

# Removal of myomas in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline

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The purpose of this systematic review is to evaluate if uterine myomas impact the likelihood of pregnancy and pregnancy loss, and if myomectomy influences pregnancy outcomes in asymptomatic women. There is insufficient evidence to conclude that the presence of myomas reduces the likelihood of achieving pregnancy. However, there is fair evidence that myomectomy (open or laparoscopic) for cavity-distorting myomas (intramural or intramural with a submucosal component) improves pregnancy rates and reduces the risk of early pregnancy loss. There is fair evidence that hysteroscopic myomectomy for cavity-distorting myomas improves clinical pregnancy rates but insufficient evidence regarding the impact of this procedure on the likelihood of live birth or early pregnancy loss. In women with asymptomatic cavity-distorting myomas, myomectomy may be considered to optimize pregnancy outcomes. (*Fertil Steril*® 2017;108:416–25. ©2017 by American Society for Reproductive Medicine.)

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## INTRODUCTION

Uterine myomas (leiomyomata, fibroids) are the most common tumor of the reproductive tract, with a cumulative incidence of 70% in women of reproductive age (1, 2). These benign monoclonal tumors are more common and are associated with the most severe symptoms in women of African descent (3, 4). Compared with Caucasian women with symptomatic myomas, women of African descent typically present to their provider at a younger age and with a significantly worse myoma burden (larger size and number) (3).

According to the US Census Bureau 2007 data, there were more than 355,000 myoma-related admissions (5). It is estimated that myoma-related hospitalizations, both surgical and nonsurgical, will increase 23% by 2050, mostly related to the changing

demographics of the country (5). According to the 2007 Nationwide Inpatient Sample (NIS) database ([www.hcup-us.ahrq.gov](http://www.hcup-us.ahrq.gov)), myomectomy accounts for only 30,000 of these admissions. The rate of myomectomy is reported to be 9.2 per 10,000 women years in black women and 1.3 per 10,000 women years in white women (5).

Prior studies illustrate the successful use of myomectomy for symptom relief and improvement of health-related quality of life (6). In contrast, there has been significant controversy regarding the impact of uterine myomas on fertility and pregnancy outcomes and whether removal of myomas in asymptomatic women improves fertility or pregnancy outcomes.

It is important to use consistent terminology for the location of fibroids to discuss the impact of various types of fibroids on reproduction. Most societies and clinical research trials use the In-

ternational Federation of Gynecology and Obstetrics (FIGO) staging scheme for fibroid location (7) (Fig. 1).

## Limitations of the Literature

Data evaluating reproductive outcomes related to myomas are derived primarily from observational studies. Such studies are problematic as they are prone to selection bias and confounding variables. For example, women with myomas tend to be older, compared with women without myomas, and tend to represent different well-defined ethnic groups. Regarding the studies assessing the benefits of myomectomy, the literature mostly consists of level-II and -III studies which include small heterogeneous patient populations (infertile vs fertile; symptomatic vs asymptomatic), characterize myomas inconsistently (in terms of location, size, and number of myomas), and often do not consistently or comprehensively evaluate clinically relevant reproductive outcomes such as time to pregnancy, clinical pregnancy rate, live-birth rate, and miscarriage rate. In addition, heterogeneity

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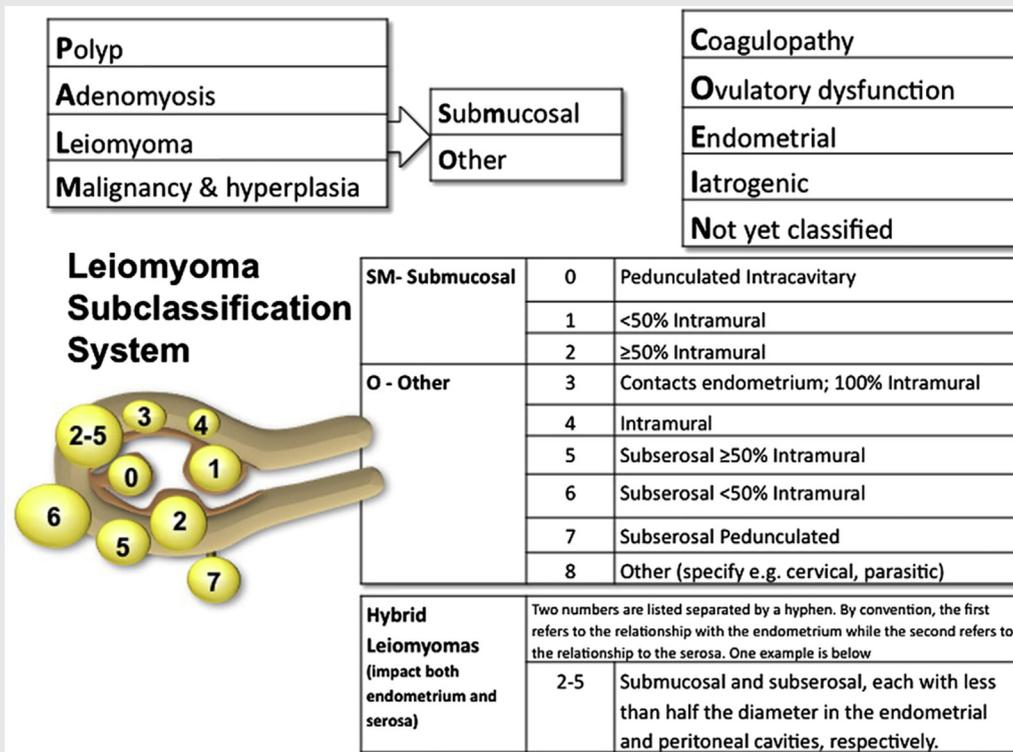
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FIGURE 1



International Federation of Gynecology and Obstetrics (FIGO) classification system for fibroid location. (Adapted from Munro MG, Critchley HO, Broder MS, Fraser IS; for the FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *Int J Gynecol Obstet* 2011;113:3-13. Published by Elsevier Ireland Ltd. Reprinted by permission of Elsevier [7].).

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seen in the size and location of myomas makes it difficult to generalize results as both these variables are inconsistently characterized in studies and both modify the associated symptoms and surgical outcomes. Laparoscopic studies more commonly include patients with subserosal myomas and rarely include patients with myomas with a submucosal component—more common in abdominal myomectomy series, which are usually comprised of patients with a large myoma burden. Additionally, many studies focus on the assisted reproductive technology (ART) population; however, others include “infertile” women and lack descriptive results about the mode of conception postoperatively. The majority of systematic reviews include subjects with spontaneous conceptions as well as pregnancies from advanced reproductive technologies. Furthermore, most studies are small, with insufficient power to detect clinically relevant associations. As a result, interpreting data regarding the impact of different surgical routes of myomectomy on conception and the rate of pregnancy loss has been difficult. Definitive clinical recommendations are difficult to generate because of the heterogeneity seen in location and size of leiomyomata, the variety of resulting clinical symptoms, and the range of methodology and endpoints of available literature. The purpose of this systematic review is to evaluate if there is evidence that uterine myomas impact the likelihood of pregnancy and early preg-

nancy loss, respectively, and if myomectomy influences pregnancy and live-birth rates in asymptomatic women of reproductive age. While obstetrical outcomes are important to consider, discussion of them is outside the scope of this document.

## METHODS

This clinical practice guideline was based on a systematic review of the literature performed in the electronic database MEDLINE through PubMed on March 3, 2016. No limit or filter was used for the time period covered or English language, but articles were subsequently culled for English language. This electronic search and examination of reference lists from primary and review articles yielded 1,785 studies, of which 88 studies were included.

A combination of the following medical subject headings or text words were used: abortion; ART; assisted reproductive techn\*; birth; embolization; embolization/therapeutic; embryo transfer; endoscopic; endoscopy; fertility; fertilization in vitro; fibroid; fibroma; fibromyoma; hysteroscopy; intra-uterine; intrauterine insemination; intrauterine pathology; intrauterine pathologies; in vitro fertilization; in vitro fertilisation; IUI; IVF; laparoscopic; laparoscopy; laparotomy; leiomyoma; metroplast\*; miscarriage; myoma; myomect\*;

**TABLE 1****Summary of inclusion/exclusion criteria.****Include**

Level I and II studies

Human studies  
English  
Studies with a comparison group  
IVF, ART, IUI studies  
Infertile patients  
Women of reproductive age  
Women with recurrent pregnancy loss  
Myomas/fibroids/leiomyomas

**Exclude**

Level III studies: Descriptive studies, case series, case reports, letters, nonsystematic reviews, off-topic studies, opinions, and reports of expert committees

Animal studies  
Non-English  
Studies without a comparison group  
Peri- and postmenopausal women  
Studies that focus on diagnosis of fibroids/myomas  
Adenomyosis  
Endometrial polyps  
Comparisons of specific types of surgical treatments  
Studies that focus on adhesions  
Studies that focus on morcellation  
Uterine artery embolization

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pregnancy; pregnancy outcome; removal; reproductive techniques, assisted; uterine; uterine myomectomy; uterine neoplasms; uterus.

Initially, titles and abstracts of potentially relevant articles were screened and reviewed to develop inclusion/exclusion criteria (Table 1). Only studies that met the inclusion criteria were assessed in the final analysis. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated with an outcome measure (pregnancy, ovulation, or live-birth rates); meta-analyses; and relevant articles from bibliographies of identified articles.

Four members of an independent task force reviewed the full articles of all citations that potentially matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and resolved by consensus or arbitration after consultation with an independent reviewer/epidemiologist.

The level of the evidence was evaluated using the following grading system and is assigned for each reference in the bibliography:

## Level I

- Systematic review of randomized controlled trials (RCTs)
- RCTs

## Level II

- Systematic review of a combination of RCTs, controlled trials without randomization, and cohort studies
- Controlled trials without randomization
- Cohort studies
- Case-control studies

## Level III

- Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions based on clinical experience, and reports of expert committees.

The strength of the recommendations was evaluated as follows:

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

## WHAT IS THE IMPACT OF LEIOMYOMAS ON REPRODUCTIVE OUTCOME?

Uterine leiomyomas can cause clear anatomical disruption of the standard uterine architecture. In particular, submucosal leiomyomas may impact the endometrial cavity, thereby plausibly impacting embryo implantation and development. Alternatively, leiomyomas may exist in the myometrium or in a subserosal location. Such leiomyomas may grow to large sizes prior to inducing symptoms of pelvic pressure or pain, but could potentially disrupt fertility and maintenance of pregnancy. This section reviews evidence from observational studies comparing reproductive outcomes in women with and without fibroids and excludes studies that assess the impact of surgical removal of fibroids on outcomes. The section is divided into two parts: studies that evaluate the impact of fibroids on the likelihood of achieving pregnancy and studies that evaluate the impact of fibroids on the likelihood of maintaining pregnancy.

### Likelihood of Achieving Pregnancy

**Unassisted pregnancy rate.** There are limited data assessing the impact of asymptomatic fibroids on the likelihood of unassisted pregnancy. Only one observational study compared self-reported time to pregnancy in pregnant women with and without fibroids who did not receive fertility treatments. In this study, there was no significant association between the presence, type, location, or size of fibroids on time to pregnancy (8). The major limitation of this study is that only pregnant women were recruited, so fertility was not assessed prospectively in a nonpregnant population. Therefore, this

study design may have biased the results toward not finding a significant association.

**Assisted pregnancy rate.** Most available data include studies assessing the impact of fibroids on the success of fertility treatments, particularly in vitro fertilization (IVF). Several prospective cohort studies have investigated the impact of leiomyomas in achieving pregnancy with IVF. The largest study demonstrated a decrease in clinical pregnancy rate per embryo transfer (23.3% in women with intramural fibroids  $\leq 5$  cm [mean size was 2.3 cm and 90% range was 2.1–2.5 cm] compared to 34.1% in women without fibroids) (9). However, this study has been criticized, as the women who had leiomyomas ( $n=112$ ) were older (36.4 years compared to 34.6 years in the unaffected group [ $n=322$ ]), and as such, the results may have been confounded by age. A prospective study of women with non-cavity-distorting fibroids and infertile women without fibroids as controls demonstrated reduced clinical pregnancy rates and deliveries (10). There were 34 clinical pregnancies (37%) and 30 deliveries (33%) in the myoma group, and 48 clinical pregnancies (53%) and 44 deliveries (48%) in the control group. The mean of the largest myoma size was 28.7 mm. Another prospective cohort study found that women with non-cavity-distorting myomas ( $n=77$ ) had similar pregnancy rates per embryo transfer compared to women without myomas ( $n=312$ ) (11). Several other studies addressing this issue are retrospective and most are underpowered to demonstrate a difference between the affected and unaffected groups (12–21). Of the remaining retrospective studies assessed, there are data to support (22–29) and refute (23, 30–33) the negative impact of leiomyomas on clinical pregnancy or live-birth rates. Attempts to consolidate the data are impaired by the substantial variation in characteristics of the patient populations and leiomyomas studied.

This diversity of leiomyoma and patient characteristics also limits the ability to determine whether leiomyoma size and location impact reproductive outcomes. For example, a 2.5 cm leiomyoma that is identified as subserosal may have minimal impact on pregnancy outcome, while a similar size submucosal leiomyoma may have a greater impact. Furthermore, many women suffer from multiple leiomyomas, and it is difficult to recruit women who have the same number, size, and location of leiomyomas to eliminate these confounders. Therefore, studies have demonstrated conflicting reproductive outcomes related to myoma size. For example, some data support the notion that larger leiomyomas  $>2.85$  cm (23) or  $>3.0$  cm (34) negatively impact reproduction, while other studies suggest that leiomyomas  $<5$  cm do not (8, 16, 18, 24, 30, 31). In addition, studies demonstrate that location and number are not good predictors of reproductive function (16, 28, 30, 35, 36), but many of these studies specifically excluded women who had submucosal leiomyomas. Given the conflicting results, no specific recommendation can be made.

### Likelihood of Maintaining Pregnancy

There are no high-quality studies to address the likelihood of maintaining pregnancy in women with fibroids. One of the

largest epidemiologic studies investigating the association between fibroids and miscarriage enrolled over 5,500 women during the first trimester of pregnancy and followed them for birth outcomes. After adjusting for potential confounders, they did not find a difference in miscarriage risk among women with and without fibroids (37). On the other hand, a small retrospective study reported a higher pregnancy loss rate (14% vs 7.6%,  $P<.05$ , Fisher's exact test) in 143 pregnant women with fibroids, compared with 715 women without fibroids after documentation of fetal heart tones during the first trimester (38). Both of these studies are limited by potential selection bias, since women were recruited during pregnancy (38). The method and timing of ascertainment (either once seeking prenatal care or during anatomic scans during the second trimester) may artificially bias the results toward finding no association. Moreover, it is important to recognize that women who achieve pregnancy with leiomyomas may be a subgroup of women different from those women who are burdened with leiomyomas and attempting to achieve pregnancy.

### Summary Statements

- Heterogeneous study designs, inconsistent nomenclature, continuous nature of leiomyoma size and location, and insufficient patient recruitment significantly limit the interpretation of results from existing studies that evaluate the impact of fibroids on the likelihood of achieving pregnancy and maintenance of pregnancy.
- There is insufficient evidence to conclude that myomas reduce the likelihood of achieving pregnancy with or without fertility treatment. (Grade C)
- There is insufficient evidence to determine that a specific myoma size, number, or location (excluding submucosal myomas or intramural myomas impacting the endometrial cavity contour) is associated with a reduced likelihood of achieving pregnancy or an increased risk of early pregnancy loss. (Grade C)

## DOES MYOMECTOMY IMPROVE FERTILITY OUTCOMES FOR WOMEN WITH INTRAMURAL OR SUBSEROSAL FIBROIDS?

### Impact of Myomectomy on Unassisted Pregnancy Rate

Women with infertility and myomas present a unique challenge to physicians. When significant myoma-related symptoms occur, such as heavy menstrual bleeding or bulk symptoms, the removal of myomas is usually advised for symptomatic relief. However, when women present with infertility or recurrent pregnancy loss in the absence of symptoms otherwise related to myomas, treatment recommendations are less clear given the quality of the literature regarding the impact of myomectomy on fertility outcomes. Given the heterogeneity of the data, studies that evaluate fertility outcomes after an abdominal approach (laparoscopic, robotic, and open abdominal myomectomy) were combined to help summarize available evidence regarding the impact of myomectomy on reproductive outcomes.

There is only one randomized controlled trial (RCT) that compared myomectomy to no surgery in women with myomas and infertility (39). In this study, 181 women with a solitary myoma  $\leq 4$  cm in size and at least 1 year of infertility were randomized to surgery (laparotomy or hysteroscopy) ( $n=92$ ) for fibroid removal vs no surgery ( $n=89$ ). Follow-up was limited to 1 year. Participants were encouraged to have “fertility-related intercourse” postoperatively, and none received fertility treatments. Clinical pregnancy rates were assessed based on location of myomas and the intervention. Myomectomy was not associated with improvements in pregnancy rates in women with intramural ( $n=23$ , 56.5%, not significant [NS]) or subserosal ( $n=11$ , 63.6%, NS) myomas  $\leq 4$  cm. (See section below on submucosal fibroids.) Unfortunately, the 1-year length of follow-up was relatively short, and the number of women in each subgroup was small, which limits the interpretation of these results.

Several level-II studies have demonstrated an improvement in pregnancy rates and live-birth rates after myomectomy. In a prospective, nonrandomized cohort study of 318 women with recurrent pregnancy loss ( $\geq 2$  miscarriages) or unexplained infertility, reproductive outcomes were compared among those undergoing laparoscopic myomectomy, those with myomas and no surgery, and a control group (unexplained infertility and no myomas) (40). Women undergoing laparoscopic myomectomy had higher live-birth rates when compared to those with myomas who did not undergo surgery (42% [44/106] vs 11% [12/106],  $P<.001$ , respectively), and to those with unexplained infertility and those without myomas (25% [27/106],  $P<.001$ ). The authors did not comment on differences in ages between groups, and did not control for patient age when comparing pregnancy rates, thus limiting the impact of these results. Nonrandomized studies such as this one are potentially limited by selection bias in that women who underwent surgery had different types of myomas than women who did not have surgery.

### Impact of Myomectomy on ART Pregnancy Rate

There are several level-II studies that evaluate the impact of fibroid removal on pregnancy rates, but very few that utilize an appropriate control group with myomas left in situ. Of the studies that do utilize an appropriate control group, definitive benefits of myomectomy on outcomes after ART have not been demonstrated. One cohort study compared 63 infertile women with intramural myomas to 100 age-matched controls without myomas undergoing the same stimulation protocol for IVF (35). Of the 63 women with myomas, 19 underwent myomectomy prior to IVF (35).

Clinical pregnancy rates were not statistically different between groups (36% myomectomy vs 29% intramural myoma with no myomectomy vs 36% controls,  $P=.25$ ) (35). Similar results were found in a retrospective cohort study of 58 women undergoing ART with a history of prior myomectomy ( $n=47$ ) or myomas in situ ( $n=11$ ) (41). A total of 10 of the 11 subjects with myomas in situ had subserosal myomas, and 50.7% of the myomectomy group had subserosal myomas removed (41). The groups were similar in age and duration of infertility, but the myomectomy group had a

significantly higher incidence of primary infertility compared with the myoma group (74.5% vs 45.5%,  $P<.001$ ) (41). There were similar clinical pregnancy rates between the groups, and in comparison to the overall IVF population (41). However, the impact of this study is limited given the inclusion of primarily subserosal myomas in the in situ group which likely have very little impact on reproductive outcomes. An additional limiting factor includes the fact that overall pregnancy rates were much lower when this study was performed during the early days of ART.

While the aforementioned studies assessed removal of primarily intramural and subserosal myomas, the following study evaluated reproductive outcomes after ART for submucosal myomas and intramural myomas with a submucosal extension. Women were categorized according to the type of myoma they had removed either hysteroscopically or via abdominal approach (submucosal versus submucosal with intramural extension or intramural alone), as well as autologous vs donor oocyte IVF and were compared to controls without prior surgery and no myomas (42). There were no differences in ongoing pregnancy rates or live-birth rates between groups, suggesting that removing the fibroids did not compromise fertility (42). Similar results were seen in a study evaluating reproductive outcomes after tuboplasty (43). This study assessed women with tubal infertility and the impact of myomectomy at the time of tuboplasty. No differences were detected in pregnancy rates or live-birth rates between groups (43). These studies suggest that removal of myomas does not reduce pregnancy rates. However, these data do not clearly demonstrate an improvement in outcomes after myomectomy compared with no surgery. It must be recognized that many of these studies are underpowered, and the inclusion/exclusion criteria of the size and location of myomas in study subjects are inconsistent.

In contrast to these findings, a trial of 168 women with non-cavity-distorting myomas (one–five myomas; at least one  $>5$  cm and no submucosal component) compared outcomes among those who underwent laparoscopy before ART vs women with myomas and no surgery prior to ART. Investigators reported a superior cumulative pregnancy rate (34% [28/84] vs 15% [13/84],  $P<.05$ ) and live-birth delivery rate (25% [21/84] vs 12% [10/84],  $P<.05$ ) in the group undergoing laparoscopy compared with the non-surgical group (44). Benefit of myomectomy was observed in the surgical group of women who had at least one fibroid with a diameter  $>5$  cm and a normal uterine cavity, but age differences between groups were not reported or taken into consideration in the analysis. Additional limitations include lack of comparison of fibroid size and number between groups and potential selection bias as the subjects chose which intervention they received (surgery vs no surgery). Thus, while these trials suggest that myomectomy may improve pregnancy rates, concerns about selection bias and confounding by age make it difficult to recommend myomectomy to improve pregnancy and live-birth rates.

Of the systematic reviews published, most concluded that there is insufficient evidence regarding the effect of removal of intramural myomas (laparoscopic or open) on reproductive outcomes in infertile women (45, 46). A recent systematic

review (45) focused entirely on outcomes after ART, while a 2009 systematic review (46) included studies with a variety of fertility treatments and several studies with no treatment postoperatively. These findings were replicated by a systematic review, which included women with subfertility and in whom postoperative treatment included both expectant management with timed intercourse and ART (47). This systematic review found no significant effect of myomectomy on clinical pregnancy rates based on the type of fibroid removed (intramural: odds ratio [OR] 1.88, confidence interval [CI] 0.57–6.14, one RCT, 45 women; submucosal: OR 2.04, CI 0.62–6.66, 52 women; intramural-subserosal: OR 2.0, CI 0.40–10.09, 31 women; intramural-submucosal: OR 3.24, CI 0.72–14.57, 42 women) (47). These data were based on one randomized trial (39). While two other systematic reviews have shown improvements in reproductive outcomes in women with subfertility and infertility after myomectomy, both are poor in quality. Postoperative treatment included both expectant management with timed intercourse and ART, respectively (48, 49).

### Summary Statements

- There is insufficient evidence that removal of subserosal fibroids improves fertility. (Grade C)
- There is fair evidence that myomectomy does not impair reproductive outcomes (clinical pregnancy rates, live-birth rates) following ART. (Grade B)

### DOES MYOMECTOMY IMPACT THE LIKELIHOOD OF PREGNANCY LOSS?

Compared to common study endpoints such as conception and live-birth rate, the rate of early pregnancy loss following myomectomy has been less frequently studied. This is due in part to the fact that few studies evaluating myomectomy utilize pregnancy loss as a primary outcome, and may only assess it as a secondary outcome. Moreover, the lack of appropriately controlled studies and inconsistent study designs have limited conclusions about the impact of myomectomy on early pregnancy loss rates.

Only one randomized trial assessed miscarriage rates in women with myomas and 1 year of infertility (39). Miscarriage rates appeared lower only in women with submucosal myomas after abdominal myomectomy (5/13, 38.5% [surgery] vs 3/6, 50% [no surgery]), but this difference did not reach statistical significance (39). There was no difference in miscarriage rates among women with intramural or submucosal myomas randomized to surgery or no surgery (39).

A systematic review (47) assessed the effect of open vs laparoscopic myomectomy on miscarriage rates in subfertile patients, according to two studies (50, 51). The same systematic review showed no difference in miscarriage rates by type of fibroid removed after myomectomy vs no intervention, based on one study (39): intramural: OR .89, CI 0.14–5.48, 22 women; submucosal: OR 0.63, CI 0.09–4.40, 19 women; intramural-subserosal: OR 0.25, CI 0.01–4.73, 9 women; intramural-submucosal: OR 0.50, CI 0.03–7.99, 11 women (47). In some systematic reviews, investigators determined

either no difference in miscarriage rates after laparoscopic or open myomectomy or insufficient evidence regarding benefits of myomectomy on reproductive outcomes (45–47).

In two prospective, randomized trials that compared laparoscopy to laparotomy in patients with symptomatic leiomyomas or unexplained infertility, the rates of pregnancy loss prior to 12 weeks' gestation were similar (50, 51). Similarly, no reduction in early pregnancy loss has been observed between surgical groups in several contemporary retrospective cohort studies and systematic reviews (46, 47, 52, 53). In contrast, one retrospective cohort study of women with myomas and recurrent pregnancy loss reported a reduction in early pregnancy loss following laparoscopic myomectomy (40). Given the small numbers of subjects with early pregnancy loss ( $n=15$ ), it is difficult to evaluate the impact of laparoscopic myomectomy on the rate of pregnancy loss in this study.

A cohort study of patients with subserosal and intramural myomas who received either laparotomy or laparoscopy reported a benefit of the laparoscopic approach. In this retrospective study, the rates of pregnancy loss were reduced from a preoperative rate of 63.6% to a postoperative rate of 7.1% ( $P=.007$ ) in the laparoscopic group (54). In the abdominal myomectomy group, the preoperative loss rate was 60% and declined to 20% postoperatively ( $P=.06$ ) (54). However, the small number of subjects ( $N=41$ ) in this study with a lack of comparison between groups limits interpretation of these findings.

As seen in studies evaluating conception and live birth as primary outcomes, studies that assess early pregnancy loss have variable results and are difficult to interpret due to very limited study population sizes and limited generalizability. As with the studies assessing pregnancy rates after myomectomy, laparoscopic studies often exclude those with cavity-distorting myomas, while those assessing the open approach demonstrate benefit from removal of these myomas; it is unknown whether the laparoscopic removal improves outcomes.

### Summary Statement

- There is insufficient evidence that myomectomy (laparoscopic or open) reduces miscarriage rates. (Grade C)

### DOES RESECTION OF SUBMUCOSAL FIBROIDS (TYPE 0, 1, OR 2) IMPROVE FERTILITY?

A single RCT has assessed reproductive outcomes with and without hysteroscopic myomectomy in women with submucosal myomas (39). This trial examined 52 women with submucosal myomas  $\leq 4$  cm and otherwise unexplained infertility. Thirty women randomized to hysteroscopic myomectomy followed by 3 months' abstinence were compared with 22 women randomized to continued attempts at conception. Follow-up at 1 year demonstrated a clinical pregnancy rate of 43.3% (13/30) in women who had undergone surgery compared with 27.2% (6/22) in those who had not ( $P<.05$ ) (39). Similar findings were demonstrated in a separate comparison of 42 women with both intramural and submucosal myomas, with pregnancy rates at 1 year of 36.4% (8/22) in

women who underwent hysteroscopic myomectomy compared with 15.0% (3/20) in women who did not ( $P < .05$ ) (39). While the authors report that their findings met statistical significance, reanalysis of the data by the ASRM Practice Committee and by a subsequent systematic review suggests that the differences did not meet statistical significance (47). The study had several additional limitations. No power calculation was presented, and no information was provided about the randomization process or blinding. The authors also did not specify whether there was a lower limit on the size of the included myomas, and live birth was not assessed. Two systematic reviews have examined fertility after hysteroscopic resection of submucosal myomas (47, 55), both of which only included the single randomized trial previously mentioned (39). While the two reviews differed in their respective interpretations of the quality of the data, both concluded that there was insufficient evidence to conclusively demonstrate an effect of hysteroscopic myomectomy on improving reproductive outcomes, but that the possibility of a clinical effect could not be excluded.

Despite these negative findings from a single small RCT, a systematic review (46) incorporating both level-I (39) and level-II data (27, 33, 40–42, 56–58) contributed additional insight by performing a stratified analysis comparing women undergoing hysteroscopic myomectomy for submucosal myomas with two different control populations: women with myomas remaining in situ and infertile women with normal uterine cavities. In this more comprehensive analysis, women who underwent hysteroscopic myomectomy of submucosal fibroids had higher rates of clinical pregnancy when compared with women with myomas in situ (relative risk [RR] 2.03, CI 1.08–3.82,  $P = .028$ ), but comparable rates of clinical pregnancy when compared with infertile women with normal uterine cavities (RR 1.55, CI 0.99–2.39, NS). Live-birth rates in women after hysteroscopic myomectomy were similar to control subjects in both comparisons.

Data from several retrospective cohort studies (16, 41, 42, 57–59) also support the conclusion that clinical pregnancy rates are higher among women with submucosal myomas who undergo surgical resection, though the significance of this finding varies based on the individual series and the selected control group. Live-birth rates were not consistently assessed.

### Summary Statement

- There is fair evidence that hysteroscopic myomectomy for submucosal fibroids improves clinical pregnancy rates. (Grade B)

### DOES HYSTEROSCOPIC RESECTION OF SUBMUCOSAL MYOMAS AFFECT MISCARRIAGE RATES?

Miscarriage rates were lower after hysteroscopic myomectomy in the previously mentioned randomized trial, but numbers were too small to draw conclusions, and no significance testing was performed (39). At the 1-year follow-up of 30 women with submucosal myomas randomized to hysteroscopic myomectomy, there were five miscarriages and eight

ongoing pregnancies (miscarriage rate of 38.5%). Of the 22 women who were managed expectantly, there were three miscarriages and three ongoing pregnancies (miscarriage rate of 50%) (39).

A 2009 systematic review of myomectomy in women with infertility and fibroids did not demonstrate a significant difference in miscarriage rates after hysteroscopic resection of submucosal myomas compared with either women with myomas remaining in situ (RR 0.77, CI 0.36–1.66) or infertile women with normal cavities (RR 1.24, CI 0.48–3.24) (46).

Data on miscarriage rates were also widely inconsistent in retrospective cohort studies, many of which were significantly underpowered to address this outcome.

### Summary Statement

- There is insufficient evidence to conclude that hysteroscopic myomectomy reduces the likelihood of early pregnancy loss in women with infertility and a submucous fibroid. (Grade C)

### CONCLUSIONS

There has been significant controversy regarding the impact of uterine myomas on fertility and pregnancy outcomes. As a result, the benefit of myomectomy (likelihood of conception and live birth, reduction of pregnancy loss) in women with asymptomatic myomas has also been uncertain. Based upon a comprehensive review of existing high-quality studies, there is insufficient evidence to conclude that myomas reduce the likelihood of achieving and maintaining pregnancy. There is fair evidence that hysteroscopic myomectomy for cavity-distorting fibroids improves clinical pregnancy rates, but insufficient evidence regarding the impact of this procedure on the likelihood of early pregnancy loss or live birth. Myomectomy is generally not advised to improve pregnancy outcomes in asymptomatic infertile women with non-cavity-distorting myomas. However, myomectomy may be reasonable in some circumstances including but not limited to severe distortion of the pelvic architecture complicating access to the ovaries for oocyte retrieval.

An association between a specific number, size, and location of myomas (excluding submucosal myomas or intramural myomas impacting endometrial cavity contour) and pregnancy outcomes has not been confirmed.

Unfortunately, prospective high-quality RCTs exclude subjects with submucosal fibroids or cavity-distorting intramural fibroids, and the impact of this subgroup of fibroids on the rate of conception, pregnancy loss, and live birth has been incompletely studied. Furthermore, heterogeneous study populations and designs, inconsistent use of controls, variable nomenclature classification for location, inconsistent primary endpoints (conception vs clinical pregnancy vs live birth vs early pregnancy loss), lack of adjustment for confounders of pregnancy outcomes, and lack of racial/ethnic diversity have limited our ability to interpret existing data. To this end, continued investigation of the association between myomas and pregnancy outcomes (both spontaneous and with elective fertility therapy) and if

myomectomy confers a benefit for fertility and pregnancy outcomes is warranted.

Given the paucity of contemporary RCTs examining the impact of myomectomy, it is recommended that future multicenter prospective studies be performed with consistent patient selection and primary endpoints, validated myoma nomenclature for location, inclusion of reference groups who are infertile with myomas left in situ (no myomectomy performed) and infertile women without fibroids, respectively, and inclusion of patients with cavity-distorting intramural myomas. In addition to examining outcomes following ART, future studies should also evaluate outcomes in women undergoing less intensive treatments such as ovulation induction, intrauterine insemination, as well as attempts at timed-intercourse conception. In patients undergoing elective fertility therapy, consistent adjustments for age, ovarian-reserve testing, fertility diagnoses, and myomectomy approach (open, conventional laparoscopic, robot-assisted laparoscopic, and hysteroscopic) should also be implemented. Given the disparity in disease severity in women of African descent, it is also necessary to conduct prospective studies with larger groups of underrepresented minority women to assess for any ethnic-specific effects of fibroids following myomectomy and during attempts to become pregnant. While outside the scope of this document, more data are needed to determine the impact of fibroids and myomectomy on long-term obstetric outcomes.

## UNANSWERED QUESTIONS

- What is the impact of leiomyomas on fecundability?
- Does the degree of cavity distortion impact the benefit of myomectomy? Better assessment of the cavity in clinical trials is needed.
- What is the true impact of intramural fibroids with no submucosal component on reproductive outcomes?
- What is the value of myomectomy on ART outcomes?

## SUMMARY

- There is insufficient evidence to conclude that myomas reduce the likelihood of achieving pregnancy with or without fertility treatment. (Grade C)
- There is insufficient evidence to determine that a specific myoma size, number, or location (excluding submucosal myomas or intramural myomas impacting the endometrial cavity contour) is associated with a reduced likelihood of achieving pregnancy or an increased risk of early pregnancy loss. (Grade C)
- There is insufficient evidence that removal of subserosal fibroids improves fertility. (Grade C)
- There is fair evidence that myomectomy does not impair reproductive outcomes (clinical pregnancy rates, live-birth rates) following ART. (Grade B)
- There is insufficient evidence that myomectomy (laparoscopic or open) reduces miscarriage rates. (Grade C)

- There is fair evidence that hysteroscopic myomectomy for submucosal myomas improves clinical pregnancy rates. (Grade B)
- There is insufficient evidence to conclude that hysteroscopic myomectomy reduces the likelihood of early pregnancy loss in women with infertility and a submucous fibroid. (Grade C)

## RECOMMENDATIONS

- In asymptomatic women with cavity-distorting myomas (intramural with a submucosal component or submucosal), myomectomy (open or laparoscopic or hysteroscopic) may be considered to improve pregnancy rates.
- Myomectomy is generally not advised to improve pregnancy outcomes in asymptomatic infertile women with non-cavity-distorting myomas. However, myomectomy may be reasonable in some circumstances, including but not limited to severe distortion of the pelvic architecture complicating access to the ovaries for oocyte retrieval.

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