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BULLETIN

Alternatives to Hysterectomy in the Management of Leiomyomas

Uterine leiomyomas (also called fibroids) are the most common solid pelvic tumors in women and the leading indication for hysterectomy. Although many women with uterine leiomyomas are asymptomatic and can be monitored without treatment, some will require more active measures. Hysterectomy remains the most common surgical treatment for leiomyomas because it is the only definitive treatment and eliminates the possibility of recurrence. Many women seek an alternative to hysterectomy because they desire future childbearing or wish to retain their uteri even if they have completed childbearing. As alternatives to hysterectomy become increasingly available, the efficacies and risks of these treatments are important to delineate. The purpose of this bulletin is to review the literature about medical and surgical alternatives to hysterectomy and to offer treatment recommendations.

Background

The two most common symptoms of uterine leiomyomas for which women seek treatment are abnormal uterine bleeding and pelvic pressure. The most common kind of abnormal uterine bleeding associated with leiomyomas is heavy or prolonged menstrual bleeding, which frequently results in iron deficiency anemia (1). This heavy flow may result in significant disruption of a woman's daily activities. However, not all bleeding is caused by leiomyomas; therefore, other causes of abnormal bleeding should be ruled out. The pelvic and abdominal discomfort that women experience with leiomyomas often is described as pressure. In addition to pelvic pressure, leiomyomas may interfere

with adjacent structures, leading to dyspareunia and difficulty with urination or defecation.

Uterine leiomyomas are very common, with some studies reporting leiomyomas in 70% of white women and more than 80% of black women by age 50 years (2). Leiomyomas can vary greatly in size and may be present in subserosal, submucosal, intramural, pedunculated, or combined locations. Symptoms and treatment options are affected by the size, number, and location of the leiomyomas. The lack of a simple, inexpensive, and safe long-term medical treatment means that most symptomatic leiomyomas are still managed surgically.

Alternatives to Hysterectomy

In choosing an alternative to hysterectomy, both safety and efficacy need to be considered for each treatment. It must be recognized that all alternatives to hysterectomy allow the possibility for new leiomyomas to form, and preexisting small or undetected leiomyomas may exhibit significant growth, necessitating another treatment. The risk of recurrence must be balanced against the potential benefits of uterine-sparing procedures, such as decreased rates of morbidity and continued fertility. However, procedural complications may rarely lead to an unanticipated hysterectomy.

Medication

Contraceptive Steroids and Nonsteroidal Antiinflammatory Drugs

Contraceptive steroids (estrogen and progestin combinations and progestin alone) are widely used for the control of abnormalities of menstruation. These agents often are first-line therapy for control of abnormal bleeding and painful menstruation in women with and without leiomyomas. However, evidence-based reviews suggest that current medical therapies tend to give only short-term relief, and the crossover rate to surgical therapies is high (3).

Data are limited about the effects of estrogen and progestin treatment of leiomyomas. Estrogen and progestin treatment, usually with oral contraceptives, may control bleeding symptoms without stimulating further leiomyoma growth. However, studies of progestin therapy have demonstrated mixed results. Although several small studies have shown a decrease in leiomyoma size during progestin therapy (4, 5), other studies using progestin therapy alone or in conjunction with a gonadotropin-releasing hormone (GnRH) agonist identify an increase in leiomyoma volume or uterine volume during therapy (6–10). Therefore, when contraceptive steroid therapy is initiated, close monitoring of both leiomyoma

and uterine size is recommended. Epidemiologic studies also suggest that both combined oral contraceptives and progestin-only contraceptives also may decrease the risk of developing clinically significant leiomyomas (11, 12). Nonsteroidal antiinflammatory drugs are effective in reducing dysmenorrhea, but there are no studies that document improvement in women with dysmenorrhea caused by leiomyomas.

The levonorgestrel intrauterine system leads to minimal systemic effects, and the localized endometrial effect is beneficial for treatment of menorrhagia (3). Small studies suggest that the levonorgestrel intrauterine system may be effective for treatment of heavy uterine bleeding in women with leiomyomas (13). However, these women may have a higher rate of expulsion and vaginal spotting.

Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone agonists lead to amenorrhea in most women and provide a 35–65% reduction in leiomyoma volume within 3 months of treatment (14). The GnRH agonist leuprolide acetate is approved by the U.S. Food and Drug Administration (FDA) for preoperative therapy in women with anemia in conjunction with supplemental iron, and it is most useful in women with large leiomyomas. The effects of GnRH agonists are temporary, with gradual recurrent growth of leiomyomas to previous size within several months after cessation of treatment. In addition, the significant symptoms of pseudomenopause and adverse impact of the induced hypoestrogenism on bone density limit their suggested use to no more than 6 months without hormonal add-back therapy.

If treatment is continued for more than 6 months, low-dose steroidal add-back therapy should be considered to minimize continued bone loss and vasomotor symptoms. Whereas contraceptive steroid add-back therapy can be used for some diseases, for leiomyomas only low-dose preparations, equivalent to menopausal hormonal therapy, have been studied. It also appears that using a sequential regimen, in which a GnRH agonist is first used to achieve down regulation to which steroids are added after 1–3 months of therapy, gives maximal results. However, the addition of progestin add-back therapy results in an increase in mean uterine volume to 95% of baseline within 24 months (9).

Aromatase Inhibitors

Aromatase inhibitors block ovarian and peripheral estrogen production and decrease estradiol levels after 1 day of treatment (15). Based on their mechanism of action, these agents may have fewer side effects than GnRH

analogues, with the benefit of a rapid effect. Several small studies and case reports have identified reductions in leiomyoma size and symptoms with the use of aromatase inhibitors (16–18). Overall, little data exist about the use of aromatase inhibitors to treat uterine leiomyomas, and further research is necessary to elucidate their clinical use. These medications are not FDA approved for the treatment of leiomyomas.

Progesterone Modulators

Antiprogesterone agents act at the level of the progesterone receptors found in high concentration in leiomyomatous uteri (19, 20). Mifepristone is the most extensively studied progesterone-modulating compound; recent studies have shown its usefulness in controlling leiomyoma symptoms (21, 22). Several studies of high-dose mifepristone have reported a reduction of leiomyoma volume of 26–74% (23, 24). This reduction is comparable to those achieved through the use of analogues, and leiomyomas appear to have a slower rate of recurrent growth after cessation of mifepristone treatment (23). Amenorrhea also is a common result of mifepristone use, with rates up to 90%, coupled with stable bone mineral density and improvements in pelvic pressure (21, 23).

Potential side effects of mifepristone include endometrial hyperplasia without atypia (14–28%) and transient elevations in transaminase levels (4%) necessitating liver-function monitoring (23, 25). In addition, mifepristone requires a compounding pharmacy to produce clinically relevant doses and, thus, has limited availability. Significantly lower doses may be effective without increasing the risk of atypical hyperplasia (21, 22). Antiprogesterone agents may have a short-term role in the preoperative management of leiomyomas, but further study is needed.

Myomectomy

For women who desire uterine preservation, myomectomy may be an option. The goal of a myomectomy procedure is to remove the visible and accessible leiomyomas and then reconstruct the uterus. Traditionally, most myomectomies have been performed by laparotomy; however, endoscopic options increasingly are being used.

Abdominal Myomectomy

Although early studies suggested that the rate of morbidity associated with myomectomy was increased compared with hysterectomy, subsequent research suggests that the risks of the two procedures are similar (26–28). Clinical experience and pooled results of numerous small studies suggest that abdominal myomectomy significantly improves menorrhagia symptoms (overall 81% resolution; range 40–93%), with similar results for resolution of pelvic pressure (29). Therefore, abdominal myomectomy is a safe and effective option for treatment of women with symptomatic leiomyomas.

However, women choosing myomectomy face the risk of recurrence of leiomyomas. A number of studies have examined the use of ultrasonography to assess the recurrence risk of leiomyomas after abdominal myomectomy, but the accuracy of the estimate depends on the sensitivity of the measuring instrument (10, 30–32). Studies have indicated that women who experience childbirth after a myomectomy appear to have a decreased recurrence risk (30, 31). There have been conflicting reports over whether the preoperative use of GnRH agonists affects recurrence risk (10, 32).

The clinically relevant endpoint is whether a second surgical procedure is needed after conservative surgery. In a relatively large series (125 patients monitored at least 5 years and up to 23 years), there was evidence that recurrence depended on the number of leiomyomas present. Of those women who had a single leiomyoma, 27% had recurrent tumors and 11% required hysterectomy. Of those women who had multiple leiomyomas, 59% experienced recurrent tumors. Of the women in the multiple leiomyoma group, 26% required repeat myomectomy, hysterectomy, or both procedures (33).

Another risk of myomectomy is the possibility of undergoing an unexpected hysterectomy because of intraoperative complications. This risk appears to be low (less than 1%) even when uterine size is substantial (28, 34–37). Blood loss and the risk of transfusion may be increased in women with larger uteri (28, 37).

Laparoscopic Myomectomy

Endoscopic myomectomy is a treatment option for some women (38). Laparoscopic myomectomy minimizes the size of the abdominal incision, resulting in a quicker postoperative recovery. Because of the complex nature of laparoscopic dissection and suturing, special surgical expertise typically is required.

There are a number of case series of laparoscopic myomectomies, the largest reporting on more than 2,000 patients over a 6-year period (39). These cohorts report overall complication rates between 8% and 11%, with subsequent pregnancy rates between 57% and 69% (39, 40).

Two randomized controlled trials including a total of 284 patients have compared laparoscopic myomectomy with a minilaparotomy myomectomy (41, 42). The first trial demonstrated shorter operating room duration

for minilaparotomy. Laparoscopic myomectomy resulted in less blood loss, reduced length of postoperative ileus, a shorter time to hospital discharge, reduced analgesic requirements, and a more rapid recuperation (41). A second trial compared minilaparotomic myomectomy and laparoscopic myomectomy in patients with unexplained infertility and concluded that both techniques improve reproductive outcomes to a similar degree (42).

Recommendations differ regarding cases amenable to a laparoscopic approach. Previous recommendations have suggested avoiding laparoscopy for leiomyomas larger than 5–8 cm, multiple leiomyomas, or the presence of deep intramural leiomyomas (43, 44). A prospective study compared laparoscopic myomectomy for the management of leiomyomas greater than 80 g with laparoscopic myomectomy in those smaller than 80 g. Operative time (121 minutes versus 79 minutes) and estimated blood loss (346 mL versus 123 mL) were significantly greater in the group with the larger uterine leiomyomas. However, no difference was seen in length of stay or overall complication rates (45).

A large retrospective series of 512 patients reported a leiomyoma recurrence rate of 11.7% after 1 year and up to 84.4% after 8 years, but a reoperation rate for recurrence of 6.7% at 5 years and 16% at 8 years (46). A case series described a 33% recurrence risk at 27 months (47). Successful outcomes from laparoscopic myomectomy have been reported primarily by surgeons with expertise and advanced laparoscopic skills, including laparoscopic myomectomy, and may not be generalizable to surgeons with less laparoscopic experience.

Robot-assisted laparoscopic surgery also has been used to perform myomectomy (48). It may have the advantage of improved optics, including a three-dimensional view, and enhanced surgeon dexterity. Disadvantages with robot-assisted surgery in general include diminished haptic (tactile) sensation, additional operating room time, and increased cost. Further studies, including randomized clinical trials, are needed to better determine clinical outcomes and cost-effectiveness.

Hysteroscopic Myomectomy

Hysteroscopic myomectomy is an accepted method for the management of abnormal uterine bleeding caused by submucous leiomyomas. Submucosal leiomyomas are estimated to be the cause of 5–10% of cases of abnormal uterine bleeding, pain, and subfertility and infertility (4). Submucous leiomyomas are classified based on the amount of leiomyoma within the uterine cavity, with type 0 leiomyomas completely intracavitary, type I leiomyomas less than 50% intramural, and type II leiomyomas more than 50% intramural (49). This classi-

fication has been shown to be predictive of the likelihood of complete surgical resection, which is the most predictive indicator of surgical success. Uterine size and the number of leiomyomas also have been shown to be independent prognostic variables for recurrence (50).

Studies have shown successful removal of the leiomyoma at the initial hysteroscopy at a rate of 65–100%, with most ranging from 85–95% (51). Subsequent surgery is needed in approximately 5–15% of cases, and most of these cases involve a second hysteroscopic procedure. As with abdominal leiomyomectomy, the effectiveness of the procedure decreases over time. One study of 274 procedures, with follow-up of more than 5 years, reported a success rate of 94.6% at 1 year, which decreased to 76.3% at 5 years (52).

Leiomyoma classification is an important predictor of the ability to achieve complete resection, although there have been some reports of success with type II leiomyomas. One retrospective study of 235 patients reported a 95% rate of complete leiomyoma resection in a population that included 70% type II leiomyomas. The 3-year success rate was reported as 97%; however, 36% underwent concomitant endometrial ablation (52).

The reported complication rate for hysteroscopic myomectomy ranges between 1% and 12%, with rates of 1–5% reported in most studies (51). Potential surgical complications include fluid overload with secondary hyponatremia, pulmonary edema, cerebral edema, intraoperative and postoperative bleeding, uterine perforation, gas embolism, and infection.

Uterine Artery Embolization

Uterine artery embolization for the treatment of leiomyoma, performed primarily by interventional radiologists, is a procedure in which the uterine arteries are embolized via a transcutaneous femoral artery approach, resulting in uterine leiomyoma devascularization and involution. The uterine arteries are embolized using polyvinyl alcohol particles of trisacryl gelatin microspheres. Supplemental metal coils also may be used to assist with vascular occlusion.

A large multicenter study of more than 500 patients undergoing uterine artery embolization reported favorable 3-month outcomes for dominant leiomyoma volume reduction (42%) and decreased median leiomyoma life-impact scores, mean menstrual duration, dysmenorrhea, and urinary frequency or urgency (53). The Uterine Artery Embolization in the Treatment of Symptomatic Uterine Fibroid Tumors (EMMY) randomized trial compared uterine artery embolization to total abdominal hysterectomy. In this trial, patients undergoing uterine artery embolization had significantly less pain during the first

24 hours postoperatively and returned to work sooner (28.1 versus 63.4 days) than patients who underwent hysterectomy (54). The rates of major complications were similar, 4.9% for uterine artery embolization and 2.7% for hysterectomy. Minor complications, such as vaginal discharge, leiomyoma expulsion, and hematoma were higher in the group that had uterine artery embolization compared with those that had hysterectomy (58% versus 40%) as well as higher readmission rates for those undergoing uterine artery embolization (11.1% versus 0%) (55). Similar clinical findings were reported in a multicenter trial of uterine artery embolization versus myomectomy (56). Analysis of three randomized clinical trials comparing uterine artery embolization with myomectomy and hysterectomy confirmed that the uterine artery embolization resulted in shorter hospital stay, quicker return to activities, and a higher minor complication rate after discharge (57). The overall complication rates for uterine artery embolization have been reported to be approximately 5% (58).

Long-term outcomes have been reported in several studies. One case–control study comparing uterine artery embolization with myomectomy reported a higher reoperation rate of 29% in the uterine artery embolization group (15 of 51) compared with 3% (1 of 30) in the myomectomy group (59). However, when subjective variables, such as symptom worsening and patient dissatisfaction, were considered, 39% (20 of 51) in the uterine artery embolization group were considered clinical failures, compared with 30% (9 of 30) in the myomectomy group. In 5-year follow-up results of 200 patients treated with uterine artery embolization, a 20% reoperation rate (hysterectomy 13.7%, myomectomy 4.4%, repeat embolization 1.6%) and failure to control symptoms in 25% were documented (60). Another trial reported a reintervention rate of 6% in the myomectomy group, compared with a rate of 33% for those undergoing uterine artery embolization (61). Based on long- and short-term outcomes, uterine artery embolization is a safe and effective option for appropriately selected women who wish to retain their uteri. Women who wish to undergo uterine artery embolization should have a thorough evaluation with an obstetrician–gynecologist to help facilitate optimal collaboration with the interventional radiologists and to ensure the appropriateness of therapy, taking into account the reproductive wishes of the patient.

Magnetic Resonance Imaging-Guided Focused Ultrasound Surgery

In 2004, the FDA granted approval for the use of a magnetic resonance imaging (MRI)-guided system for the localization and treatment of uterine leiomyomas with focused ultrasound therapy. This noninvasive approach uses high-intensity ultrasound waves directed into a focal volume of a leiomyoma. The ultrasound energy penetrates soft tissue and produces well-defined regions of protein denaturation, irreversible cell damage, and coagulative necrosis.

Outcomes of 109 patients undergoing MRI-guided focused ultrasound surgery were reported at 6 months and 12 months (62, 63). Although only modest uterine volume reductions were noted (13.5% at 6 months and 9.4% at 12 months, using intention to treat analysis), 71% of patients reported symptom reduction at 6 months. At 12 months, 51% had symptom reduction. Adverse events included heavy menses, requiring transfusion (5); persistent pain and bleeding (1); hospitalization for nausea (1); and leg and buttock pain caused by sonification of the sciatic nerve in the far field (1), which eventually resolved. Case series suggest that improvement in symptoms at 12 months and 24 months is related to the thoroughness of treatment and that adverse events decrease with increasing experience (64–66). Whereas short-term studies show safety and efficacy, long-term studies are needed to discern whether the minimally invasive advantage of MRI-guided focused ultrasound surgery will lead to durable results beyond 24 months. Protocols for treating larger leiomyoma volumes are being studied.

Clinical Considerations and Recommendations

▶ *In women with leiomyomas who are candidates for surgery, does the use of adjunctive medical treatment result in better outcomes?*

Preoperative Adjuvants

Gonadotropin-releasing hormone agonists have been used widely for preoperative treatment of uterine leiomyomas, both for myomectomy and hysterectomy. They may be beneficial when a significant reduction in uterine volume could change the surgical approach, such as allowing a transverse incision, an endoscopic procedure, or a vaginal hysterectomy.

By inducing amenorrhea, GnRH agonists have been shown to improve hematologic parameters, shorten hospital stay, and decrease blood loss, operating time, and postoperative pain when given for 2–3 months preoperatively (67–69). However, no study has shown a significant decrease in transfusion risk or improvement in quality of life, and the cost of these medications is substantial. Therefore, the benefits of preoperative use of GnRH agonists should be weighed against their cost and

side effects for individual patients. It also is worth noting that in a study that achieved hematologic improvement with GnRH agonist treatment in 74% of women, there was a 46% improvement rate in the placebo group with iron supplementation alone (68). One surgical disadvantage to preoperative GnRH agonist therapy is that it may make the leiomyomas softer and the surgical planes less distinct. Although many studies find the operative time equivalent for laparotomies, one study of laparoscopic myomectomies found that overall operating time decreased after GnRH agonist treatment. However, in the subgroup in which the largest leiomyoma was hypoechoic, operative time was longer because of the difficulty in dissection (69).

Gonadotropin-releasing hormone antagonists are now available and have the advantage of not inducing an initial steroidal flare as seen with GnRH agonists. The rapid effect of the antagonist allows a shorter duration of side effects with presurgical treatment. The antagonist has been shown to reduce leiomyoma volume by 25–40% in 19 days, thereby allowing surgery to be scheduled sooner (70). As with the agonist, the reduction of leiomyoma and uterine volumes are transient. Although GnRH antagonists are not currently FDA approved for preoperative treatment of leiomyomas, they may be beneficial.

Intraoperative Adjuvants

Several studies suggest that the infiltration of vasopressin into the myometrium decreases blood loss at the time of myomectomy. A study of 20 patients demonstrated that vasopressin significantly decreased blood loss compared with saline injection in a randomized myomectomy study (71). Two studies compared the use of physical vascular compression, primarily a tourniquet around the lower uterine segment, with pharmacologic vasoconstriction (vasopressin administration). In one study that used a Penrose drain tourniquet and vascular clamps, there was no significant difference between the two techniques (37). The other study, which compared the use of a Foley catheter tourniquet with vasopressin administration, found significantly greater blood loss in the tourniquet group (72). There are no studies that compare tourniquet use with placebo. Additionally, one study demonstrated that injection of vasopressin into the cervix at the time of operative hysteroscopy decreased blood loss, fluid intravasation, and operative time (73).

▶ *In pregnant women who have undergone a myomectomy, does a planned cesarean delivery versus a trial of labor help prevent uterine rupture?*

A trial of labor is not recommended in patients at high risk of uterine rupture, including those with previous classical or T-shaped uterine incisions or extensive transfundal uterine surgery. Because myomectomy also can produce a transmural incision in the uterus, it often has been treated in an analogous way. There are no clinical trials that specifically address this issue; however, one study reports no uterine ruptures in 212 deliveries (83% vaginal) after myomectomy (74).

Pooled data from several case series of laparoscopic myomectomy involving more than 750 pregnancies identified one case of uterine rupture (39, 40, 75–77). Other case reports have described the occurrence of uterine rupture before and during labor (78–80), including rare case reports of uterine rupture remote from term after traditional abdominal myomectomy (81, 82). Most obstetricians allow women who underwent hysteroscopic myomectomy for type O or type I leiomyomas to go through labor and give birth vaginally; however, there are case reports of uterine rupture in women who experienced uterine perforation during hysteroscopy (83–85). It appears that the risk of uterine rupture in pregnancy after laparoscopic or hysteroscopic myomectomy is low. However, because of the serious nature of this complication, a high index of suspicion must be maintained when managing pregnancies after this procedure.

▶ *In women with leiomyomas who desire to become pregnant, does surgical removal of leiomyomas increase the pregnancy rate?*

As with any woman with asymptomatic leiomyomas, those who desire future fertility should be managed expectantly because they have no indication for surgery. For mildly symptomatic women, given the risk of recurrence, intervening as close to the desired pregnancy as practical is desirable. For symptomatic women, prior treatment history should be considered, as well as possible benefit of normalization of the endometrial cavity, the particular fertility consequences of each technique, and the risk of pregnancy complications with untreated leiomyomas.

The contribution of leiomyomas to infertility is difficult to assess because of the high prevalence of leiomyomas in the general population and because the incidence of leiomyomas increases with age, as does infertility. Furthermore, many women with uterine leiomyomas conceive and have uncomplicated pregnancies. Leiomyomas are present in approximately 5–10% of women with infertility and are the sole factor identified in 1–2.4% of women with infertility (29, 86, 87). However, leiomyomas should not be considered the cause of infertility, or significant component of infertility,

without completing a basic fertility evaluation to assess the woman and her partner.

Intramural and submucosal leiomyomas can cause distortion of the uterine cavity or obstruction of the tubal ostia or cervical canal and, thus, may affect fertility or lead to pregnancy complications (88–90). When abdominal myomectomies have been performed on women with otherwise unexplained infertility, the subsequent pregnancy rates have been reported to be 40–60% after 1–2 years (29, 91–93). Studies of the effect of laparoscopic or hysteroscopic myomectomy on fertility have shown similar results (94–96). However, the use of additional fertility treatments may have contributed to these marked positive effects.

Several studies have investigated the effect of leiomyomas on reproductive outcomes after in vitro fertilization (IVF). In the setting of an abnormal, distorted uterine cavity caused by leiomyomas (submucosal or intramural), significantly lower IVF pregnancy rates were identified (90–98). In addition, after myomectomy was performed for submucosal leiomyomas, pregnancy rates markedly increased (90). Subserosal leiomyomas have not been shown to have an impact on reproductive outcomes (90). However, in the setting of a nondistorted uterine cavity, the impact of intramural leiomyomas on IVF outcomes remains unclear. Intramural, nondistorting leiomyomas may have a subtle impact on IVF outcomes (97), but there are no definitive data supporting routine prophylactic myomectomy before IVF for women with leiomyomas and normal uterine cavities (98). It should be noted that most studies included women with leiomyomas of 5 cm or less, and women with larger leiomyomas were often excluded from these studies (99). Therefore, although leiomyomas that distort the uterine cavity clearly affect reproductive outcomes, further data about leiomyoma size and reproductive outcomes are needed.

Some surgeons believe that a prophylactic myomectomy may be appropriate for select women with large leiomyomas who wish to preserve future fertility. With a skilled surgeon, the evidence demonstrates that the myomectomy complication rate is low even with substantial uterine size; thus, surgery may be reasonable (28, 30, 31, 34, 36). However, the high risk of recurrent leiomyomas makes this procedure a less effective treatment (30, 31). Additionally, myomectomy can lead to pelvic adhesive disease, which could cause tubal impairment or obstruction and, hence, infertility (100).

When assessing a woman with infertility and leiomyomas, targeted evaluation of the uterus and endometrial cavity to assess leiomyoma location, size, and number is indicated. The data suggest that before infertility treatment, surgical treatment for a distorted uterine cavity caused by leiomyomas is indicated. In addition, myomectomy should be considered for a woman with uterine leiomyomas who has undergone several unsuccessful IVF cycles despite appropriate ovarian response and good quality embryos. There are potential adverse effects of nondistorting leiomyomas on IVF outcomes, although these effects are unconfirmed.

▶ *In women with leiomyomas planning future pregnancies, what is the impact on future fertility of uterine artery embolization and magnetic resonance imaging-guided focused ultrasonography?*

Successful pregnancies can occur following uterine artery embolization (101). Notably, early series demonstrated successful term pregnancies in women who would be expected to have a high rate of infertility (102). There are two issues of specific concern related to uterine artery embolization for women intending to become pregnant. The first is that there appears to be an age-related risk of impairment of ovarian function, as demonstrated by amenorrhea (53). Originally, this risk was attributed only to the circumstances of misembolization, but an understanding of the collateral blood supply of the uterus suggests this can occur with technically correct uterine artery embolization. Although this risk is low in young women (3%), given the prevalence of decreased ovarian reserve as an infertility factor, long-term studies are necessary. A recent report of antimüllerian hormone in women participating in a randomized clinical trial of uterine artery embolization versus hysterectomy suggests that both procedures cause similar impairment of ovarian reserve (103).

There are case reports of pregnancy complications after uterine artery embolization, but this may represent publication bias. However, the most significant data come from the Ontario cohort that includes close follow-up (104). In this case series of 24 pregnancies occurring in women with prior uterine artery embolization, there was a 12% risk of placentation problems (two placenta previa and one placenta accreta), and all occurred in nulliparous patients who were otherwise unlikely to have this type of complication. Thus, because there is biologic plausibility of uterine artery embolization causing compromised endometrial perfusion resulting in abnormal placentation in women not otherwise at risk, this approach should be used with caution for women who are pursuing pregnancy. The effect of uterine artery embolization on pregnancy remains understudied.

Case reports of pregnancy with term delivery have been reported after MRI-guided focused ultrasonography (65, 105–107). However, larger experience is necessary before drawing conclusions.

▶ *In menopausal women with leiomyomas, what is the effect of hormone therapy on leiomyoma growth, bleeding, and pain?*

For many years, health care providers have counseled patients that leiomyomas are a self-limiting problem that will resolve when a woman completes the transition to menopause. Because leiomyomas are responsive to estrogen, the hypoestrogenism of menopause results in uterine shrinkage for most women. However, for women electing hormone therapy, there is the possibility that symptoms associated with leiomyomas may persist into menopause.

There is some evidence that women with leiomyomas who take hormone therapy are more likely to have abnormal bleeding. In a study using hysteroscopy to evaluate women with abnormal bleeding who were taking hormone therapy (using women with no abnormal bleeding as controls), women with structural abnormalities of the cavity, including endometrial polyps and submucosal leiomyomas, had an increased likelihood of abnormal bleeding (108).

A small pilot study examined whether hormone therapy during menopause caused an increase in size of asymptomatic leiomyomas (109). This study showed a significant increase in leiomyoma dimension after 1 year of transdermal hormone therapy but no increase with oral conjugated estrogens. Hormone therapy may cause some modest increase in uterine leiomyoma size, but it does not appear to have an impact on clinical symptoms. Therefore, this treatment option should not be withheld from women who desire or need such therapy.

▶ *In asymptomatic women with leiomyomas, does expectant management produce a better outcome than surgical treatment in relation to long-term morbidity?*

Expectant management in an asymptomatic patient should be the norm, but in some instances an asymptomatic leiomyomatous uterus might require treatment. Historically, it has been argued that uterine size alone should be an indication for hysterectomy. The argument usually has been twofold. The first issue was that a large leiomyomatous uterus made assessment of the ovaries and early surveillance for ovarian cancer impossible. However, the National Institutes of Health and National Cancer Institute Consensus Conference acknowledged the futility of routine pelvic examinations in the identification of early ovarian cancer (110).

Second, the argument is made that, because of the increased rate of morbidity during surgery for a large uterus, surgery is a safer option when the uterus is smaller.

Although some studies have shown increased rates of morbidity, others show no differences in perioperative complications (9, 27, 28, 111). This currently does not appear to be a cogent argument for intervention.

In rare circumstances, the uterus causes significant compression of the ureters that could lead to compromised renal function. A small retrospective review demonstrated ureteral dilation in 56% of patients with uterine size greater or equal to 12 weeks, but no dilation in patients with uterine size less than 12 weeks (112). However, in no studies have the effects of uterine size on renal function been evaluated.

If there is concern that the mass is not a leiomyoma but instead a sarcoma, further evaluation is warranted. Traditionally, the major clinical sign used to make this distinction was rapid growth in uterine size. However, in a study of 1,332 hysterectomy specimens for which the preoperative diagnosis was uterine leiomyomas, sarcomas were rare (2–3/1,000) and no more common in the subgroup of women who had experienced rapidly enlarging uterine size (113). The clinical diagnosis of rapidly growing leiomyomas should not be used as an indication for myomectomy or hysterectomy.

If a comparison is made between the prevalence of leiomyosarcomas discovered incidentally (1/2,000) and the mortality rate for hysterectomy for benign disease (1–1.6/1,000 for premenopausal women), the decision to proceed to hysterectomy to find potential sarcomas should be made cautiously (111). Other risk factors for sarcomas, including increasing age, a history of prior pelvic radiation, tamoxifen use, or having a rare genetic predisposition resulting in hereditary leiomyomatosis and renal cell carcinoma syndrome may influence this decision (114). Alternatively, both endometrial biopsy and MRI appear to be useful in diagnosing sarcomas and differentiating them from other intrauterine lesions (115–117).

In conclusion, there is insufficient evidence to support hysterectomy for asymptomatic leiomyomas solely to improve detection of adnexal masses, to prevent impairment of renal function, or to rule out malignancy.

Summary of Recommendations

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

▶ Abdominal myomectomy is a safe and effective alternative to hysterectomy for treatment of women with symptomatic leiomyomas.

- Based on long- and short-term outcomes, uterine artery embolization is a safe and effective option for appropriately selected women who wish to retain their uteri.

- Gonadotropin-releasing hormone agonists have been shown to improve hematologic parameters, shorten hospital stay, and decrease blood loss, operating time, and postoperative pain when given for 2–3 months preoperatively. Benefits of preoperative use of GnRH agonists should be weighed against their cost and side effects for individual patients.

- Several studies suggest that the infiltration of vasopressin into the myometrium decreases blood loss at the time of myomectomy.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- The clinical diagnosis of rapidly growing leiomyomas should not be used as an indication for myomectomy or hysterectomy.

- Hysteroscopic myomectomy is an accepted method for the management of abnormal uterine bleeding caused by submucosal leiomyomas.

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

- There is insufficient evidence to support hysterectomy for asymptomatic leiomyomas solely to improve detection of adnexal masses, to prevent impairment of renal function, or to rule out malignancy.

- Leiomyomas should not be considered the cause of infertility, or significant component of infertility, without completing a basic fertility evaluation to assess the woman and her partner.

- Hormone therapy may cause some modest increase in uterine leiomyoma size but does not appear to have an impact on clinical symptoms. Therefore, this treatment option should not be withheld from women who desire or need such therapy.

- The effect of uterine artery embolization on pregnancy remains understudied.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and December 2007. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I   Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.