Myomas and reproductive function

The Practice Committee of the American Society for Reproductive Medicine in collaboration with The Society of Reproductive Surgeons

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The purpose of this Educational Bulletin is to examine the relationship between myomas and reproductive function and to review current methods for their management. (Fertil Steril® 2008;90:S125–30. ©2008 by American Society for Reproductive Medicine.)

Uterine myomas (fibroids) occur in 20%–50% of reproductive-age women (1) and can be identified by ultrasound in approximately 80% of African-American women and in almost 70% of white American women by the time they reach menopause (2). Approximately 175,000 hysterectomies and 20,000 myomectomies are performed for the management of myomas in the United States each year (3, 4). The purpose of this document is to examine the relationship between myomas and reproductive function and to review current methods for their management.

PATHOPHYSIOLOGY

Myomas arise from genetic alternations in a single myometrial cell and thus often are described as clonal (5, 6). Although estrogen may stimulate myoma development and growth, myomas also may grow when circulating estrogen levels are low, possibly because ovarian and adrenal androgens may be converted to estrogens by aromatase activity within myoma cells. Growth of myomas is clearly also regulated by P and a number of local growth factors (7–10), and the genetic basis for myoma growth may relate primarily to these factors and their receptors. Whereas most women with uterine myomas are asymptomatic, many may have significant symptoms, including pelvic and abdominal pressure or pain and excess bleeding. Other symptoms of myomas may result from their imposition on adjacent organs such as the bladder (urinary frequency) or rectum (tenesmus).

MYOMAS AND INFERTILITY

An older, but often cited study found that although uterine myomas may be identified in approximately 5%–10% of infertile women, only 2%–3% of infertility may be attributed to the effects of myomas when all other causes are excluded (11). The impact of myomas on fertility may have been underestimated because the diagnosis of myomas at that time was based primarily on bimanual examination rather than on ultrasound or other imaging. In a prospective cohort study of women with otherwise unexplained infertility, 11% of women with myomas conceived without intervention, compared with 25% of those without myomas and with 42% of women who underwent laparoscopic myomectomy (12). Other evidence indicates that myomas also may adversely affect outcomes achieved with IVF. Whereas some investigators have found that uterine myomas have no effect on IVF outcomes unless they distort or displace the uterine cavity (13, 14), other investigators have suggested that IVF success rates also are lower in women with intramural myomas (15), particularly when larger than 5 cm in diameter (16).

The mechanisms by which myomas may adversely affect fertility are several:

1. Displacement of the cervix that may reduce exposure to sperm
2. Enlargement or deformity of the uterine cavity that may interfere with sperm migration and transport
3. Obstruction of the proximal fallopian tubes
4. Altered tubo-ovarian anatomy, interfering with ovum capture
5. Increased or disordered uterine contractility that may hinder sperm or embryo transport or nidation
6. Distortion or disruption of the endometrium and implantation due to atrophy or venous ectasia over or opposite a submucous myoma
7. Impaired endometrial blood flow
8. Endometrial inflammation or secretion of vasoactive substances

MYOMAS AND PREGNANCY

Myomas are observed in 2.7%–12.6% of pregnant women (17). Whereas often it has been suggested that the high levels of sex steroids during pregnancy promote the growth of uterine myomas, such growth usually occurs only in the first trimester, and many myomas, particularly those that are large, often shrink later in pregnancy (18, 19). The incidence of symptoms related to the degeneration of myomas during pregnancy is relatively low. Myomas have been reported to increase the risk of malpresentation (odds ratio [OR], 2.9; 95% confidence interval [CI], 2.6–3.2), cesarean section (OR, 3.7; 95% CI, 3.5–3.9), preterm delivery (OR, 1.5;

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95% CI, 1.3–1.7), and spontaneous miscarriage (OR, 1.6; 95% CI, 1.3–2.0) (17). A review of pregnancy outcomes among 1,941 women who underwent myomectomy observed that 19% of pregnancies ended in spontaneous abortion after surgery, compared with 41% before myomectomy (11).

At least two retrospective studies suggest that the specific location of myomas is important to outcomes in pregnancy. Those adjacent to the placental site have been associated with increased risks for bleeding, abruption, and premature rupture of membranes (20, 21). Although myomectomy rarely is indicated in pregnancy, case reports suggest that the procedure can be performed safely when necessary (22).

EVALUATION

Symptoms of myomas include pelvic pressure and/or pain, increasing abdominal girth, urinary or rectal symptoms, and reproductive failure. Abnormal bleeding is common and usually involves increasingly heavy or prolonged menses, often with dysmenorrhea. Women having regular cycles and a consistent pattern of premenstrual molimina may be presumed ovulatory; a luteal phase serum P concentration greater than 3 ng/mL confirms the clinical impression. In such cases, endometrial biopsy is rarely indicated because the risk of hyperplasia or malignancy is remote (23, 24). Uterine enlargement usually is determined by clinical examination. The size, number, and location of myoma(s) may be documented by ultrasound. Transvaginal ultrasound in conjunction with the introduction of sterile saline (sonohysterography) can determine whether a centrally located myoma impinges directly on the uterine cavity and may be amenable to treatment by hysteroscopic resection rather than by abdominal myomectomy. Whereas intramural or subserosal myomas are more likely to cause pressure, pain, and distortion of adjacent organs, submucous and intracavitary myomas most often are associated with menorrhagia and intermenstrual bleeding and, as discussed above, also are more likely to have adverse effects on reproductive function. Although not usually necessary, computed tomography or magnetic resonance imaging (MRI) may be helpful in planning surgery in selected cases, especially when contemplating laparoscopic myomectomy (which does not allow palpation for locating deep intramural myomas).

In infertile women with uterine myomas, thorough evaluation to exclude other common and possibly coexisting causes of infertility should be completed before concluding that a specific treatment of myomas is indicated (11). Hysterosalpingography (HSG) is indicated to assess the uterine cavity and tubal patency. If a balloon catheter is used to perform the HSG, it should be deflated at the end of the procedure to allow for complete evaluation of the cavity. Hysteroscopy is unnecessary when the uterine cavity contour is normal (25). When HSG reveals a filling defect in the uterine cavity, sonohysterography or office hysteroscopy can more precisely define the location and attachment of the lesion(s) and determine whether a submucous myoma(s) is (are) amenable to hysteroscopic resection. Evidence indicates that sonohysterography is highly sensitive for identifying intrauterine lesions and yields results that correlate well with those obtained by hysteroscopy (26). Sonohysterography generally causes little discomfort and is easier to perform and less costly than office or outpatient hysteroscopy (27).

CLINICAL MANAGEMENT

Expectant Management

Women with uterine myomas and otherwise unexplained infertility may be managed expectantly, but there are no data to predict the monthly fecundity that might be expected. In the past, surgical treatment for asymptomatic myomas generally was recommended for women whose uterus exceeded 12 weeks' size, but the recommendation was based on assumptions that have since been effectively refuted (28):

1. The adnexae cannot be assessed by palpation. Surgery for this indication presumed that palpation of the adnexae was important for the early detection and treatment of ovarian cancer. However, most ovarian cancers are identified only after the disease has spread beyond the ovary, and ultrasound or other types of imaging can assess the adnexae accurately regardless of the uterine size (29).
2. The myomas will eventually cause symptoms that require treatment. The growth, regression, and symptoms of myomas vary widely and cannot be predicted; surgery is not indicated for the treatment of symptoms that may never occur.
3. Surgery that is postponed will be more difficult technically. At least two studies have demonstrated that complication rates associated with myomectomy and with hysterectomy for large (12–20 weeks' size) or smaller myomatous uteri (12 weeks' size or less) are comparable (28, 30, 31).
4. Rapid growth may be an indication of leiomyosarcoma. The incidence of leiomyosarcoma in hysterectomy specimens obtained from women receiving surgical treatment for uterine myomas increases with age, from as low as 0.1% among women of reproductive age (1) to a high of 1.7% among women who receive surgical treatment for uterine myomas after age 60 (32), and does not relate to uterine size or to the rate of uterine growth (32, 33). These observations imply that more women may die as a result of complications of hysterectomy performed for asymptomatic myomas during the reproductive years (1 to 1.6 per 1,000) (3) than would be saved from death by excision of a leiomyosarcoma.

Medical Treatment

Several medical treatments have been demonstrated to reduce the size and to relieve the symptoms of myomas. Gonadotropin-releasing hormone (GnRH) agonists cause myoma

shrinkage by inducing hypoestrogenemia and have been the standard medical treatment for myomas over the past two decades. Androgen therapy with gestrinone or danazol has been effective in small studies, but the frequency of adverse side effects has limited its use (34, 35). The P antagonist mifepristone has been observed to decrease the size and symptoms of myomas in a small placebo-controlled randomized trial (36). Other agents currently under investigation include selective estrogen and P receptor modulators and aromatase inhibitors, but none currently is approved or recommended for clinical use. Although myoma volume may be reduced approximately 50% by medical treatments, the uterus typically returns to pretreatment size after the medications are discontinued. There is no evidence that fertility improves with medical therapy (37). Medical therapy also may delay more effective treatments and therefore cannot be recommended for the treatment of infertility.

Surgical Treatment

Hysterectomy is the definitive surgical treatment for symptoms relating directly to uterine myomas. Myomectomy is the only treatment option for women interested in future fertility and may be considered by women who have completed childbearing but prefer not to have their uterus removed.

Women contemplating myomectomy should receive careful and thorough counseling regarding the likely results of surgery and its intrinsic risks. Preoperative HSG, sonohysterography, or hysteroscopy should identify submucous and intracavitary myomas that may be amenable to hysteroscopic surgery.

Hysteroscopic Myomectomy Hysteroscopic myomectomy is indicated for intracavitary myomas and submucous myomas having at least 50% of their volume within the uterine cavity. Myomas may be removed using hysteroscopic scissors, monopolar or bipolar electrosurgical techniques, or mechanical morcellators or by laser methods. The procedure can be challenging technically, and complications include uterine perforation, hemorrhage, fluid overload, and hyponatremia (when distension media other than saline are used). The additional risk of postoperative intrauterine adhesions increases with the size and number of myomas and the extent of endometrial disruption. Measures commonly used in efforts to decrease the risk of postoperative adhesions include inserting a balloon catheter in the uterus to prevent apposition of denuded surfaces for approximately 1 week after surgery, treatment with high doses of estrogen to promote proliferation of the endometrium, and early "second-look" hysteroscopy for lysis of recurrent adhesions. However, none of these techniques has been evaluated rigorously. There have been no randomized controlled trials aimed at assessing fertility after hysteroscopic myomectomy. In a small prospective cohort study, 72% of women with primary infertility conceived within 4 years after surgery and without further intervention; the miscarriage rate after surgery was 26%, compared with 62% before hysteroscopic myomectomy for women having a previous miscarriage (38).

Abdominal Myomectomy Various techniques have been applied effectively to reduce intraoperative blood loss during abdominal myomectomy. These include applying a tourniquet around the uterine isthmus to occlude the uterine vessels; placement of vascular clamps on the infundibulopelvic ligaments; transverse uterine incisions, parallel to myometrial vessels; and injection of dilute vasopressin into the overlying serosa and adjacent myometrium (39, 40). The incidence of adhesions is extremely high (94%) when myomectomy requires incisions on the posterior wall of the uterus and is lower, but still relatively high (55%), when the anterior surface of the uterus is incised (41); posterior pelvic adhesions also tend to be more dense and severe. Consequently, anterior uterine incisions are preferable, whenever possible. Postoperative adhesions that distort the adnexal anatomy may compromise future fertility. Whereas oxidized regenerated cellulose (Interceed; Ethicon, Women's Health and Urology, Somerville, NJ) (42), sodium hyaluronate/carboxymethyl cellulose (Seprafilm; Genzyme, Cambridge, MA), and expanded polytetrafluoroethylene (Gore-Tex Surgical Membrane; W.L. Gore Corp., Flagstaff, AZ) surgical adhesion barriers have been demonstrated to be effective for reducing postoperative adhesions after myomectomy, there is no substantial evidence that their use improves fertility, reduces pain, or decreases the incidence of postoperative bowel obstruction (43). In many cases, surgery may be performed via a minilaparotomy, resulting in an earlier recovery and a more cosmetic scar.

Laparoscopic Myomectomy Laparoscopic myomectomy has been advocated as a minimally invasive alternative to traditional open abdominal myomectomy. Two randomized studies observed no differences in operative time or blood loss but noted that laparoscopy was associated with less postoperative pain, a shorter length of stay, and a more rapid recovery (44, 45); one also noted no significant differences in pregnancy and spontaneous abortion rates between the two techniques.

Case reports have described uterine rupture during pregnancy after laparoscopic myomectomy. Some have speculated that the greater use of electrocautery to achieve hemostasis and the technical difficulties of myometrial reconstruction during laparoscopic myomectomy may predispose to a higher incidence of subsequent rupture (46, 47). Although the complication appears rare, there are no reliable data allowing direct comparison of the incidence of uterine rupture during pregnancy after open and laparoscopic myomectomy. Laparoscopic-assisted myomectomy has been advocated as a means to reduce the risk of uterine rupture and to reduce operative time (48). The technique involves laparoscopic excision of the myomas, followed by minilaparotomy to facilitate removal of the specimens and secure repair of the myometrium.

A multicenter trial in which patients were randomized to myomectomy by laparoscopy or minilaparotomy observed that minilaparotomy was easier, quicker, and associated with no more blood loss than laparoscopy when myomas were anterior, fundal, or lateral; operating time and blood loss were lower with laparoscopy when myomas were

posterior or located within the broad ligaments. Overall, patients who underwent laparoscopic myomectomy required less analgesia and had a shorter hospital stay, but postoperative pain and time to full recovery for the two groups were comparable (49, 50). Cumulative pregnancies and live births after 12 months also were similar in the two groups, although the pregnancy and live-birth rates (per cycle) were higher after laparoscopic myomectomy.

Another laparoscopic technique, myolysis, involves thermal destruction of myomas via insertion of cryoprobes, electrocautery needles, or fiberoptic lasers. A nonsurgical method for myolysis involving MRI-guided focused ultrasonic treatment also has been described (51). Data relating to the short- and long-term outcomes achieved with such treatments are still lacking and, until they become available, myolysis cannot be recommended for women hoping to maintain or improve their fertility.

Preoperative Treatment with GnRH Agonists A number of studies have evaluated the utility of preoperative treatment with a GnRH agonist before myomectomy (52–58). Overall, results support the following conclusions:

1. Preoperative treatment with a GnRH agonist and iron supplementation significantly increases the preoperative hemoglobin and hematocrit in anemic women.
2. In the only randomized controlled trial involving preoperative treatment with a GnRH agonist, treatment increased operating time significantly and had no discernible effect on estimated blood loss, postoperative fever, length of stay, and pregnancy rates (59).
3. GnRH agonist pretreatment may increase the technical difficulty of myomectomy by causing myomas to become soft and thus obscuring the proper plane of dissection.
4. Preoperative treatment with a GnRH agonist may increase the likelihood of recurrent/persistent myomas (60) and the likelihood that laparoscopic myomectomy must be abandoned in favor of an open technique (61).

The clinical utility of preoperative treatment with a GnRH agonist before hysteroscopic myomectomy has not been evaluated. Some investigators have suggested that such treatment facilitates the procedure by causing atrophy of adjacent tissue and, to some extent, by reducing the size of the myomas, but there is no consensus of expert opinion on the issue.

Outcomes Achieved with Myomectomy Up to 80% of women report relief from symptoms after myomectomy (11). Life table analysis yields a 10-year clinical recurrence rate of approximately 27% (62). Recurrence appears more common after the removal of multiple myomas than after removal of a solitary myoma (63). In one study, reoperation generally was not required until 3 or more years after the original surgery. Term pregnancy rates after myomectomy range between 40% and 50% (1, 11). However, virtually all studies of success rates are retrospective and have not employed contemporary methods of statistical analysis. Although the duration of follow-up has varied among studies, some investigators have observed that the majority of women who conceive after myomectomy do so within 1 year; the observation is consistent with pregnancy rates observed after other surgical treatments for infertility. The number and size of myomas removed does not appear to correlate with postoperative pregnancy rates (11). Although data describing fertility after hysteroscopic and laparoscopic myomectomy are quite limited, the results achieved appear comparable to those after abdominal myomectomy (45, 64, 65).

The impact of myomectomy on miscarriage risk has not been evaluated carefully. As discussed above, one large retrospective study observed that 19% of pregnancies ended in spontaneous abortion after surgery, compared with 41% before myomectomy (11), but the inherent limitations of the study design prevent a confident conclusion. The effects of myomectomy on the incidence of adverse obstetrical outcomes such as premature labor and malpresentation also have not been studied adequately. Although it generally is recommended that women who undergo abdominal myomectomy not be allowed to labor and should deliver by cesarean section, there is no direct evidence to support the recommendation, which derives, by inference, from observations relating to the risk of uterine rupture during pregnancy after classical cesarean section. At least one study observed no uterine ruptures associated with 212 births after myomectomy, 83% of which were vaginal deliveries (66).

Uterine Artery Embolization

Uterine artery embolization (UAE) has been used for the treatment of myomas since the early 1990s. Several small series have reported that UAE reduces the overall size of the uterus, and that of dominant myomas, by 40%–50% in approximately 90% of cases (67, 68). Up to 80% of women treated by UAE have observed decreased menstrual flow and pain, but the intervals of follow-up have been relatively brief. Nausea, vomiting, pain, and fever are common during the 48 hours immediately after the procedure. Adverse events following UAE have included infectious complications requiring hysterectomy, transcervical expulsion of a myoma, pelvic pain, nonpurulent vaginal discharge, delayed diagnosis of leiomyosarcoma, and diminished ovarian reserve or premature ovarian failure, particularly in older women. Successful pregnancies after UAE have been described, but data relating to fertility and pregnancy outcomes after UAE are still quite limited, and the procedure therefore cannot be recommended for women planning a later pregnancy (69, 70). One randomized controlled trial in which 58 women were randomized to UAE and 63 to myomectomy found that UAE was less invasive, as effective for treatment of symptoms, and as safe as myomectomy; among women trying to conceive, there were 33 pregnancies in 40 women after myomectomy and 17 pregnancies among 26 women after UAE during the first 2 years of follow-up (71).

A new noninvasive technique (Flostat; Vascular Control Systems, San Juan Capistrano, CA) employs a Doppler-guided device that is applied transvaginally to the cervix to mechanically compress and occlude the uterine arteries for an interval of hours. After its removal, normal myometrium reperfuses

but myomas do not, and they subsequently degenerate. Results of feasibility studies suggest the method can decrease myoma volume by approximately 40%–50% (72), but studies of subsequent reproductive function have not yet been performed.

SUMMARY AND CONCLUSIONS

- The effects of myomas on reproductive function outcome are not well defined. Overall, evidence suggests that myomas are the primary cause of infertility in a relatively small proportion of women.
- Myomas that distort the uterine cavity and larger intramural myomas may have adverse effects on fertility.
- Medical treatment for myomas does not improve infertility. Preoperative medical treatment with a GnRH agonist should be considered for women who are anemic and those who might be candidates for a less invasive procedure if the volume of their myoma(s) was moderately smaller.
- In infertile women and those with recurrent pregnancy loss, myomectomy should be considered only after a thorough evaluation has been completed.
- Myomectomy is a relatively safe surgical procedure associated with few serious complications. However, postoperative adhesions are common after abdominal myomectomy and pose a significant potential threat to subsequent fertility.
- UAE, myolysis, and MRI-guided ultrasonic treatment should not be recommended for women with myomas seeking to maintain or improve their fertility because their safety and effectiveness in such women has not been established.

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