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The Management of Uterine Fibroids in Women With Otherwise Unexplained Infertility

This clinical practice guideline was prepared by the Reproductive Endocrinology and Infertility Committee, reviewed by Family Physician Advisory and Clinical Practice Gynaecology Committees, and approved by the Executive and Board of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To provide recommendations regarding the best management of fibroids in couples who present with infertility. Usual and novel treatment options for fibroids will be reviewed with emphasis on their applicability in women who wish to conceive.

Options: Management of fibroids in women wishing to conceive first involves documentation of the presence of the fibroid and determination of likelihood of the fibroid impacting on the ability to conceive. Treatment of fibroids in this instance is primarily surgical, but must be weighed against the evidence of surgical management improving clinical outcomes, and risks specific to surgical management and approach.

Outcomes: The outcomes of primary concern are the improvement in pregnancy rates and outcomes with management of fibroids in women with infertility.

Evidence: Published literature was retrieved through searches of PubMed, MEDLINE, the Cochrane Library in November 2013 using appropriate controlled vocabulary (e.g., leiomyoma, infertility, uterine artery embolization, fertilization in vitro) and key words (e.g., fibroid, myomectomy). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English and French. There were no date restrictions. Searches were updated on a regular basis and incorporated in the guideline to November 2013. Grey (unpublished literature) was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described by the Canadian Task Force on Preventive Health Care (Table).

Benefits, harms, and costs: These recommendations are expected to allow adequate management of women with fibroids and infertility, maximizing their chances of pregnancy by minimizing risks introduced by unnecessary myomectomies. Reducing complications and eliminating unnecessary interventions are also expected to decrease costs to the health care system.

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Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in here has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[52]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[52]

Summary Statements

1. Subserosal fibroids do not appear to have an impact on fertility; the effect of intramural fibroids remains unclear. If intramural fibroids do have an impact on fertility, it appears to be small and to be even less significant when the endometrium is not involved. (II-3)
2. Because current medical therapy for fibroids is associated with suppression of ovulation, reduction of estrogen production, or disruption of the target action of estrogen or progesterone at the receptor level, and it has the potential to interfere in endometrial development and implantation, there is no role for medical therapy as a stand-alone treatment for fibroids in the infertile population. (III)
3. Preoperative assessment of submucosal fibroids is essential to the decision on the best approach for treatment. (III)
4. There is little evidence on the use of Foley catheters, estrogen, or intrauterine devices for the prevention of intrauterine adhesions following hysteroscopic myomectomy. (II-3)
5. In the infertile population, cumulative pregnancy rates by the laparoscopic and the minilaparotomy approaches are similar, but the laparoscopic approach is associated with a quicker recovery, less postoperative pain, and less febrile morbidity. (II-2)
6. There are lower pregnancy rates, higher miscarriage rates, and more adverse pregnancy outcomes following uterine artery embolization than after myomectomy. (II-3) Studies also suggest that uterine artery embolization is associated with loss of ovarian reserve, especially in older patients. (III)

ABBREVIATIONS

CPR	clinical pregnancy rates
FSH	follicle-stimulating hormone
IR	implantation rates
IVF	in vitro fertilization
LBR	live birth rates
MR	miscarriage rates
MRGfUS	magnetic resonance-guided focused ultrasound surgery
MRI	magnetic resonance imaging
OBR	ongoing pregnancy rates
RCT	randomized control trial
UAE	uterine artery emolization

Recommendations

1. In women with infertility, an effort should be made to adequately evaluate and classify fibroids, particularly those impinging on the endometrial cavity, using transvaginal ultrasound, hysteroscopy, hysterosonography, or magnetic resonance imaging. (III-A)
2. Preoperative assessment of submucosal fibroids should include, in addition to an assessment of fibroid size and location within the uterine cavity, evaluation of the degree of invasion of the cavity and thickness of residual myometrium to the serosa. A combination of hysteroscopy and transvaginal ultrasound or hysterosonography are the modalities of choice. (III-B)
3. Submucosal fibroids are managed hysteroscopically. The fibroid size should be < 5 cm, although larger fibroids have been managed hysteroscopically, but repeat procedures are often necessary. (III-B)
4. A hysterosalpingogram is not an appropriate exam to evaluate and classify fibroids. (III-D)
5. In women with otherwise unexplained infertility, submucosal fibroids should be removed in order to improve conception and pregnancy rates. (II-2A)
6. Removal of subserosal fibroids is not recommended. (III-D)
7. There is fair evidence to recommend against myomectomy in women with intramural fibroids (hysteroscopically confirmed intact endometrium) and otherwise unexplained infertility, regardless of their size. (II-2D) If the patient has no other options, the benefits of myomectomy should be weighed against the risks, and management of intramural fibroids should be individualized. (III-C)

8. If fibroids are removed abdominally, efforts should be made to use an anterior uterine incision to minimize the formation of postoperative adhesions. (II-2A)
9. Widespread use of the laparoscopic approach to myomectomy may be limited by the technical difficulty of this procedure. Patient selection should be individualized based on the number, size, and location of uterine fibroids and the skill of the surgeon. (III-A)
10. Women, fertile or infertile, seeking future pregnancy should not generally be offered uterine artery embolization as a treatment option for uterine fibroids. (II-3E)

INTRODUCTION

Uterine fibroids, myomas, or leiomyomata are smooth muscle cell tumours and are the most common benign gynaecologic tumour in women of reproductive age.[1] They are often found as part of the investigation of a couple presenting with infertility, and their origin is monoclonal.[2] They are rarely found before menarche and usually regress after menopause.[3] They are hormonally responsive, and estrogens appear to promote their growth.[4,5] Local estrogen concentrations have been shown to be higher in myomas than in the surrounding myometrium, possibly because of a higher concentration of aromatase.[6] Hormonal responsiveness appears to be greater in submucosal than subserosal myomas.[7]

EVALUATION AND CLASSIFICATION OF FIBROIDS

Submucosal fibroids have a negative impact on rates of implantation, clinical pregnancy, ongoing pregnancy, miscarriage, and live birth. An important feature of fibroid classification systems is the evaluation of the uterine cavity in order to define a fibroid as submucosal. Many studies have not included proper evaluation of the cavity, and therefore potential biases can be expected in their results. Imaging is now recognized as a necessary tool in the preoperative evaluation of myomas, especially for uterus-sparing procedures.[8]

Ultrasound has been shown to be an adequate, rapid, safe, and cost-effective means of evaluating the size, number, and location of fibroids.[9] Transvaginal ultrasound may identify fibroids of up to 4 to 5 mm in diameter.[10] Ultrasound may, however, be suboptimal for multiple fibroids, because of acoustic shadowing, and for the proper evaluation of endometrial impingement. Interobserver variation has also been found to be greater with this technique than with MRI.[11]

MRI has been well studied in the evaluation of fibroid uteruses, especially for fibroid mapping and submucosal penetration. It was shown to be the most reliable method of evaluation when compared with vaginal ultrasound, hysterosonography, and hysteroscopy, with 100% sensitivity and 91% specificity (gold standard was pathological examination).[9] The main drawbacks of MRI evaluation are lack of accessibility and high cost.[8]

Hysterosalpingography is often performed to assess tubal patency in women with infertility and to exclude intrauterine pathology. However, the sensitivity and positive predictive value of this test for the identification of intrauterine lesions can be as low as 50% and 28.6% respectively.[12] Hysterosalpingography cannot therefore be considered reliable to exclude endometrial distortion secondary to submucosal myomas.

Hysterosonography, which has the advantages of pelvic ultrasound, has been advocated as superior to transvaginal ultrasound alone[13] and equal to hysteroscopy in the evaluation of endometrial impingement.[14] It has been shown to be highly sensitive and specific in the identification of submucosal myomas. Its main drawbacks are the risk of infection (approximately 1%) and the discomfort associated with the injection of sterile saline.[13]

No studies to date have evaluated the optimal mode of evaluating uterine myoma in women presenting with infertility. It is also unclear whether all women with infertility should have the integrity of their endometrial cavity evaluated. However, it seems clear that part of the heterogeneity in the results of studies attempting to clarify the relationships between fibroids and infertility and the impact of treatment on conception is due to inadequate classification of fibroids, and in particular their impact on the endometrial cavity.

Recommendations

1. In women with infertility, an effort should be made to adequately evaluate and classify fibroids, particularly those impinging on the endometrial cavity, using transvaginal ultrasound, hysteroscopy, hysterosonography, or magnetic resonance imaging. (III-A)
2. Preoperative assessment of submucosal fibroids should include, in addition to an assessment of fibroid size and location within the uterine cavity, evaluation of the degree of invasion of the cavity and thickness of residual myometrium to the serosa. A combination of hysteroscopy and transvaginal ultrasound or hysterosonography are the modalities of choice. (III-B)
3. Submucosal fibroids are managed hysteroscopically. The fibroid size should be < 5 cm, although larger fibroids have been managed hysteroscopically, but repeat procedures are often necessary. (III-B)
4. A hysterosalpingogram is not an appropriate exam to evaluate and classify fibroids. (III-D)

IMPACT OF FIBROIDS ON REPRODUCTIVE FUNCTION

The prevalence of fibroids in the infertile population of women is controversial. According to Donnez,[15] approximately 5% to 10% of women presenting with infertility are found to have one or multiple fibroids. However, when all other causes of infertility are excluded, fibroids are found in only 1% to 2% of the remaining women.[16] Both infertility and age have been associated with the presence of myomas and may therefore confound results of studies attempting to clarify the relationship between fibroids and infertility.[17] There have been no appropriately designed studies to demonstrate a direct causal relationship between the presence of fibroids and infertility.

Many hypotheses have been generated to explain how fibroids might cause infertility. Perfusion studies have shown that blood flow to uterine fibroids is less than that to the adjacent myometrium.[18–20] Blood flow to the uterine arteries is also different in fibroid uteruses than non-fibroid uteruses.[21] This and the fact that there may be endometrial inflammation and an altered local hormonal environment may impede embryo implantation. Myomas also seem to alter uterine contractility possibly interfering with sperm and ovum interaction or embryo migration.[4,15] This may especially be true in uteruses with multiple large fibroids with important cavity distortion.

Six systematic reviews or meta-analyses published between 2001 and 2010[15,22–26] assessed whether fibroids have an impact on fertility. On the whole, it appears that women with fibroids have decreased fertility. The presence of fibroids, regardless of location, significantly decreases both implantation and clinical pregnancy rates (RR 0.821; 95% CI 0.722 to 0.932, $P = 0.002$ and RR 0.849; 95% CI 0.734 to 0.982, $P < 0.03$ respectively).[25] The impact of fibroid number and size on fertility has not been clearly elucidated.[17] Reproductive success does, however, seem to be related to fibroid location.

Subserosal fibroids do not appear to have an impact on fertility; all systematic reviews and meta-analyses agreed on this point. Submucosal fibroids (fibroids with endometrial impingement), however, have been shown uniformly to have a negative impact on rates of implantation, clinical pregnancy, miscarriage, and live birth/ongoing pregnancy, although available studies are few and small (IR: RR 0.283; 95% CI 0.123 to 0.649, $P = 0.003$; CPR: RR 0.363; 95% CI 0.179 to 0.737, $P = 0.005$; MR: RR 1.678; 95% CI 1.373 to 2.051, $P = 0.022$; LBR/OPR: RR 0.318; 95% CI 0.119 to 0.850, $P < 0.001$).[25]

The greatest debate remains on the impact and treatment of intramural fibroids. Part of the disagreement between studies may result from inappropriate evaluation of the endometrial cavity causing the erroneous inclusion of submucosal fibroids in the group of intramural fibroids. Considering only the most recent good quality meta-analysis, intramural fibroids do seem to have an impact on both IR and CPR (RR 0.684; 95% CI 0.587 to 0.796, $P < 0.001$ and RR 0.810; 0.696 to 0.941, $P = 0.006$, respectively) but less than that of submucosal fibroids. Although the number of studies reporting this outcome was small, there was no impact found on LBR/OPR.[25] This finding remained significant regardless of study design and when looking exclusively at studies on IVF, except that Sunkara et al.[27] found a reduction in LBR in women undergoing IVF in the presence of intramural fibroids (RR 0.79; 95% CI 0.70 to 0.88, $P < 0.001$). This discrepancy in IVF studies could be explained by the authors' not controlling for age and number of IVF cycles. Considering only studies that included an adequate hysteroscopic evaluation of the uterine cavity, implantation remains the only rate significantly affected by the presence of intramural fibroids.[25] Fibroid size did not seem to have an impact on these results, although large intramural fibroids would presumably have been treated surgically and hence not included in such studies. Most studies included intramural fibroids < 5 cm. No studies have examined the distance between fibroid edge and endometrium. Only one retrospective study evaluated the impact of a single intramural fibroid on IVF outcomes for severe male factor. Endometrial cavity was assessed using hysteroscopy in all patients. Fibroid sizes ranged from 5 to 43 mm. IR and CPR were similar between cases (n = 61) and controls (n = 444).[28] Miscarriage rates were found to be increased in women with intramural fibroids (RR 1.747; 95% CI 1.22 to 2.489, $P = 0.002$), but this effect was lost when only studies with adequate cavity involvement evaluation were included.[25]

Another way of assessing whether a uterine pathology has an impact on conception rates is to evaluate whether pregnancy rates increase more after removal than after expectant management. It is equally important to ensure that treatment does not have an intrinsically negative impact on fertility, particularly in surgical treatments that can result in the formation of scar tissue and adhesions known to have deleterious effects on conception rates. Studies on treatment for leiomyomas in women with infertility have been few and small. Two types of control groups have been used: women with fibroids left in situ and women with unexplained infertility without fibroids.

No large trials have evaluated the impact of myomectomy in women with submucosal fibroids. A meta-analysis of

the small studies available found an apparent benefit of hysteroscopic myomectomy over fibroids left in situ on CPR (RR 2.034, 95% CI 1.081 to 3.826, $P = 0.028$). Pregnancy rates after myomectomy become statistically similar to those in women with infertility without fibroids.[25] In the matter of the surgical removal of intramural fibroids to improve fertility, data fail to show a clear benefit of myomectomy over myomas left in situ.

Summary Statement

1. Subserosal fibroids do not appear to have an impact on fertility; the effect of intramural fibroids remains unclear. If intramural fibroids do have an impact on fertility, it appears to be small and to be even less significant when the endometrium is not involved. (II-3)

MEDICAL MANAGEMENT

Contemporary medical management of uterine fibroids exploits the estrogen- and progesterone-responsiveness of uterine fibroids; however, no pharmacological agent is curative of fibroids. As a result, medical therapy is essentially a treatment option for the control of symptoms. Several agents exist for the management of uterine fibroids through symptom control, reduction in fibroid volume, and reduction in menstrual blood loss. Most commonly used agents have been GnRH analogues. Newer, novel therapies including aromatase inhibitors, mifepristone, selective estrogen receptor modulators, and selective progesterone receptor modulators have shown promise in symptom improvement and fibroid regression without the hypoestrogenic symptoms associated with GnRH analogues.

Summary Statement

2. Because current medical therapy for fibroids is associated with suppression of ovulation, reduction of estrogen production, or disruption of target action of estrogen or progesterone at the receptor level, and it has the potential to interfere in endometrial development and implantation, there is no role for medical therapy as stand-alone treatment for fibroids in the infertile population. (III)

SURGICAL MANAGEMENT

Well-designed surgical intervention trials for myomectomy and infertility are sparse, with a single RCT published to date.[28] This study demonstrated an improvement in spontaneous conception rates after the surgical removal of submucosal fibroids, but pregnancy rates following the removal of intramural or subserosal fibroids were no more improved than in the expectant management group of women with intramural-subserosal fibroids in situ. A recent meta-analysis demonstrated similar findings, with an improvement in pregnancy rates in infertile patients undergoing surgical removal of submucosal fibroids, but not in those undergoing surgical removal of intramural fibroids.[25]

Surgical treatment of fibroids can be associated with morbidity. It has been associated with both pelvic and intrauterine adhesions, so any potential benefit from the removal of the fibroids may be negated by the detrimental effect of the surgery on uterine integrity. In addition, the consequences of myomectomy on pregnancy outcomes are not negligible. It is therefore imperative that surgical management of fibroids for infertility be undertaken only when there is evidence to support improvement in pregnancy outcomes through surgical intervention. There may, however, be instances when surgical removal of fibroids in an infertile patient may be undertaken for reasons other than fertility enhancement, such as relief of pressure symptoms or surgical management of menstrual disturbances secondary to fibroids.

Recommendations

5. In women with otherwise unexplained infertility, submucosal fibroids should be removed in order to improve conception and pregnancy rates. (II-2)
6. Removal of subserosal fibroids is not recommended. (III-D)
7. There is fair evidence to recommend against myomectomy in women with intramural fibroids (hysteroscopically confirmed intact endometrium) and otherwise unexplained infertility, regardless of the size of the fibroids. (II-2D) If the patient has no other options, the benefits of myomectomy should be weighed against the risks, and management of intramural fibroids should be individualized. (III-C)

Surgical approach to fibroids can be either vaginal or abdominal. The abdominal approach may be either by laparotomy or laparoscopy. The specific approach will depend on fibroid size and location and on skill of the practitioner. The decision to proceed with myomectomy for improvement in fertility outcomes, especially when laparotomy is recommended, should be weighed against the patient's clinical fertility history, subsequent plans for fertility treatment, and estimated fecundability with or without myomectomy.

Hysteroscopic Myomectomy

Hysteroscopic myomectomy is the least invasive surgical approach to fibroid removal. It is most effective for patients with submucosal fibroids completely within the uterine cavity (Type 0) or with at least 50% of the fibroid

volume within the uterine cavity (Type I). Fibroids with less than 50% of the fibroid volume in the cavity (Type II) are much more difficult to resect completely and are more often associated with the need for repeated procedures.[29,30] Additionally, it has generally been recommended that hysteroscopic myomectomy be undertaken with fibroids under 5 cm; however fibroids greater than 5 cm and Type II fibroids have been resected hysteroscopically.[31]

Summary Statement

3. Preoperative assessment of submucosal fibroids is essential to the decision on the best approach for treatment. (III)

Of late, complications that may further impair fertility after hysteroscopic myomectomy, intrauterine adhesions are the most concerning. The incidence of intrauterine adhesions after hysteroscopic myomectomy was shown in one study to be 7.5%.[32] Postoperative adjuvant therapy, including estrogen therapy for 4 to 8 weeks or insertion of an intrauterine device, pediatric Foley catheter, or other balloon for 1 week postoperatively, have all been used to prevent further adhesion development. However, there is scant evidence to support the use of these postoperative therapies.[33,34]

Summary Statement

4. There is little evidence on the use of Foley catheters, estrogen, or intrauterine devices for the prevention of intrauterine adhesions following hysteroscopic myomectomy. (II-3)

Abdominal Myomectomy

Abdominal myomectomy is an effective surgical procedure for women wishing to preserve their fertility and who have pressure symptoms due to the mass effect of large fibroids. It may also be performed in women wishing to preserve their fertility with symptomatic menorrhagia that is neither controlled by medical management nor effectively managed by hysteroscopic myomectomy. With improvements in hysteroscopic myomectomy techniques, the use of abdominal myomectomy to improve fecundity has narrowed to a small subgroup of infertile patients with fibroids. The current indication for abdominal myomectomy is for infertile patients with large (> 5 cm) Type II submucosal fibroids or Type II fibroids with < 1 cm between the external surface of the fibroid and the uterine serosa. The goal, similar to that of hysteroscopic myomectomy for infertility, is to remove the fibroid in its entirety and to restore normal uterine cavity size and architecture. Abdominal myomectomy may be conducted through a subumbilical vertical incision for large fibroids, as a mini-laparotomy through a Pfannenstiel incision for smaller fibroids (typically < 10 cm), or laparoscopically.

Postoperative formation of adhesions after myomectomy is extremely high: in one study it was 94% with uterine incisions on the posterior wall and 55% when the incision occurred on the anterior uterine wall. Obviously these adhesions may have a negative impact on fertility in women where this is already a concern. These adhesions were lysed at second-look laparoscopy 6 weeks post myomectomy, with a 67% cumulative pregnancy rate 12 months post myomectomy.[35]

Recommendation

8. If fibroids are removed abdominally, efforts should be made to use an anterior uterine incision to minimize the formation of postoperative adhesions. (II-2A)

Best practice for adhesion prevention in gynaecologic surgery has been thoroughly described elsewhere.[36]

Two RCTs with a combined 267 patients compared reproductive outcomes of laparoscopic myomectomy and myomectomy by laparotomy. In the first study of patients undergoing myomectomy for infertility and at least 1 fibroid > 5 cm, pregnancy rates were similar following in the laparoscopy and laparotomy groups (53.6% vs. 55.9%).[37] There was lower febrile morbidity in the laparoscopy group (26.2% vs. 12.1%), shorter hospital stay, and a lower postoperative drop in hemoglobin. In the second study, 12 months postoperatively, cumulative pregnancy rates were similar in the laparoscopy and laparotomy groups (52.9% vs. 38.2%).[38] Miscarriage rates and preterm delivery rates were also similar between groups and similar to expected rates in the general population. Interestingly, in the subgroup of patients undergoing myomectomy for non-fertility indications the cumulative pregnancy rate was greater in the laparoscopy subgroup (73.7% vs. 50%). In this study, it appears myomectomy was not considered a contraindication to vaginal delivery, and 31% of all patients who delivered underwent a successful vaginal delivery.

Summary Statement

5. In the infertile population, cumulative pregnancy rates by the laparoscopic and minilaparotomy approaches are similar, but the laparoscopic approach is associated with a quicker recovery, less postoperative pain, and less febrile morbidity. (II-2)

Recommendation

9. Widespread use of the laparoscopic approach to myomectomy may be limited by the technical difficulty of this procedure. Patient selection should be individualized based on the number, size, and location of uterine fibroids and the skill of the surgeon. (III-A)

NEW METHODS OF TREATMENT OF FIBROIDS AND INFERTILITY

The last decade has seen increasing demand for safe and effective uterus- and "reproductive potential"-sparing treatment options for symptomatic uterine fibroids. The goal of this section is to review the important new techniques for uterus-sparing treatment of uterine fibroids and particularly their use in women with fibroids and infertility.

Newer uterus-sparing treatments include laser ablation, laparoscopic and vaginal occlusion of uterine arteries, MRGfUS, and UAE. However, many of these techniques have not been used on a large scale, and data on their reproductive outcomes in patients trying to conceive are insufficient to make recommendations. Here we review 2 techniques other than myomectomy, namely UAE and MRgFUS, that are currently being evaluated for patients who desire to keep their fertility.

Uterine Artery Embolization: Technique and Indications

UAE was first introduced in 1995 for treatment of uterine fibroids.[39] Uterine embolization has been well studied as an alternative to myomectomy and hysterectomy, mainly in women who no longer desire children, and it has progressively become one of the most widely used non-invasive conservative methods of treatment of uterine fibroids after myomectomy.

Current contraindications to UAE include pregnancy, infertility (or desire for future pregnancy), clinical findings and imaging suggestive of gynaecological malignancy, anaphylactic reaction to contrast material, renal failure, and coagulopathy.[40]

MRI studies during the hours following embolization have shown a transient ischemia of the uterine corpus and fundus affecting the endometrium and inner and middle myometrial layers, which subsides 48 to 72 hours later, but the fibroids undergo irreversible infarction.[41] Although intra-abdominal adhesions have been described to develop following this process, they are much less common than adhesions following myomectomy.[42,43] These findings imply, however, possible irreversible damage to the endometrium and formation of adhesion, which may be deleterious to women who already suffer from infertility.

Fertility in patients following UAE

Spontaneous pregnancy may be possible following UAE, but this conservative method of treatment is currently contraindicated in women seeking future pregnancy. In general, data on UAE in women with fibroids and infertility remains difficult to interpret because of patient heterogeneity (studies include women undergoing UAE for symptomatic fibroids, but also women with postpartum hemorrhage) and the almost exclusive inclusion of women who no longer desired pregnancy. The best comparative evidence available is in an RCT by Mara et al.[44] 121 patients wishing to become pregnant and having intramural fibroids > 4 cm were randomized to either UAE (n = 58) or abdominal (open or laparoscopic according to surgeon preference) myomectomy (n = 63). Of patients who attempted to conceive, 50% of the UAE group versus 78% of the myomectomy group were able to do so. The RR for UAE patients of not getting pregnant was 2.22 (95% CI 1.11 to 4.44), and of miscarriage was 2.79 (95% CI 1.25 to 6.22). Therefore, myomectomy was associated with more pregnancies and deliveries than UAE and a lower rate of miscarriage up to 2 years post therapy.

Another finding that raises concerns about the use of UAE in women with infertility is the fact that significantly more women in the UAE group presented with an FSH > 10 IU/L 6 months after the procedure (13.8% vs. 3.2%; $P < 0.05$), although the numbers were small. Other studies have found loss of ovarian reserve and an increase in ovarian failure in women undergoing UAE, particularly in women in later reproductive years. Transient or permanent amenorrhea associated with a decrease in ovarian reserve has been reported, with an incidence of 1% to 2% in women under 45.[45] A prospective study by Hovsepian et al. found that in patients between the ages of 35 and 40 there was a transient increase in FSH 3 months after UAE, but that after 6 months, FSH levels were similar to those of patients having undergone myomectomy or hysterectomy.[46] Another study found a loss of ovarian reserve in patients around 45 years of age expressed by increased FSH and decreased anti-Müllerian hormone lasting for at least 24 months following UAE and hysterectomy.[47]

It is important to mention that FSH is a poor marker of ovarian reserve and a poor predictor of ovarian response to IVF. It is also a later marker than antral follicle count or anti-Müllerian hormone, which have been shown to have much higher sensitivities and specificities for response to IVF. As IVF is usually required in women with unexplained infertility, ovarian reserve should be an important concern in treatment of fibroids. Unfortunately, no data using adequate markers were found regarding the impact of UAE on ovarian reserve in women of reproductive age.

The incidences of Caesarean section and postpartum hemorrhage were also both found to be higher following UAE (66% vs. 48.5% and 13.9% vs. 2.5%, respectively) than in control pregnancies matched for age and fibroid location.[48]

Concerns also remain about the formation of synechia from smaller particles lodging in the endometrial vasculature and about the obstetrical outcomes of women who undergo UAE and then conceive. UAE has been associated with increased risks of spontaneous miscarriage, preterm delivery, abnormal placentation, and postpartum hemorrhage.[49]

Summary Statement

6. There are lower pregnancy rates, higher miscarriage rates, and more adverse pregnancy outcomes following uterine artery embolization than after myomectomy. (II-3) Studies also suggest that uterine artery embolization is associated with loss of ovarian reserve, especially in older patients. (III)

Recommendation

10. Women, fertile or infertile, seeking future pregnancy should not generally be offered uterine artery embolization as a treatment option for uterine fibroids. (II-3E)

Magnetic Resonance-guided Focused Ultrasound Surgery

In 2004, the United States Federal Drug Administration approved the use of MRgFUS for treatment of uterine fibroids. This technique involves the destruction of uterine fibroid tissue by coagulative necrosis through heating tissue to over 70°C by focusing many high frequency ultrasound beams on the target tissue. For maximum accuracy, the ultrasound beams are guided with MRI, which has the best resolution and sensitivity to detect uterine fibroids.[50]

International experience of 54 pregnancies in 51 women following MRgFUS was recently reported from 13 sites.[51] These women had previously declared that they were not interested in future pregnancy and their mean age was 37.2 years. The miscarriage rate was 26%; 42% of the women had delivered at the time of publication, while 20% of the pregnancies were ongoing. 64% of women had a vaginal delivery and the mean weight at birth was 3.3 kg. There were 2 placenta praevia in this group of patients. Only 1 patient had a serious complication after a myomectomy done at the time of a Caesarean section. Her second pregnancy was uneventful.

There are currently no data comparing MRgFUS with myomectomy and no studies of its use in women with fibroids and infertility as their main complaints. Further studies are needed before offering this treatment to women with fibroids and otherwise unexplained infertility.

SUMMARY

Women presenting with both fibroids and a history of otherwise unexplained infertility represent a challenge. These women may or may not be symptomatic from these fibroids. They may have one or more fibroids that are only detectable through ultrasound examination or the fibroids may be easily palpable on abdominal examination. With such a heterogeneous disorder, studies are difficult to perform and adequate conclusions difficult to draw.

The effect of fibroids on reproduction remains in question. Submucosal fibroids seem to have an impact, whereas subserosal do not. Intramural fibroids might have an impact, but randomized studies with adequate evaluation of intracavitary involvement are necessary to adequately evaluate whether the benefits of treatment will outweigh the serious surgical and obstetrical risks that follow myomectomy.

Treatment of fibroids should be individualized, and symptomatology may be a decisive factor in whether or not a fibroid is removed. Myomectomy remains the gold standard for treatment.

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