

# Fertility-sparing Treatment Options for Women With Symptomatic Fibroids

Hannah Mude-Nochumson, MS; Jay Goldberg, MD

## CONTINUING MEDICAL EDUCATION

### Goal

To review medical and surgical management options for symptomatic uterine leiomyomata in women who wish to retain their childbearing capabilities.

### Objectives

1. To present an overview of fibroid symptoms with regard to impact on quality of life, potential to impede conception/fertility, and possibility of causing miscarriage.
2. To discuss medical therapies for fibroids such as nonsteroidal anti-inflammatory drugs, antiestrogens, and antiprogestogens; surgical myomectomy; and uterine artery embolization.
3. To assess the impact of each fibroid treatment on future fertility.

### Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

This activity has been peer reviewed and approved by Brian Cohen, MD, professor of clinical OB/GYN, Albert Einstein College of Medicine. Review date: October 2003. It is designed for OB/GYNs.

The Albert Einstein College of Medicine designates this educational activity for a maximum of 1 hour in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she spent in the educational activity. Participants who answer 70% or more of the questions correctly will obtain credit. To earn credit, see the instructions on page 63 and mail your answers according to the instructions on page 64.

### Disclosure

The Faculty Disclosure Policy of the College of Medicine requires that faculty participating in a CME activity disclose to the audience any relationship with a pharmaceutical or equipment company that might pose a potential, apparent, or real conflict of interest with regard to their contribution to the activity. This disclosure also applies to any discussion of unlabeled or investigational use of any commercial product or device not yet approved in the United States. Ms Mude-Nochumson and Dr Goldberg each report no conflict of interest. Dr Brian Cohen reports no conflict of interest.

**F**ibroids are benign, monoclonal tumors that develop from the smooth-muscle cells of the uterus. This paper reviews various fertility-sparing alternative treatments for women with symptomatic fibroids, including drug therapies, surgical management, and uterine artery embolization.

The etiology of fibroids is unknown, but is thought to be a multistep process. The transition from normal myometrium to myoma probably begins with a single somatic mutation, followed by influences from growth factors. The most prevalent female reproductive tumor, fibroids affect approximately 20% of women over the age of 35 years. Black women are three to nine times more likely to develop fibroids than white women. Symptoms of fibroids include pelvic pain and pressure, abnormal vaginal bleeding, dyspareunia, anemia, urinary frequency, defecation disorders, and infertility.<sup>1,2</sup>

The most common of these symptoms is abnormal bleeding, occurring in 30% of patients with myomas. Several theories attempt to explain the relationship between fibroids and abnormal bleeding, one of which suggests that abnormal growth and function of the endometrial microvasculature in the tissue surrounding the myoma may account for the bleeding. Ulceration over a submucosal fibroid could also account for abnormal bleeding, but this is a rare finding. Previously, it was thought by some that the increased surface area of the endometrium caused by fibroid bulk accounted for increased menstrual bleeding. Still, the exact relationship between fibroids and abnormal bleeding remains unclear.<sup>2,3</sup>

## DIAGNOSIS

History and physical examination are the primary tools for diagnosing fibroids. Risk factors associated

**Hannah Mude-Nochumson, MS**, is third-year medical student, and **Jay Goldberg, MD**, is clinical assistant professor, in the Department of Obstetrics and Gynecology, Jefferson Medical College, Philadelphia, Pa.

## Treatment Options for Women With Symptomatic Fibroids

with the development of fibroids include age, obesity, family history, nulliparity, and race.<sup>2,4</sup> Fibroids are often detected during routine pelvic examination by an enlarged, irregular, and firm uterus. The differential diagnosis should also include pregnancy, ovarian neoplasm, and adenomyosis. If the diagnosis is uncertain, pelvic ultrasonography is the next step in diagnosis. It is important to know the size, location, and number of fibroids, as this often dictates the method of treatment. Several different methods can be employed to characterize fibroids. Ultrasonography is normally the first-line imaging method for pelvic masses. Transvaginal ultrasonography in conjunction with uterine injection of saline (ie, sonohysterography) may provide additional information regarding the endometrial cavity. The main drawbacks to this method are that the patient may experience considerable discomfort, and the physician must possess additional time and skills to perform it. Hysteroscopy, another method for evaluating submucosal uterine myomas, involves inserting a rigid scope into the uterus to directly view the distended endometrial cavity, potentially providing treatment in addition to diagnosis. For mapping and sizing of intramural and submucosal fibroids, ultrasonography seems to be more helpful than hysteroscopy.<sup>3</sup> Magnetic resonance imaging may also be an effective tool for evaluating leiomyomas, with the added benefit of improved detection of adenomyosis.

### TREATMENT DECISIONS

While some women can be managed expectantly, many symptomatic patients require treatment. Common symptoms mandating treatment of uterine fibroids include abnormal uterine bleeding, rapid growth, growth after menopause, infertility, recurrent pregnancy loss, pelvic pain or pressure, urinary symptoms or obstruction, and anemia. Endometrial biopsy should be performed to rule out endometrial hyperplasia and cancer in women over age 35 or 40 years with abnormal bleeding. As long as cancer is not a concern, the decision to treat symptomatic fibroids is mainly a quality-of-life issue. That determination certainly has different thresholds among patients, depending on their tolerance of symptoms, age, and life-style factors. Treatment options for symptomatic fibroids in women desiring preservation of fertility include medical management, myomectomy, and uterine artery embolization (UAE). As most women requiring therapy for symptomatic fibroids are in their late 30s or 40s and desire future fertility, there is a definite time element involved. Certain therapies involving delays in conception may therefore be unacceptable. Additionally,

depending on their age and individual impact on fertility, these patients may demand more proactive treatments aimed at improving fertility rather than merely relieving symptoms.

### MEDICAL MANAGEMENT

Medical management of symptomatic fibroids includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, depo-medroxyprogesterone acetate, gonadotropin-releasing hormone (GnRH) agonists, antiestrogens, antiprogestins, aromatase inhibitors, and androgens. Delays in return of fertility, eventual rebound of fibroid symptoms, potential teratogenicity, and other unwanted side effects limit the use of most of these options in women who desire fertility.

Nonsteroidal anti-inflammatory drugs, often a first-line therapy for dysmenorrhea and pelvic pain associated with fibroids, may also improve the abnormal bleeding associated with uterine fibroids. The endometrium of women with fibroids and menorrhagia contains higher levels of prostaglandins  $E_2$  and  $F_2\alpha$ . Based on this finding, it was thought that NSAIDs could treat abnormal bleeding associated with uterine fibroids through inhibition of prostaglandin synthesis. Ylikorkala et al<sup>5</sup> showed that naproxen (500 to 1,000 mg/d) for 5 days reduced menstrual bleeding by 37.5% in patients with idiopathic menorrhagia. As many bleeding problems may be polyfactorial, a trial of NSAIDs may be of benefit to certain patients.

Given that fibroid development is sensitive to estrogen, another approach is to reduce estrogen levels. The GnRH agonists mimic the hypoestrogenic state of menopause by down-regulating the hypothalamic-pituitary-ovary feedback system. Leuprolide is the most commonly used GnRH agonist in the United States. The major benefit of this therapy is that in addition to significantly reducing the menorrhagia and pain associated with fibroids, GnRH agonists also decrease the volume of uterine fibroids by 25% to 80%, with the maximum reduction reached at 12 weeks of therapy. Total regression of fibroids only occurs for smaller tumors.<sup>3</sup> Many physicians utilize GnRH agonists as a presurgical treatment to correct anemia, reduce fibroid volume, or both. As this approach is typically aimed at allowing an abdominal hysterectomy to be converted to a vaginal hysterectomy, its use in women desiring future fertility is of questionable value.

The major disadvantages of GnRH agonist therapy are its hypoestrogenic side effect profile, its temporary effects, and its high cost. The menopause-like symptoms include vasomotor instability, mood effects,

vaginal dryness, and decreased bone density. Gonadotropin-releasing hormone agonist usage traditionally has been limited to 6 months, primarily due to its effects on bone metabolism. Bone loss associated with GnRH agonists occurs in the lumbar spine and the proximal femur at an average rate of 1% per month over a 6-month treatment period. This bone loss may be associated with damage to the microstructure of the bone, and is probably irreversible, thereby increasing the risk of osteoporosis.<sup>6</sup> Combined add-back therapy with estrogen and progesterone may permit longer treatment duration.<sup>7</sup>

The effects of GnRH agonist treatment on myomas are reversed shortly after discontinuation. Thus, other treatments are often merely delayed. It is well established that the maximal shrinking effects of GnRH agonists on fibroids occur roughly within the first 3 months of treatment, but the fibroids typically grow back to their pretreatment size by 6 months after discontinuation.<sup>2,8</sup> The delay in fertility during GnRH agonist treatment is generally unacceptable in women who immediately desire pregnancy, especially those in the later childbearing years. Additionally, the high cost of this therapy and insurance issues limit its practicality as well.

Antiprogestogens are another medical option for treating uterine fibroids. Fibroids not only express progesterone receptors in higher concentrations than the surrounding endometrial tissue, but also increase in volume in response to progestins.<sup>4</sup> These findings suggest that antiprogestins could be a useful fibroid treatment. Mifepristone (RU-486), which has anti-progesterone activity, was shown to decrease fibroid size by up to 49% after 12 weeks of treatment in a 1993 study by Murphy et al.<sup>9</sup> While the decrease in fibroid volume in patients treated with mifepristone was similar to that with GnRH agonist therapy, mifepristone did not reduce bone density. Recently, it was shown that as little as 5 mg/d of mifepristone can cause a significant reduction in fibroid volume, while producing fewer side effects than GnRH agonists. In this study, 40 premenopausal women were divided into two groups receiving 5 mg/d or 10 mg/d of mifepristone for 6 months. The mean uterine volumes shrunk 48% and 49%, respectively. The incidence of hot flashes was not significantly increased above baseline for the 5-mg group.<sup>10</sup> The exact mechanism of mifepristone's effects is unknown, and further investigation is necessary to determine whether and how it may be used in the treatment of fibroids. As with GnRH agonist treatment, the delay in fertility during mifepristone treatment due to potential teratogenic

effects may be unacceptable to women who immediately desire pregnancy.

### SURGICAL MANAGEMENT

The most common fertility-preserving procedure for the treatment of fibroids is myomectomy. Myomectomy involves surgical removal of uterine fibroids while preserving the uterus. Myomectomy can be performed via several different routes; the majority are performed by laparotomy. Abdominal myomectomy poses the risks of any major surgery, such as bleeding, adhesion formation, and infection. Although future cesarean delivery is usually recommended only if an incision has been made in the contractile segment of the uterus that invades the endometrial cavity, the authors believe that disruption of more than 50% of the myometrium raises the risk of uterine rupture enough to warrant future cesarean delivery. As most of the patients at potential risk for uterine rupture undergo scheduled elective cesarean delivery at 38 to 39 weeks' gestation, there are no good data sets regarding the risks of this complication.

A newer technique is laparoscopic myomectomy; this was first utilized in the late 1970s, but is still performed by a very limited number of skilled surgeons. It is recommended in the literature that laparoscopic myomectomy be reserved for myomas of less than 6 cm, but larger myomas have been removed laparoscopically. The size of the myoma that can be removed using laparoscopic myomectomy seems to depend mostly on the experience and skill of the surgeon. The benefits of laparoscopic myomectomy include the outpatient setting (which may reduce costs), a faster, less painful recovery, and potentially fewer surgical risks.

One of the concerns after fibroid removal by laparoscopic myomectomy is an increased risk of uterine rupture in subsequent pregnancies, even prior to the onset of labor. There have been several cases of uterine rupture reported in the literature. However, recent studies have shown that the actual risk of uterine rupture following laparoscopic myomectomy is 1%, comparable to the risk for vaginal birth after cesarean delivery. Dubuisson et al<sup>11</sup> reported on three cases of uterine rupture following laparoscopic myomectomy in 98 patients with 145 pregnancies and 100 deliveries. Only one of these three ruptures was at the site of the myomectomy scar. It is thought that the suturing of the incision, which may be inferior to that used for myomectomy via laparotomy, and the use of electrosurgery may contribute to an increased risk of uterine rupture.<sup>11-13</sup> Additionally, there is a steep learning curve with this procedure in terms of operative time and skill level.

## Treatment Options for Women With Symptomatic Fibroids

Hysteroscopic myomectomy is a method of removing submucosal uterine fibroids. The failure rate of hysteroscopic myomectomy is between 0% and 35%, with success mainly determined by the extension of the fibroid into the endometrial cavity and the size of the tumor. More than one resection may be needed to achieve control of abnormal bleeding. In one study, 69% and 88% of women had relief of bleeding after one and three surgeries, respectively.<sup>14</sup> In a separate study, 79% of women required only a single hysteroscopic resection at 4-year follow-up.<sup>15</sup> A benefit of this outpatient procedure is that no abdominal incision is made, limiting surgical complications and recovery time. The main disadvantage is that it can only be used to remove fibroids that are mainly submucosal and small. Rare operative complications include uterine perforation and electrolyte disturbances due to fluid absorption.

There are other, less common surgical procedures that can be employed to treat symptomatic fibroids while preserving the uterus. These include myolysis (myoma coagulation), laser-induced interstitial thermotherapy, and cryomyolysis. Due to economic and technical reasons, as well as better alternatives, these are rarely used in treating fibroids.

### UTERINE ARTERY EMBOLIZATION

Uterine artery embolization is a nonmedical, nonsurgical alternative to myomectomy that is gaining popularity. With UAE, the blood supply to the fibroids is decreased by embolizing the uterine arteries, ultimately causing the tumors to shrink. This procedure has been used for two decades as a method of controlling pelvic hemorrhage. In 1995, Ravina et al<sup>16</sup> initially reported UAE as a primary treatment for uterine fibroids. In one study, menorrhagia due to uterine fibroids was relieved by UAE in 87% and 90% of women after 3 months and 1 year, respectively.<sup>17</sup>

Uterine artery embolization is performed by an interventional radiologist. Most commonly using the right femoral artery approach, arteriography is performed to visualize the pelvic vasculature. A catheter is then passed into the right femoral artery, through the aorta, and down the left iliac artery to the left uterine artery. Polyvinyl alcohol particles or gelatin-based microspheres (Embospheres, 300 to 700 microns) are slowly infused until the blood supply to the fibroid is halted. The catheter is then run through the right uterine artery, where the particles are again infused into the fibroid vasculature.

The benefits of UAE are that it can be performed on an outpatient basis, and the recovery period is

decreased to 1 week. Women often experience a postembolization syndrome within the first 4 days after the procedure consisting of a low-grade fever, pain, malaise, nausea, and leukocytosis, which is usually self-limiting. While this is a relatively safe procedure, there have been reports of total uterine necrosis, transient and permanent ovarian failure, sexual dysfunction involving the external genitalia, and nontargeted vascular embolizations of the labia minora and the bladder.<sup>18-24</sup>

### FERTILITY CONSIDERATIONS

It is difficult to assess which procedure is best for a patient with fibroids desiring future fertility because of the paucity of prospective randomized studies. It is also important to note that most women with fibroids are in their late 30s and 40s, with possible diminished ovarian function confounding the fertility issue. Post-myomectomy fertility rates are relatively high. In a recent paper, the pregnancy and delivery rates were compiled for abdominal and laparoscopic myomectomy. According to these data, the average pregnancy rate after abdominal myomectomy was 45.3%, while the average pregnancy rate after laparoscopic myomectomy was 55%.<sup>25</sup> Similarly, Seracchioli et al<sup>26</sup> compared pregnancy and obstetric outcomes in women who underwent either abdominal myomectomy or laparoscopic myomectomy. No significant differences were found in pregnancy rates or obstetric outcomes between the two procedures. In his study, the pregnancy rates after abdominal myomectomy and laparoscopic myomectomy were 55.9% and 53.6%, respectively.

The connection between submucosal fibroids and infertility remains unclear. Pritts<sup>27</sup> showed that a group of infertile women with submucosal fibroids had a lower fertility rate than control couples, but removal of the submucosal fibroids by hysteroscopic myomectomy improved fertility to control levels. Bernard et al<sup>28</sup> demonstrated that fertility after hysteroscopic myomectomy may be related to the numbers of submucosal fibroids removed and of co-existing intramural fibroids. In this study, 35% of infertile women who underwent hysteroscopic myomectomy became pregnant, with a total of 13 pregnancies in 11 women. There was no difference in delivery rates based on size or location of the fibroids removed, but there was a difference based on whether the patient had one or multiple excisions.

Utilizing UAE in patients desiring future fertility is also controversial. Cases of post-UAE uncomplicated pregnancies have been documented, but there are no

controlled, randomized studies. In one study of 184 patients who had undergone UAE, there were 12 reported pregnancies. Of these, there were five miscarriages and seven deliveries, three of which were premature.<sup>16</sup> While this demonstrates that pregnancy is possible after UAE, it is difficult to make any definitive conclusions from this data. It should be noted that the goal of this study was to determine the long-term effects of UAE, and that most of the patients enrolled were older than age 40 years. Another study found that out of 52 women younger than age 40 years who had undergone UAE for symptomatic fibroids, 14 became pregnant, resulting in a total of 17 pregnancies. Ten of these women had normal term deliveries. There was a 33% (17/52) pregnancy rate and a 20% (10/52) delivery rate. These full-term delivery rates are comparable to those for abdominal myomectomy (10% to 46%) and laparoscopic myomectomy (16% to 33%).<sup>29</sup>

In addition to fertility, obstetric outcomes may also be affected by previous UAE. In 2002, Goldberg et al<sup>30</sup> analyzed the 50 reported cases of pregnancy after UAE in the world literature to determine obstetric outcomes. The data showed that for pregnant patients who had undergone UAE, there is an increased risk of preterm delivery, spontaneous abortion, postpartum hemorrhage, cesarean delivery, and malpresentation. The main criticism of this study was that it compared these patients with the general population, rather than with patients who had previously undergone myomectomy. Nonetheless, the findings do raise concerns for patients with symptomatic fibroids desiring future fertility. The study concluded that prospective, randomized trials are necessary to determine the true risks that UAE poses to future fertility.

There are no definitive guidelines for managing the infertile patient who has asymptomatic fibroids with no other identifiable etiology for her infertility. Depending on the size and location of the fibroids, as well as her obstetric history and age, management plans may differ among physicians and be based on individual patient preferences. There are no good prospective, randomized trials that definitively identify which patients benefit most from expectant management versus myomectomy, so treatment plans must be individualized on a case-by-case basis.

## CONCLUSION

Women with symptomatic fibroids who wish to preserve their fertility have several treatment options. The best approach to treatment is determined by factors including the size, location, and number of fibroids, as well as their impact on quality of life and the patient's

health status, obstetric history, overall fertility, and desire to conceive. Additional prospective, comparative studies regarding pregnancy rates and outcomes after the various treatments are needed to help physicians and patients choose the best approach to treating symptomatic fibroids while preserving fertility.

## REFERENCES

1. Floridon C, Lund N, Thomsen, S. Alternative treatment for symptomatic fibroids. *Curr Opin Obstet Gynecol.* 2001; 13(5):491-495.
2. Stenchever MA, Droegemueller W, Herbst AL, Mishell DR. *Comprehensive Gynecology.* St Louis, Mo: Mosby; 2001:497-504.
3. Farquhar C, Arroll B, Ekeroma A, et al. An evidence based guideline for the management of uterine fibroids. *Aust N Z Obstet Gynaecol.* 2001;41(2):125-140.
4. Eldar-Geva T, Healy D. Other medical management of uterine fibroids. *Baillieres Clin Obstet Gynecol.* 1998;12(2):269-288.
5. Ylikorkala O, Pekonen F. Naproxen reduces idiopathic but not fibroma-induced menorrhagia. *Obstet Gynecol.* 1986; 68(1):10-12.
6. Palomba S, Morelli M, Di Carlo C, et al. Bone metabolism in postmenopausal women who were treated with a gonadotropin-releasing hormone agonist and tibolone. *Fertil Steril.* 2002;78(1):63-67.
7. Leather AT, Studd JW, Watson NR, Holland EF. The prevention of bone loss in young women treated with GnRH analogues with "add-back" estrogen therapy. *Obstet Gynecol.* 1993;81(1):104-107.
8. DeLeo V, Morgante G, La Marca A, et al. A benefit-risk assessment of medical treatment for uterine leiomyomas. *Drug Safety.* 2002;25(11):759-779.
9. Murphy AA, Kettel LM, Morales AJ, et al. Endometrial effects of long-term low dose administration of RU 486. *Fertil Steril.* 1995;63(4):761-766.
10. Eisinger SH, Meldrum S, Fiscella K, et al. Low-dose mifepristone for uterine leiomyomata. *Obstet Gynecol.* 2003;101(2):243-250.
11. Dubuisson JB, Fauconnier A, Deffarges JV. Pregnancy outcomes and deliveries following laparoscopic myomectomy. *Hum Reprod.* 2000;15(4):869-873.
12. Seiner P, Farina C, Todros T. Laparoscopic myomectomy and subsequent pregnancy: results in 54 patients. *Hum Reprod.* 2000;15(9):1993-1996.
13. Hockstein S. Spontaneous uterine rupture in the early third trimester after laparoscopically assisted myomectomy. *J Reprod Med.* 2000;45(2):139-141.
14. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. *Obstet Gynecol.* 1993;82(5):736-740.
15. Hart R, Molnar BG, Magos A. Long term follow up of hysteroscopic myomectomy assessed by survival analysis. *Br J Obstet Gynaecol.* 1999;106(7):700-705.
16. Ravina J, Vigneron N, Aymard A, et al. Pregnancy after embolization of uterine myoma: report of 12 cases. *Fertil Steril.* 2000;73(6):1241-1243.

## Treatment Options for Women With Symptomatic Fibroids

17. Spies J, Ascher S, Roth A, et al. Uterine artery embolization for leiomyomata. *Obstet Gynecol.* 2001;98(1):29-34.
18. Demello AB. Uterine artery embolization. *AORN J.* 2001; 73(4):788-814.
19. Godfrey CD, Zbella EA. Uterine necrosis after uterine artery embolization for leiomyoma. *Obstet Gynecol.* 2001;98(5 pt 2):950-952.
20. Amato P, Roberts AC. Transient ovarian failure: a complication of uterine artery embolization. *Fertil Steril.* 2001;75(2): 438-439.
21. Lai AC, Goodwin SC, Bonilla SM. Sexual dysfunction after uterine artery embolization. *J Vasc Interventional Radiol.* 2000;11(6):755-758.
22. Vashisht A, Smith J, Thrope-Beeston G, McCall J. Pregnancy subsequent to uterine artery embolization. *Fertil Steril.* 2001; 75(6):1246-1247.
23. Yeagley T, Goldberg J, Klein T, Bonn J. Labial necrosis after uterine artery embolization for leiomyomas. *Obstet Gynecol.* 2002;100(5 pt 1):881.
24. Sultana CJ, Goldberg J, Aizenman L, Chon JK. Vesicouterine fistula after uterine artery embolization: a case report. *Am J Obstet Gynecol.* 2002;187(6):1726-1727.
25. Miller C. Myomectomy: comparison of open and laparoscopic techniques. *Obstet Gynecol Clin North Am.* 2000; 27(2): 407-420.
26. Seracchioli R, Rossi S, Govoni F, et al. Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy. *Hum Reprod.* 2000;15(12):2663-2668.
27. Pritts E. Fibroids and infertility: a systematic review of the evidence. *Obstet Gynecol Surv.* 2001;56(8):483-491.
28. Bernard G, Darai E, Poncelet C, et al. Fertility after hysteroscopic myomectomy: effect of intramural myomas associated. *Eur J Obstet Gynecol Reprod Biol.* 2000;88(1):85-90.
29. McLucas B, Goodwin S, Adler L, et al. Pregnancy following uterine fibroid embolization. *Int J Gynecol Obstet.* 2001;74(1):1-7.
30. Goldberg J, Pereira L, Berghella V. Pregnancy following uterine artery embolization: a report of two cases and review of the current literature. *Obstet Gynecol.* 2002;100(5 pt 1): 869-872.