive side effects. To date, currently approved treatments only reduce symptoms temporarily and although new agents are in development, the ideal medical therapy has remained elusive.

Myomectomy

There are different approaches to myomectomy, as it can be done laparoscopically (LM), abdominally (laparotomy), robotically, or hysteroscopically. Although myomectomies have traditionally been performed by laparotomy, In 1979, the first myomectomy by laparoscopy was performed by Dr. Semm. This approach eventually became mainstream in the early 1990's. Today, minimally invasive myomectomy approaches have become the preferred approach by patients and providers alike.

Hysteroscopy

Submucosal fibroids, in particular, lend themselves well to a hysteroscopic surgical approach. Clinicians must determine the location, number, and percentage of the fibroids that is located in the uterine cavity. The Wamsteker classification system, used by the European Society of Gynaecological Endoscopy (ESGE), can be helpful in determining the probability of successful removal of submucosal fibroids by hysteroscopic myomectomy (34). Clinicians may also use the newer STEPW system proposed by Lasmar in 2005 (34). Hysteroscopic resection of submucosal fibroids offers minimal complications and rapid recovery times. Since there have been no reported cases of uterine rupture with this technique (28), patients may attempt a vaginal delivery following hysteroscopic myomectomy.

Pregnancy Rates and Obstetrical Outcomes following Myomectomy

Myomectomy is most often used for women who desire future fertility. Pregnancy rates have reached 50-60% after both LM and abdominal myomectomy, with good obstetrical outcomes (35). Myomectomy, however, does not eliminate symptoms permanently, and is associated with surgical risks and complications (e.g. loss of blood, long procedure and hospital stay, postoperative morbidity). Postoperative adhesions are of particular concern, as it is certainly possible that they may negatively impact future fertility.

Success in myomectomy depends on the location of fibroids. Intramural and subserosal fibroids are often resected using a laparoscopic or abdominal myomectomy. After undergoing an abdominal myomectomy, the risk of uterine rupture in pregnancy is low (about 0.002%). Even though the incidence of uterine rupture is lower than that after a previous cesarean (about 0.1%), patients with transmural incisions after abdominal or laparoscopic myomectomy generally undergo cesarean delivery (28).

Myomectomy is of proven benefit. In a study by Casini et al. (36), patients who underwent myomectomy for resection of submucosal fibroids had higher clinical pregnancy rates when compared to patients with fibroids that did not undergo surgery (43.3% for operated versus 27.2% for unoperated) (36). The likelihood of live births and spontaneous abortions were similar in both groups. Summarily, data from randomized and controlled studies on the subject suggest that clinical pregnancy, live birth, and spontaneous abortion rates will normalize over time in women with submucosal fibroids following myomectomy when compared to infertile women without fibroids.

Myomectomy is also beneficial for infertile patients with intramural fibroids. Casini et al. (36) found higher pregnancy rates in patients with intramural fibroids who underwent myomectomy, as opposed to those who did not (56.5% versus 41%, respectively). As stated before, subserosal fibroids are acknowledged as having little impact on fertility (7).

Effect of Myomectomy on ART outcome

As discussed previously, evidence suggests that fibroid size prior to ART can cause lower implantation rates. In patients with intramural fibroids > 50 mm, myomectomy before IVF has been shown to positively impact pregnancy outcomes (37). A study by Bulletti et al. (37) in 2004 compared 84 women who chose to undergo myomectomy before IVF with 84 women who started IVF but did not undergo surgery. The women who did undergo surgery had a 25% rate of delivery and a clinical pregnancy rate of 33%, compared to 12% and 15% in the nonsurgical group (37). This study suggested that myomectomy before ART is likely to improve pregnancy outcomes in infertile patients with submucosal fibroids, and with intramural fibroids > 5 cm (37). For subserosal fibroids, myomectomy before ART does not affect pregnancy outcomes.

Myomectomy during Pregnancy

There is currently a lack of large, randomized, and controlled studies the safety and efficacy of myomectomies during pregnancy and cesarean sections. Thus, myomectomy during pregnancy may be useful only in certain specific instances, such as early in pregnancy and when fibroids are large, growing rapidly, and causing recurrent pain. However, the risk of pregnancy complications including miscarriage or fetal loss is of paramount concern.

Recurrence and Reintervention following Myomectomy

Fibroid recurrence has been reported in 15-51% of cases up to five years after myomectomy (38). This large variability was probably due to ethnic diversity of the study groups, as well as different criteria and methods used to diagnose recurrence. In the past, the probability of a subsequent surgery was thought to be based on the patient's age during the first myomectomy, but may actually be more affected by parity as the cumulative probability of recurrence (CPR) is decreased if a woman has children after myomectomy.

GnRHa pre-treatment before Myomectomy

GnRHa treatment prior to a myomectomy has been proposed as a means to decrease fibroid volume and thus, enhance removal while reducing complications. Vercellini et al. (39) showed that GnRHa pre-treatment had negligible effects on blood loss, postoperative morbidity, hospital stay, and operating time. Others (27) have expressed concern that GnRHa pre-treatment may increase the risk of recurrence.

MRgFUS

Magnetic Resonance Guided Focused Ultrasound Surgery (MRgFUS) for leiomyoma treatment was approved in 2004 by the Food and Drug Administration (FDA). Initial results

in symptom management are encouraging, and outcomes may be enhanced by GnRHa pre-treatment (38). Rabinovici et al. (40) reported 54 pregnancies in 51 women after MRgFUS, with a mean time to conception of 8 months after procedure with a 41% live birth rate. Of the women who conceived 28% had a spontaneous abortion, 64% delivered vaginally. Of the women who delivered, there were 6.7% (1 out of 15) preterm births, 2 cases of placenta previa (9%), and 93% term births (40). Although the preliminary results are reassuring, women who become pregnant after MRgFUS should be carefully followed during pregnancy.

UAE

Uterine Artery Embolization (UAE, aka Uterine Fibroid Embolization or UFE) is a minimally invasive procedure that involves cutting off the blood supply of the fibroids. UFE was introduced by Ravina et al. in 1995 (41). In the past decade, UAE has become popular as a successful alternative to surgery. Clinical outcomes with UAE are comparable to surgery.(35). UAE offers low rates of serious complications (42-44), as well as rapid procedure and recovery times. Early studies have shown that 80-95% of patients experienced improvement in their symptoms (42). Fibroids have also been reported to shrink by about 44% in volume in 3 months (43). As of August 2008, the American College of Gynecology (ACOG) has even recognized UFE as having “level A evidence” to support that it is safe and effective in appropriately selected women (45).

Pregnancy Rates and Obstetrical Outcomes following UAE

UAE is not recommended for women with fibroids who desire future fertility, in part due to reported cases of transient and permanent amenorrhea. The reduction in menstrual flow raises the concern for endometrial damage that may contribute to abnormal placentation and/or reduced ovarian function or failure.(46) However, the incidence of amenorrhea has been found to occur in less than 5% of patients (28, 44) and is clearly exacerbated by advanced age or perimenopausal status.

Goldberg et al. (47) suggested that pregnancies after UAE are at risk for malpresentation, pre-term birth, cesarean section, and post-partum hemorrhage when compared to the general population without fibroids. Homer and Sarodigan (48) found that rates of miscarriage, cesarean section, and post-partum hemorrhage were increased after UFE when compared to control pregnancies with fibroids. Mara et al. (49) used hysteroscopy to evaluate 127 patients 3-9 months after UAE (mean age 35.1 years) and found that 59.8% of the women had an abnormal endometrium with tissue necrosis (40.9%), intracavitary myoma protrusion (35.4%), endometrium “spots” (22.1%), intrauterine synechiae (10.2%), and “fistula” between the uterine cavity and intramural fibroid (6.3%). Necrosis and/or hyalinization were found in 35.4% of patients, even though 78% were asymptomatic (49). This high rate of intrauterine pathologies after UAE may help explain the reported increased risk of in early pregnancy loss. Since UAE is still relatively new, long-term effects on fertility and pregnancy outcomes have not yet been established, and more research is needed with larger cohorts from multiple centers.

Recurrence and Reintervention following UAE

Two large randomized trials, the REST (50) and EMMY (51) trials, addressed the safety of UAE. The REST trial was composed of patients who had undergone myomectomy, hysterectomy, and UAE in the United Kingdom. Both surgery and UAE patients had similar improvements in symptoms after 5 years, but reintervention was more likely after UAE with a fibroid recurrence rate of 32%. (50) The EMMY trial, conducted in the Netherlands, compared UAE and hysterectomy, concluding that symptoms improved at similar rates for

both procedures. A reintervention rate of 28% after 5 years was noted for patients who had undergone an UAE.(51)

UAE vs. Myomectomy

Myomectomy appears to have a higher pregnancy and delivery rate than UAE or UFE. A randomized trial of 121 women conducted by Mara et al. (52) compared UFE to myomectomy. Two years after their procedures, 78% of the myomectomy group and 50% of the UFE group became pregnant (52). The delivery rate was 48% and 19% and the abortion rate was 23% and 64%, for the myomectomy and UAE group, respectively (52). Further data with longer follow up time is needed to expound upon these findings. However, Mara et al. (52) concluded that myomectomy seems to have better reproductive outcomes at least in the first 2 years. Goldberg and Pereira (35) concurred that pregnancy after UFE likely yields higher rates of preterm delivery and malpresentation (odds ratio of 6.2 and 4.3, respectively) when compared to laparoscopic myomectomy.

The spontaneous abortion rate found in Mara et al.'s study (52) was higher than those reported by the 2005 Ontario multicenter prospective trial (16.7%) (46), the 2005 retrospective trial of Carpenter and Walker (27%) (53), and the 2006 controlled retrospective multicenter trial of Goldberg and Pereira (24% after UAE, and 15% after laparoscopic myomectomy) (35). However, all of these studies point towards the possibility that pregnancies after UAE are more likely to miscarry compared to pregnancies after myomectomy.

It should be noted that four women in Mara et al.'s cohort (52) experienced reduced ovarian function. One patient had 6 weeks of amenorrhea but a normal ovarian function (FSH =6.4 IU/L) 6 months after UAE. She subsequently became pregnant. Three women had a transient ovarian dysfunction or failure with an FSH elevation (from <10 IU/L before UAE to 15.0, 30.4, and 48.9 IU/L) accompanied by 2 months of amenorrhea in one patient with no response to progesterone.

UAE vs. MRgFUS

Rabinovici et al. (40) suggested that MRgFUS's term delivery rate was higher and cesarean section rate was lower than that of UAE (93% versus 71-82%, 36% vs. 50-73%, respectively). The authors (40) also noted an increased incidence of low birth weight infants and stillbirthss in women who had undergone an UAE. These obstetrical complications have not been reported following MRgFUS. The time to conception, miscarriage rate, and placenta previa rate were comparable between MRgFUS and UAE.

Conclusion

Available treatments for uterine fibroids include medical therapies, surgery, and newer options such as uterine artery embolization (UAE) and MRI-guided focused ultrasound (MRgFUS). The proper treatment for each individual patient will depend on the patient's age and desire to retain her uterus and/or future fertility. Current evidence supports that myomectomy is still the better choice for women who desire to have a child.. Treatment selection will also be dictated by the location, size, and number of fibroid(s). For select women, fibroids size, previous surgery or operative risk, UFE or UAE may be the best approach.

Clinicians must balance the potential for symptom relief with associated complications of the procedure. Decisions are best founded on evidence-based efficacy of available treatment options for uterine fibroids keeping in mind the goal of optimizing pregnancy rates and

obstetrical outcomes in women who desire future fertility. Designing individualized management plans will ensure optimal outcomes and maximal patient satisfaction.

Acknowledgments

The authors would like to thank Dr. Alan DeCherney, MD for his mentorship and guidance, as well as the NIH, NICHD, PRAE, and IRTA program for their support.

Disclaimers: This research was supported, in part, by the Intramural Research Program in Reproductive and Adult Endocrinology, NICHD, NIH.

References

1. Walker C, Stewart E. Uterine fibroids: the elephant in the room. Science. 2005; 308:1589–92. [PubMed: 15947177]
2. Cramer S, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol. 1990; 94:435–8. [PubMed: 2220671]
3. Day Baird D, Dunson D, Hill M, et al. High Cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol. 2003; 188:100–7. [PubMed: 12548202]
4. Ezzati M, Norian J, Segars J. Management of uterine fibroids in the patient pursuing assisted reproductive technologies. Women's Health (Lond Engl). 2009; 5:413–21. [PubMed: 19586433]
5. Peddada S, Laughlin S, Miner K, et al. Growth of uterine leiomyomata among premenopausal black and white women. PNAS. 2008; 105:19887–892. [PubMed: 19047643]
6. Cardozo E, Clark A, Banks N, et al. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol. 2012; 206:211.e1–9. [PubMed: 22244472]
7. Cook H, Ezzati M, Segars J, et al. The impact of uterine leiomyomas on reproductive outcomes. Minerva Ginecol. 2010; 62:225–36. [PubMed: 20595947]
8. Donnez J, Jadoul P. What are the implications of myomas on fertility? A need for a debate? Hum Reprod. 2002; 17:1424–30. [PubMed: 12042254]
9. Bulletti C, De Ziegler D, Polli V, et al. The role of leiomyomas in infertility. J Am Assoc Gynecol Laparosc. 1999; 6:441–5. [PubMed: 10548702]
10. Pritts E, Parker W, Olive D. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril. 2009; 91:1215–23. [PubMed: 18339376]
11. Olive D, Pritts E. Fibroids and Reproduction. Semin Reprod Med. 2010; 28:218–227. [PubMed: 20414844]
12. Somigliana E, Vercellini P, Daguati R, et al. Fibroids and female reproduction: a critical analysis of the evidence. Hum Reprod Update. 2007; 13:465–76. [PubMed: 17584819]
13. Benecke C, Kruger T, Siebert T, et al. Effect of fibroids on fertility in patients undergoing assisted reproduction. A structured literature review. Gynecol Obstet Invest. 2005; 59(4):225–30. [PubMed: 15775685]
14. Rackow B, Taylor H. Submucosal uterine leiomyomas have a global effect on molecular determinants of endometrial receptivity. Fertil Steril. 2010; 93:2027–34. [PubMed: 18555231]
15. Sinclair D, Mastroyannis A, Taylor H. Leiomyoma Simultaneously Impair Endometrial BMP-2-Mediated Decidualization and Anticoagulant Expression through Secretion of TFG-β3. J Clin Endocrinol Metab. 2011; 96:412–21. [PubMed: 21084396]
16. Pritts E. Fibroids and Infertility: A Systematic Review of the Evidence. Obstet Gynecol Surv. 2001; 56:483–91. [PubMed: 11496160]
17. Coronado G, Marshall L, Schwartz S. Complications in Pregnancy, Labor, and Delivery with Uterine Leiomyomas: a Population-Based Study. Obstet Gynecol. 2000; 95:764–769. [PubMed: 10775744]
18. Qidwai G, Caughey A, Jacoby A. Obstetric Outcomes in Women with Sonographically Identified Uterine Leiomyomata. Obstet Gynecol. 2006; 107:376–382. [PubMed: 16449127]

19. Laughlin S, Baird D, Savitz D, et al. Prevalence of Uterine Leiomyomas in the First Trimester of Pregnancy: An Ultrasound-Screening Study. Obstet Gynecol. 2009; 113:630–5. [PubMed: 19300327]
20. De Vivo A, Mancuso A, Giacobbe A, et al. Uterine myomas during pregnancy: a longitudinal sonographic study. Ultrasound Obstet Gynecol. 2011; 37:361–365. [PubMed: 20922776]
21. Stout M, Odibo A, Graseck A, et al. Leiomyomas at Routine Second Trimester Ultrasound Examination and Adverse Obstetric Outcomes. Obstet and Gynecol. 2010; 116:1056–1063.
22. Laughlin S, Hartmann K, Baird D. Postpartum factors and natural fibroid regression. Am J Obstet Gynecol. 2011; 204:496. [PubMed: 21492823]
23. Ouyang DW, Economy KE, Norwitz ER. Obstetric complications of fibroids. Obstet Gynecol Clin North Am. 2006; 33:153–69. [PubMed: 16504813]
24. Exacoustòs C, Rosati P. Ultrasound Diagnosis of Uterine Myomas and Complications in Pregnancy. Obstet Gynecol. 1993; 82:97–101. [PubMed: 8515934]
25. Johnson, NL.; Norwitz, E.; Segars, JH. Fibroids: Gynecology in Practice. 1st. Oxford: Wiley-Blackwell; Management of fibroids in pregnancy. in press
26. Lee H, Norwitz E, Shaw J. Contemporary management of Fibroids in Pregnancy. Rev Obstet Gynecol. 2010; 3:20–38. [PubMed: 20508779]
27. Olive D, Lindheim S, Pritts E. Non-surgical management of leiomyoma: impact on fertility. Curr Opin Obstet Gynecol. 2004; 16:239–43. [PubMed: 15129053]
28. Stewart E. Uterine fibroids. Lancet. 2001; 357:293–8. [PubMed: 11214143]
29. Parsanezhad M, Azmoon M, Alborzi S, et al. A randomized, controlled clinical trial comparing the effects of aromatase inhibitor (letrozole) and gonadotropin-releasing hormone agonist (triptorelin) on uterine leiomyoma volume and hormonal status. Fertil Steril. 2010; 93:192–8. [PubMed: 19135657]
30. Donnez J, Tomaszewski J, Vazquez F, et al. Ulipristal Acetate versus Leuprolide Acetate for Uterine Fibroids. N Engl J Med. 2012; 366:421–32. [PubMed: 22296076]
31. Donnez J, Tatarchuk T, Bouchard P, et al. Ulipristal Acetate versus Placebo for Fibroid Treatment before Surgery. N Engl J Med. 2012; 366:409–20. [PubMed: 22296075]
32. Wilkens J, Chwalisz K, Han C, et al. Effects of the Selective Progesterone Receptor Modulator Asoprisnil on Uterine Artery Blood Flow, Ovarian Activity, and Clinical Symptoms in Patients with Uterine Leiomyomata Scheduled for Hysterectomy. J Clin Endocrinol Metab. 2008; 93:4664–71. [PubMed: 18765509]
33. Williams A, Critchley H, Osei J, et al. The effects of the selective progesterone receptor modulator asoprisnil on the morphology of uterine tissues after 3 month treatment in patients with symptomatic uterine leiomyomata. Hum Reprod. 2007; 22:1696–1704. [PubMed: 17339234]
34. Lasmar R, Xinmei Z, Indman P, et al. Feasibility of a new classification of submucous myomas: a multicenter study. Fertil Steril. 2011; 95:2773–7.
35. Goldberg J, Pereira L. Pregnancy outcomes following treatment for fibroids: uterine fibroid embolization versus laparoscopic myomectomy. Curr Opin Obstet Gynecol. 2006; 18:402–406. [PubMed: 16794420]
36. Casini M, Rossi F, Agostini R, et al. Effects of the position of fibroids on fertility. Gynecol Endocrinol. 2006; 22:106–9. [PubMed: 16603437]
37. Bulletti C, DE Ziegler D, Levi Setti P, et al. Myomas, pregnancy outcome, and in vitro fertilization. Ann N Y Acad Sci. 2004; 1034:84–92. [PubMed: 15731301]
38. Al Hilli M, Stewart E. Magnetic Resonance-Guided Focused Ultrasound Surgery. Semin Reprod Med. 2010; 28:242–249. [PubMed: 20414847]
39. Vercellini P, Trespidi L, Zaina B, et al. Gonadotropin-releasing hormone agonist treatment before abdominal myomectomy: a controlled trial. Fertil Steril. 2003; 79:1390–95. [PubMed: 12798887]
40. Rabinovici J, David M, Fukunishi H, et al. Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. Fertil Steril. 2010; 93(1):199–209. [PubMed: 19013566]
41. Ravina J, Herbreteau C, Ciracu-Vigneron N, et al. Arterial embolization to treat uterine myomata. Lancet. 1995; 346:671–672. [PubMed: 7544859]

42. Freed M, Spies J. Uterine Artery Embolization for Fibroids: A Review of Current Outcomes. Semin Reprod Med. 2010; 28:235–41. [PubMed: 20414846]
43. Spies J, Ascher S, Roth A, et al. Uterine Artery Embolization for Leiomyomata. Obstet Gynecol. 2001; 98:29–34. [PubMed: 11430952]
44. Spies J, Roth A, Gonsalves S, et al. Ovarian Function after Uterine Artery Embolization for Leiomyomata: Assessment with Use of Serum Follicle Stimulating Hormone Assay. J Vasc Interv Radiol. 2001; 12:437–42. [PubMed: 11287529]
45. American College of Obstetricians and Gynecologists. ACOG practice bulletin: alternatives to hysterectomy in the management of leiomyomas. Obstet Gynecol. 2008; 112:387–400. [PubMed: 18669742]
46. Pron G, Mocarski E, Bennett J, et al. Pregnancy after uterine artery embolization for leiomyomata: the Ontario multicenter trial. Obstet Gynecol. 2005; 105:67–76. [PubMed: 15625144]
47. Goldberg J, Pereira L, Berghella V. Pregnancy After Uterine Artery Embolization. Obstet Gynecol. 2002; 100(5):869–872. [PubMed: 12423843]
48. Homer H, Sarodigan E. Uterine artery embolization for fibroids is associated with an increased risk of miscarriage. Fertil Steril. 2010; 92:324–330. [PubMed: 19361799]
49. Mara M, Horak P, Kubinova K, et al. Hysteroscopy after uterine fibroid embolization: Evaluation of intrauterine findings in 127 patients. J Obstet Gynaecol Res. 2012; 38(5):823–31. [PubMed: 22413922]
50. Moss J, Cooper K, Khaund A, et al. Randomised comparison of uterine artery embolisation (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5-year results. BJOG. 2011; 118:936–944. [PubMed: 21481151]
51. van der Kooij S, Hehenkamp W, Volkers N, et al. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 5-year outcome from the randomized EMMY trial. Am J Obstet Gynecol. 2010; 203:105.e1–13. [PubMed: 20579960]
52. Mara M, Maskova J, Fucikova Z, et al. Midterm Clinical and First Reproductive Results of a Randomized Controlled Trial Comparing Uterine Fibroid Embolization and Myomectomy. Cardiovasc Invtervent Radiol. 2008; 31:73–85.
53. Carpenter T, Walker W. Pregnancy following uterine artery embolization for symptomatic fibroids: a series of 26 completed pregnancies. BJOG: an International Journal of Obstetrics and Gynaecology. 2005; 11:321–325. [PubMed: 15713147]
54. Klatsky P, Tran N, Caughey A, et al. Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. Am J Obstet Gynecol. 2008; 198:357–66. [PubMed: 18395031]
55. Vergani P, Locatelli A, Ghidini A, et al. Large Uterine Leiomyomas and Risk of Cesarean Delivery. Obstet Gynecol. 2007; 109:410–414. [PubMed: 17267843]
56. Rice J, Kay H, Mahony B. The clinical significance of uterine leiomyomas in pregnancy. Am J Obstet Gynecol. 1989; 160:1212–1216. [PubMed: 2658611]
57. Parker W. Uterine myomas: management. Fertil Steril. 2007; 88:255–71. [PubMed: 17658523]
58. Esteve J, Acosta R, Pérez Y, et al. Treatment of uterine myoma with 5 or 10 mg mifepristone during 6 months, post-treatment evolution over 12 months: double-blind randomized clinical trial. Eur J Obstet Gynecol Reprod Biol. 2012; 161:202–8. [PubMed: 22269473]
59. Levens E, Potlog-Nahari C, Armstrong A, et al. CDB-2914 for uterine leiomyomata treatment: a randomized controlled trial. Obstet Gynecol. 2008; 111:1129–36. [PubMed: 18448745]
60. Chwalisz K, Larsen L, Mattia-Goldberg C, et al. A randomized, controlled trial of asoprisnil, a novel selective progesterone receptor modulator, in women with uterine leiomyomata. Fertil Steril. 2007; 87:1399–412. [PubMed: 17307170]

Synopsis

Fibroids affect 35-77% of reproductive age-women. When selecting a treatment for symptomatic fibroids, the fibroid location, size, and number must be considered. In this review, we examined medical therapies, UAE, MRgFUS, and myomectomy (via hysteroscopy, laparoscopy, or laparotomy), paying particular attention to pregnancy rate, obstetrical outcomes, and post-operative outcomes. Myomectomy remains the preferred method for women with fibroid-related infertility who wish to have children or maintain fertility. Currently available medical therapies reduce symptoms in the short-term but may involve side effects when used long-term. Initial fertility studies on MRgFUS and UAE are encouraging, but RCT's are needed. At this time, UAE is not recommended for women desiring to become pregnant. Notably, recent medical advances have led to minimally-invasive approaches for women with fibroid disease. However, there is a strong demand for additional treatment options, including non-surgical and preventative medical therapies.

Key Points

1. When selecting a treatment for symptomatic uterine fibroids, the fibroid location, size, and number will often dictate the proper intervention.
2. Myomectomy is usually the best option for women desiring future fertility.
3. Currently available medical therapies for uterine fibroids reduce symptoms, but are limited and most are confined to short-term use.
4. Initial fertility studies on MRgFUS and UAE are encouraging, but RCT's need to be done. At this time, UAE is not recommended for women desiring to become pregnant.
5. Additional options for treating symptomatic uterine fibroids, including non-surgical and preventative medical therapies, are still needed.

Table 1
Risk of Obstetrical Outcomes in Women with Symptomatic Uterine Fibroids

Outcome	Increased Risk with Fibroids
Preterm Labor	1.0-4.0
Malpresentation	1.5-4.0
Placenta Previa	1.8-3.9
Placental Abruption	0.5-16.5
Cesarean Section	1.1-6.7
Postpartum Hemorrhage	1.6-4.0
Retained Placenta	2.0-2.7

* All values are OR unless stated otherwise.

* Data are from References 11, 24, 54-56.

Table 2

Summary of Current Medical Treatment Options for Women with Symptomatic Uterine Fibroids

Medications	Decreased Size/Volume	Decreased Bleeding	Side Effects	Usage
Progestins	No	Yes	Induces uterine fibroid proliferation	Off-label
OCPs	No	Yes	Minimal	Off-label
NSAIDS	No	Yes, 36% decrease found in one study (57)	Negligible	Off-label
Tranexamic acid	No	Yes		Recently approved by FDA, Can be used for women with or without uterine fibroids
GnRHa	Yes, 35-65% reduction in fibroid volume, mostly occurring in the first 3 months following treatment (27)	Yes, in 97% of patients by 6 months. However, menses resumed in most patients 4-8 weeks following discontinuation (57) Controlled uterine bleeding in 89% of patients for 3.75 mg monthly injection of leuprolide acetate (30)	Estrogen deprivation	Only pre-operatively
Mifepristone	Yes, 48.1% and 39.1% reduction in fibroid volume for 5 and 10 mg dose, respectively (58)	Yes, induced amenorrhea in 60-65% of patients (27)	Linked with endometrial thickening	Long-term use is limited by potential for endometrial hyperplasia, 28% incidence (59)
SPRMs (CDB 2914, aka ulipristal acetate)	Yes, 36% and 21% reduction in fibroid volume for 10 and 20 mg dose of CDB-2914, respectively (59) 36% and 42% median reduction in fibroid volume for 5 and 10 mg dose of ulipristal acetate, taken daily for 3 months. This reduction was maintained for 6 months in most patients (30)	Yes, amenorrhea in 81% and 90% of patients for 5 and 10 mg dose of CDB-2914, respectively (59) Amenorrhea in 73% and 82%, Controlled bleeding in 91% and 92% of patients for 5 and 10 mg dose of ulipristal acetate, respectively, taken daily for 13 weeks (31)	Linked with altered endometrial development	In Europe, ulipristal acetate is used to treat bleeding pre-operatively
SPRMs (Asoprisnil)	Yes, 36% reduction in fibroid volume for 25 mg dose of Asoprisnil (60)	Yes, suppressed uterine bleeding in 28% 64%, and 83% of patients for 5, 10, and 25 mg dose of Asoprisnil, respectively (60) Suppressed bleeding in 91% of patients for 25 mg dose of Asoprisnil taken for 12 weeks (32)	Linked with altered endometrial morphology	
Aromatase inhibitors (e.g. letrozole)	Yes, 45.6% reduction in fibroid volume (29)	No	Linked with ovarian stimulation	Off-label

*Data are from References 27, 29, 30-32, 57-60.