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 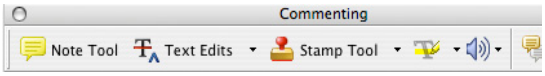

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 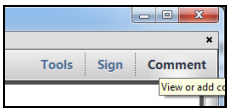

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 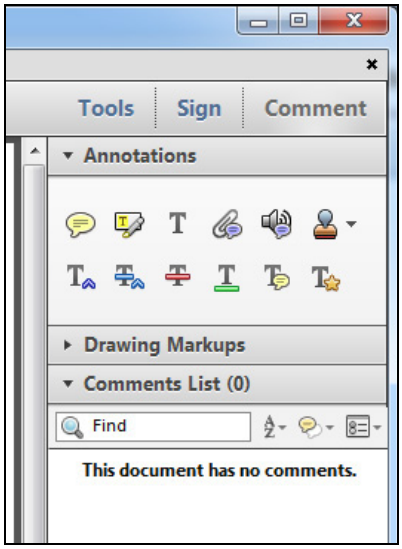
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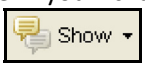
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
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Reintervention risk and quality of life outcomes after uterine-sparing interventions for fibroids: a systematic review and meta-analysis

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Objectives: To compare uterine-sparing treatment options for fibroids in terms of reintervention risk and quality of life.
Design: Systematic review and meta-analysis according to PRISMA guidelines.
Setting: Not applicable.
Patient(s): Women with uterine fibroids undergoing a uterine-sparing intervention.
Interventions(s): Not applicable.
Main Outcome Measure(s): 1) Reintervention risk after uterine-sparing treatment for fibroids after 12, 36, and 60 months; and 2) quality of life outcomes, based on validated questionnaires. Two separate analyses were performed for the procedures that used an abdominal approach (myomectomy, uterine artery embolization [UAE], artery ligation, high-intensity focused ultrasound [HIFU], laparoscopic radiofrequency ablation [RFA]) and for the procedures managing intracavitary fibroids (hysteroscopic approach, including hysteroscopic myomectomy and hysteroscopic RFA).
Result(s): There were 85 articles included for analysis, representing 17,789 women. Stratified by treatment options, reintervention risk after 60 months was 12.2% (95% confidence interval 5.2%–21.2%) for myomectomy, 14.4% (9.8%–19.6%) for UAE, 53.9% (47.2%–60.4%) for HIFU, and 7% (4.8%–9.5%) for hysteroscopy. For the other treatment options, no studies were available at 60 months. For quality of life outcomes, symptoms improved after treatment for all options. The HIFU procedure had the least favorable outcomes.
Conclusion(s): Despite the substantial heterogeneity of the study population, this meta-analysis provides valuable information on relative treatment efficacy of various uterine-sparing interventions for fibroids, which is relevant when counseling patients in daily practice. Furthermore, this study demonstrates that long-term data, particularly for the newest uterine-sparing interventions, are urgently needed. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Reintervention risk, quality of life, uterine-sparing treatment option

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Fibroids are the most common benign tumors of the female genital tract, with a symptomatic occurrence rate of 20%–40% in reproductive-age women (1). For women requiring surgical treatment but desiring uterine conservation, myomectomy has typically been the first choice for intervention. Yet technologic advances have led to a wider range of available options, depending on the location and number of fibroids, the indication for treatment, patient preference, and technologic facilities of hospitals. Uterine artery embolization (UAE) is one of the alternatives, and this well studied technique has been used in many countries for more than three decades (2). Other treatment options include, among others, radiofrequency ablation (RFA), (laparoscopic) ligation, and cryoablation. Advanced techniques, such as high-intensity focused ultrasound (HIFU), also have

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recently emerged, and are applicable without the need for surgical intervention.

Data regarding the feasibility of these uterine-sparing treatment options vary, and limited information exists on relative efficacy. Guidelines from the American College of Obstetricians and Gynecologists (3), the National Institute for Health and Care Excellence (United Kingdom) (4), and the Society of Obstetricians and Gynecologists of Canada (5) on this topic state that patients should be counseled about the different available treatment options but do not define a preferred intervention. The objective of the present systematic review and meta-analysis was to evaluate the relative efficacy of the various uterine-sparing options for treating fibroids. We specifically aimed to compare the different techniques in terms of reintervention risk and quality of life.

MATERIALS AND METHODS

Eligibility Criteria, Information Sources, Search Strategy

A systematic review was conducted following the PRISMA guidelines (6). No study protocol was available. A literature search was set up in collaboration with a clinical librarian, and original articles were identified though Pubmed, Medline, Embase, and Web of Science. The exact search terms are presented in Supplemental Appendix 1 (Supplemental Appendices 1–4 are available online at www.fertstert.org). The literature search was restricted to studies published from January 2000 through February 2017. By selecting only recent studies, we aimed to provide an overview of current treatment options. We considered randomized controlled trials (RCT) and cohort studies (both noncomparative and comparative) only. Review articles, technical reports, animal studies, non-English studies, published abstracts without a full manuscript, and reports from meetings were excluded.

Studies eligible for inclusion were studies evaluating at least one of our primary outcomes: 1) surgical reintervention risk after uterine-sparing treatment; and 2) quality of life after treatment. In addition, studies had to have a minimum follow-up time of 12 months. We defined reintervention as any additional treatment needed ≥ 1 year after treatment owing to symptomatic recurrence of fibroids. Reinterventions directly related to procedure complications were excluded, and dilation and curettage was not considered to be reintervention. Because we aimed to study the reintervention risk after a first treatment for fibroids, studies were also excluded when all women in the cohort had an earlier history of intervention for fibroids. To reliably compare the quality of life outcomes, we limited our selection to studies using the Severity Symptom Score (SSS) or the Health-Related Quality of Life questionnaire (HRQL). Both have been validated for assessment of fibroid-related symptoms (7). The SSS and HRQL are scored from 0 to 100. When symptoms improve, the SSS score decreases whereas the HRQL score increases.

Study Selection

The first two authors (E.M.S. and F.H.M.P.T.) independently screened titles and abstracts for relevance. Potentially relevant studies were obtained in full text and assessed for inclusion. In case of disagreement, a third author (F.W.J.) was consulted. The references of the selected articles were cross-checked to identify other potentially relevant studies.

Data Extraction

From the included studies, we extracted data regarding primary outcomes (reintervention risk and quality of life) and baseline characteristics. Variables of interest included study characteristics (study design, type(s) of treatment, country where the study was conducted, and potential source of funding) and patient characteristics (age, body mass index [BMI], and fibroid weight).

Data were pooled for meta-analysis for our primary outcomes at 12, 36, and 60 months after intervention. For the comparative studies included, each intervention group was assessed separately. Two separate analyses were performed for procedures approaching the fibroids through the abdomen (henceforth called abdominal approach) and for procedures managing intracavitary fibroids (henceforth called hysteroscopic approach). Additional subanalyses were performed to specifically evaluate the number of women undergoing hysterectomy after initial therapy.

Assessment of Risk of Bias

To assess the risk of bias for each study, the following criteria were employed: 1) inclusion of consecutive patients (if it was not stated that patients were consecutively included, risk of bias was assessed as unclear); 2) rate of patients that had infertility as indication for treatment, because it may influence or limit treatment choice (<10% of the study population with infertility indication was considered to indicate low risk of bias and >20% high risk); and 3) loss to follow-up rate (<10% loss to follow-up was considered to indicate low risk of bias and >20% high risk). The template of Review Manager (version 5.1) was used for data organization.

Data Synthesis and Statistical Analysis

Descriptive characteristics were summarized with the use of SPSS version 23.0. Continuous data were presented as range and categoric data as frequency with percentage. Meta-analysis was performed with the use of Stata (version 14, Statacorp). The reintervention risk and the difference of the means of the quality of life scores were pooled in a random effects model, and 95% confidence intervals (95% CIs) were reported. In cases where only median and range were available, instead of the mean and standard deviation, data were transformed as described by Hozo et al. (8).

RESULTS

Study and Patient Characteristics

The search strategy identified 3,250 unique articles. Full texts of more than 600 articles were reviewed because the reintervention risk was usually not a primary end point in studies and therefore not explicitly mentioned in the abstract.

As demonstrated in Supplemental Figure 1 (available online at www.fertstert.org), 85 original articles were deemed eligible for inclusion in this review. Eight of the studies were randomized controlled studies (9–16) and 77 were cohort studies (17–93). Fourteen studies, of which six were RCTs, compared two different uterine-sparing treatment options (e.g., myomectomy vs. UAE) (9, 10, 12–15, 21, 35, 59, 60, 64, 75, 84, 93). These studies were therefore included in two main categories. Supplemental Appendix 2 provides a summary of the characteristics of the included studies.

Fifteen studies included at least in part the same cohort of patients (9, 10, 12, 15, 32, 35, 42, 59, 63, 69, 72, 77, 94–96). Efforts were made to ensure that data from each patient was not included more than once. Two studies were eventually excluded because we could not correct for the overlapping study period (95, 97).

Of the included studies, 33 originated from Europe (38.8%), 23 from North America (27.0%), 22 from Asia (25.9%), four from Africa (4.7%), two from Australia (2.4%), and one from Latin America (1.2%). In 29 studies (34.1%), disclosures regarding funding were reported: In 14 studies, research had been funded by a medical device company (Biocompatibles, Biosphere Medical, Boston Scientific, Gynesonics, Halt Medical, and Insightec); the other 15 studies were funded by governmental funds, research institutes, and charity organizations.

Data regarding ten treatment options was identified: abdominal, laparoscopic or robotic myomectomy, hysteroscopic myomectomy, UAE, (laparoscopic) ligation, HIFU, laparoscopic and hysteroscopic RFA, percutaneous microwave ablation, and cryoablation. An eleventh treatment option, laparoscopic uterine artery occlusion, was described in studies (98–100), but none of those studies met our inclusion criteria. For the analysis, the data of abdominal, laparoscopic, and robotic myomectomy were combined (henceforth called myomectomy), as were the data of laparoscopic RFA and percutaneous microwave ablation, both thermal ablations. The abdominal approach included six different interventions: myomectomy, UAE, artery ligation, HIFU, laparoscopic RFA, and cryoablation. The hysteroscopic approach consisted of hysteroscopic myomectomy and hysteroscopic RFA.

Baseline characteristics of the study population are summarized in Table 1. The total study population included 17,789 women. A total of 15,348 women (87.8%) had undergone an abdominal approach and 1,912 (12.2%) a hysteroscopic approach. The UAE group had the largest study population (8,244), followed by myomectomy (5,114) and hysteroscopic myomectomy (1,741). For the laparoscopic cryoablation and artery ligation procedures, one study was available for each treatment option.

The mean ages of the studied populations ranged from 29.3 to 47.9 years, the mean BMIs from 21.2 to 56.6 kg/m^2, and the mean fibroid weights from 18.8 to 538.5 g. Because only means were available from every individual study, it was not possible to calculate if the outcome measures of these baseline characteristics were statistically different between the different treatment options.

Risk of Bias of the Included Studies

A summary of risk of bias for the individual studies is depicted in Supplemental Appendix 3. In the myomectomy group and the hysteroscopic myomectomy group, none of the studies excluded infertility as indication of treatment. For the other treatment options, approximately one-half of the studies explicitly mentioned excluding infertility. For "loss to follow-up," a high risk of bias was observed in all groups. This was mainly attributed to studies focusing on long-term quality of life questionnaires after treatment.

Primary Outcomes

Additional figures of the data from this section are available in Supplemental Appendix 4.

Reintervention risk for the abdominal procedures. The reintervention risks for the six abdominal procedures are presented in Table 2. Almost all analyses demonstrated considerable statistical heterogeneity. At 12 months, the reintervention risk for these abdominal procedures varied from 0.3% (laparoscopic RFA, 95% CI 0–1.6%; $I^2 = 0\%$, 6 studies) up to 15% (cryoablation, 1 study). At 36 months, the reintervention risk varied from 1.2% (myomectomy, 0–5.2%, 4 studies) to 34.7% (HIFU, 27.3%–42.4%, 4 studies). At 60 months, reintervention risks were 12.2% (5.2%–21.2%; $I^2 = 95.2\%$; 10 studies) for myomectomy, 14.4% (9.8%–19.6%; $I^2 = 65.9\%$; 17 studies) for UAE, and 53.9% (47.2%–60.4%; $I^2 = 99.5\%$; 2 studies) for HIFU (Fig. 1). For artery ligation, laparoscopic RFA, and cryoablation, no studies were available at 60 months.

Subanalysis for abdominal procedures: Hysterectomy as reintervention. A hysterectomy was performed 12 months after the primarily uterine-sparing abdominal intervention in 0.8% of the cases (95% CI 0.3%–1.5%; $I^2 = 66.8\%$; 44 studies). At 36 months, the reintervention risk for hysterectomy varied from 0.6% (myomectomy, 0–2.3%; $I^2 = 60.2\%$; 4 studies) to 8.1% (laparoscopic RFA, 1 study). By 60 months, 7% (2.5%–13.2%; $I^2 = 90.6\%$; 8 studies) of the patients who had undergone myomectomy required a hysterectomy, compared with 9.4% after UAE (5.5%–14.2%; $I^2 = 93.6\%$; 15 studies). For the HIFU treatment, one study reported the reintervention risk at 60 months and noted that 8 of the 36 women (22.2%) required a hysterectomy (59). For the other treatment options, no long term data on hysterectomy reintervention rate were available.

Reintervention risk for hysteroscopic procedures. For the two hysteroscopic procedures, data demonstrated at 12 months a reintervention risk after hysteroscopic RFA of 11.1% (95% CI 3.3%–22.2%), 3 studies), compared with 6.6% after hysteroscopic myomectomy (0.6%–17.6%; $I^2 = 94.0$; 4 studies; Table 2). At 36 and 60 months, no data were available for hysteroscopic RFA.

Subanalysis for hysteroscopic procedures: Hysterectomy as reintervention. For the reintervention risk for hysterectomy, 1.1% (95% CI 0–6.8%, 3 studies) of the patients in the hysteroscopic myomectomy group required a hysterectomy at 12 months, compared with 2% (0–5.9%, 3 studies) after hysteroscopic RFA. At 36 and 60 months, no data were available for hysteroscopic RFA.

TABLE 1

Baseline characteristics.

Approach	No. of studies or substudies	No. of patients	Age, y (no. of studies or substudies)	BMI, kg/m^2 (no. of studies or substudies)	Fibroid weight, g (no. of studies or substudies)
Overall	96	17,489	29.3–47.9 (81)	21.2–56.6 (24)	18.8–538.5 (32)
Abdominal approach					
Myomectomy	20	5,114	29.3–43.5 (15)	21.2–27.5 (7)	–
UAE	40	8,244	32.3–47.0 (34)	23–28.4 (5)	59–538.5 (12)
Artery ligation	1	50	39.6 (1)	–	180.9 (1)
Laparoscopic RFA	8	652	40.0–43.6 (8)	22.7–30.5 (5)	76.8–95.0 (2)
(MR/US)–HIFU	17	1,548	36.2–46.0 (14)	21.6–56.6 (6)	53.2–396.3 (13)
Laparoscopic cryoablation	1	20	46.9 (1)	27.6 (1)	75 (1)
Total	87	15,348	29.3–47.0 (74)	21.2–56.6 (24)	53.2–538.5 (29)
Hysteroscopic approach					
Hysteroscopic myomectomy	6	1,741	31.4–47.9 (5)	–	–
Hysteroscopic RFA	3	120	40.1–40.8 (2)	–	18.8–112.4 (3)
Total	9	1,912	31.4–47.9 (7)	–	18.8–112.4 (3)

Note: Data are presented as range of the means. (MR-US)–HIFU = magnetic resonance– or ultrasound-guided high-intensity focused ultrasound; RFA = radiofrequency ablation; UAE = uterine artery embolization.

Sandberg. Reintervention after fibroid treatments. Fertil Steril 2017.

Quality of life for abdominal procedures. For the abdominal procedures, the postoperative SSS and HRQL scores were reported in 18 and 11 studies, respectively. An overview of the outcomes is presented in Table 3. The mean difference of SSS between baseline and 12 months after treatment was −31.2 (95% CI −36.9 to −25.5). Most mean differences of the treatment options ranged from −37 to −35, with the exception of the HIFU treatment option. The HIFU group had a mean difference of −24.5 (−90.8 to −18.1; I^2 = 96.9; 8 studies) and thus the least improvement of symptoms over time.

For HRQL, the mean difference in scores at 12 months was 36.1 (31.8–40.4; I^2 = 89.4%; 11 studies). Again the HIFU group was associated with the least favorable outcomes, with a mean difference of 24.6 (13.4–35.8, 1 study). At 36 and 60 months, too few studies were available to pool data, but all studies showed improvement of symptoms over time or normalization of the scores after treatment.

Quality of life for hysteroscopic procedures. For hysteroscopic procedures, three studies of hysteroscopic RFA were analyzed (Table 3). All of those studies demonstrated improvement of symptoms after treatment. No data were available for quality of life after hysteroscopic myomectomy.

DISCUSSION

Because limited evidence exists on the relative efficacy of the different uterine-sparing treatment options, choosing the best option for a patient might not always be evident. When counseling a patient about the different treatment options, long-term outcomes on reintervention risk and quality of

TABLE 2

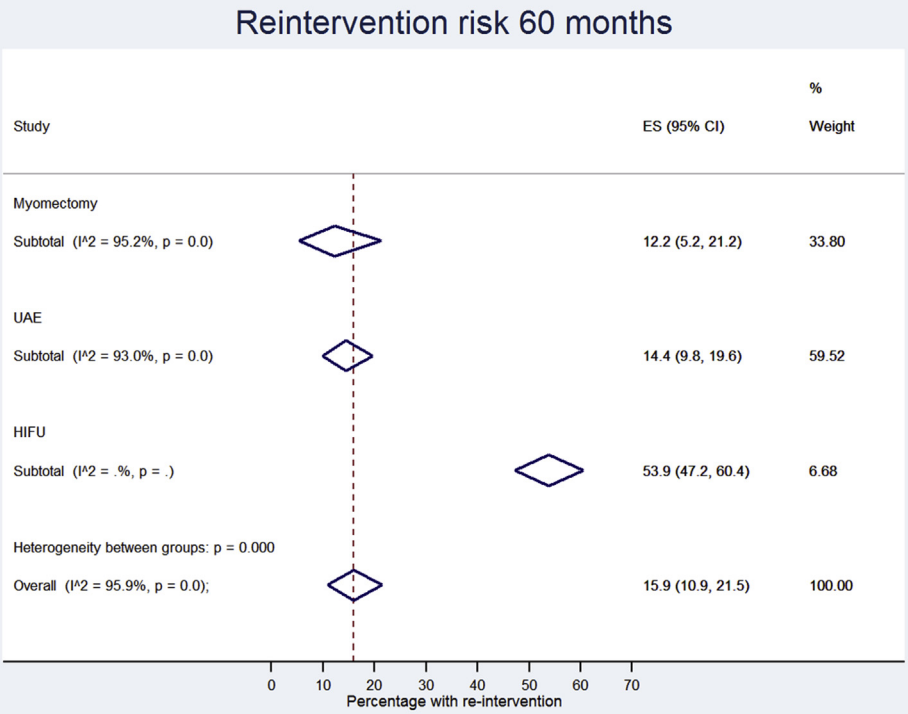
Overall reintervention risk at 12, 36, and 60 months.

	12 mo			36 mo			60 mo		
Approach	% (95% CI)	I^2	No. of studies or substudies	% (95% CI)	I^2	No. of studies or substudies	% (95% CI)	I^2	No. of studies or substudies
Abdominal approach									
Myomectomy	1.1 (0.0–3.7)	89.9	8	1.2 (0–5.2)	65.9	4	12.2 (5.2–21.2)	95.2	10
UAE	3.6 (2.4–4.9)	61.9	26	7.4 (0.9–10.7)	–	3	14.4 (9.8–19.6)	65.9	17
Artery ligation	–	–	0	6	–	1	–	–	0
Laparoscopic RFA	0.3 (0.0–1.6)	0	6	10.4	–	1	–	–	0
HIFU	9.7 (4.0–17.3)	88.3	10	34.7 (27.3–42.4)	47.0	4	53.9 (47.2–60.4)	–	2
Cryoablation	15	–	1	–	–	0	–	–	0
Total	3.6 (2.5–4.8)	80.5	51	10.4 (4.6–18.1)	96.8	13	15.9 (10.9–21.5)	95.9	29
Hysteroscopic approach									
Hysteroscopic myomectomy	6.6 (0.6–17.6)	94.0	4	3.2 (0.0–10.2)	–	3	7.0 (4.8–9.5)	–	2
Hysteroscopic RFA	11.1 (3.3–22.2)	–	3	–	–	0	–	–	0
Total	8.3 (2.7–16.0)	89.1	7	3.2 (0.0–10.2)	–	3	7.0 (4.8–9.5)	–	2

Note: I^2 = study heterogeneity; HIFU = high-intensity focused ultrasound; RFA = radiofrequency ablation; UAE = uterine artery embolization.

Sandberg. Reintervention after fibroid treatments. Fertil Steril 2017.

FIGURE 1



Reintervention risk 60 months after abdominal approach.

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life are, among others, important aspects to consider. In the present meta-analysis based on 85 studies, these two clinically relevant outcomes were evaluated for all available uterine-sparing treatment options for fibroids. For the treatment options with an abdominal approach (all types of myomectomy, UAE, HIFU, laparoscopic RFA, cryoablation, and artery ligation), we demonstrated that 60 months after initial therapy, myomectomy had a risk of reintervention of 12.2%, UAE 14.4%, and HIFU 54%. For the HIFU group, it is important to note that only a few studies were available on the long term. Despite the limited evidence, it is interesting to observe that the HIFU treatment option, which is one of the newest techniques, is currently associated with the least promising outcomes. The authors of the included studies suggested themselves that the high reintervention risk after HIFU might be the result of inadequate patient selection (59, 72, 78). Defining the right patient population is indeed one of the key factors associated with success (2). HIFU treatment has been Food and Drug Administration (FDA) approved since 2004 for a selected patient population, and this treatment option seems attractive in terms of procedural morbidity (78, 103). However, the findings of this review show that this advanced technique still needs to be further evaluated, especially regarding its long-term outcomes. Obviously, this also applies to the other approaches, such as cryoablation, artery ligation, and laparoscopic RFA, that are currently lacking long-term outcomes data.

Looking specifically at myomectomy and UAE procedures, available evidence was more robust. It is important to note that confounding by indication, particularly infertility, could have influenced these reintervention risk data. Specifically for UAE, our reintervention risk was lower than in the two RCTs included in our analysis that compared UAE and surgery (myomectomy or hysterectomy) in women not desiring future pregnancy (15, 16). Those studies demonstrated after UAE a 5-year reintervention risk of 28.4%–32% (15, 16). Both study groups also analyzed the costs associated with UAE compared with myomectomy or hysterectomy and concluded that the costs of UAE were substantially lower than after surgery at 12 (15) and 24 months (105). However at 60 months, the benefit of costs disappeared because of the increased reintervention risk (15). As a result, studies have argued whether women undergoing embolization who were not interested in future pregnancy would not be better served by an initial definitive solution (e.g., hysterectomy) (105). On the other hand, it can also be reasoned that ~70% of the women included in these studies have avoided a more invasive procedure (105). Although we did not perform a cost-effectiveness analysis, our findings demonstrated that <10% of the patients required a hysterectomy in the long term after UAE.

It would have been interesting in our analysis to correct for infertility as indication of treatment, but the available evidence did not allow it. Reintervention management can be expected to be different for women with future pregnancy desire compared with women without future pregnancy desire. For patients with fibroids and infertility, myomectomy is the criterion standard. Most other interventions remain a relative contraindication and have not yet been cleared by the FDA for this indication (104, 105). This was also reflected in our risk assessment of the included studies: Only in the treatment group of myomectomy and hysteroscopic myomectomy were studies included that specifically enrolled patients with infertility as indication of treatment. Although successful pregnancies have been reported after embolization, it has also been associated with a higher risk of pregnancy and/or delivery complications (spontaneous abortion, malpresentation, postpartum hemorrhage, premature delivery) (106) and an increased risk of ovarian dysfunction (107). For laparoscopic RFA and HIFU, evidence regarding pregnancy outcomes is currently poor. The safety and effectiveness of these treatments in women wishing to maintain their fertility has not been established (108, 109). For the hysteroscopic treatment options, available evidence was limited for the two procedures (hysteroscopic myomectomy and hysteroscopic RFA), especially in the long term. A systematic review has demonstrated the benefits of intracavitary fibroid removal in general for infertility treatment, but data on reintervention are currently lacking to formulate recommendations on the most favorable treatment option (110).

Regarding quality of life after treatment (based on SSS and HRQL scores), all studies showed improvement of symptoms 12 months after therapy. Long-term outcomes were scarce for all categories although they were in line with the 12-month outcomes. Based on current evidence and with the most appropriate available questionnaires, we can conclude that in terms of quality of life, no difference was observed between the treatment options, except potentially for HIFU. That treatment option was associated in both questionnaires with the least favorable outcomes. Although the reason for this finding is unclear, it is important to realize that the necessity of reintervention probably affects quality of life and may lead to lower scores (111). Furthermore, it is interesting to mention that one of the included RCTs evaluated quality of life in 22 patients after HIFU compared with placebo treatment (11). They demonstrated similar symptoms reduction in the first 4 weeks, showing the potential strong impact of placebo therapy on symptom relief. However, at 12 weeks in that study, the symptoms of patients in the placebo group were significantly worse than in the treatment group.

The main limitation of the present systematic review and meta-analysis was the substantial heterogeneity observed. We are aware that patient characteristics (including age, menopause status, or indication for treatment) might influence the choice of procedure and the risk of reintervention. However, further subanalysis by patient characteristics was not possible, because most studies reported only a mean or overall percentage of their cohort, and such data presentation does not allow for further specific modifications. Because of potential confounding, we should be careful about comparing the outcomes of the different procedures with each other, and our data should not be interpreted as a comparative effectiveness analysis. Nevertheless, this meta-analysis provides insights into current reintervention risks based on a large study population. These findings can be directly applicable in daily practice for counseling patients that are often eligible for more than one treatment option. Another limitation that should be considered is that we did not evaluate the safety of the procedures (i.e., complications risk), costs, or subsequent pregnancy rates in patients desiring fertility preservation. These findings would have also been interesting to determine relative efficacy of the procedures and should be considered in future research. Strengths of this review include the description of a wide variety of treatment options with quantifiable outcomes. In addition, by focusing on reintervention risk, we evaluated only the recurrence of clinically symptomatic fibroids. We think that data on recurrence of fibroids according to periodic diagnostic follow-up may not be representative or relevant, because a proportion of patients

TABLE 3

Quality of life at 12 months.

Approach	% (95% CI)	I^2	No. of studies or substudies
Abdominal approach			
SSS			
Myomectomy	−37.6 (43.8 to −31.4)	–	1
UAE	−35.8 (−40.6 to −30.9)	82.5	4
Artery ligation	–		
Laparoscopic RFA	−37 (−44.6 to −29.4)	85.6	4
HIFU	−24.5 (−90.8 to −18.1)	96.9	8
Laparoscopic cryoablation	−37.5 (−48.1 to −26.9)	–	1
Total	−31.2 (−36.9 to −25.5)	98.4	18
HRQL			
Myomectomy	39.9 (33.0–46.8)	–	1
UAE	38.9 (35.8–41.9)	35.9	3
Artery ligation	–		
Laparoscopic RFA	35.1 (28.7–41.6)	79.4	5
HIFU	24.6 (13.4–35.8)	–	1
Laparoscopic cryoablation	41.3 (29.1–53.5)	–	1
Total	36.1 (31.8–40.4)	89.4	11
Hysteroscopic approach			
SSS			
Hysteroscopic myomectomy	–		
Hysteroscopic RFA	−42.6 (−68.1 to −17.2)	98.6	3
Total	−42.6 (−68.1 to −17.2)	98.6	3
HRQL			
Hysteroscopy	–		
Hysteroscopic RFA	38.1 (22.9–53.4)	94.8	3
Total	38.1 (22.9–53.4)	94.8	3

Note: HIFU = high-intensity focused ultrasound; HRQL = Health-Related Quality of Life questionnaire; RFA = radiofrequency ablation; SSS = Severity Symptom Score; UAE = uterine artery embolization.

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remain asymptomatic. Moreover, a periodic follow-up could lead to unnecessary anxiety for patients and eventually extra unnecessary interventions and costs.

Over the past decades, many new uterine-sparing surgical treatments have been developed in attempts to minimize the invasiveness of the procedure and to improve women's quality of life. It is interesting to consider why some new techniques are being widely adopted while others, sometimes with promising results, never achieve widespread popularity. For example, the first publication on cryoablation dates from 1996 (113), but only one relevant article was found in our search after the year 2000 (39). In the present review almost 15% of the studies were directly sponsored by a medical devices company, and it must be considered that marketing and financial resources play a role in the success of an instrument. Sponsoring innovation is not necessarily unwarranted, but should not be ignored in terms of publication bias.

Although almost all treatment options studied in this review have been approved by the FDA and appeared to be safe, it is important to keep evaluating the long-term outcomes, especially for more newly introduced treatment options. In contrast to the introduction of new drugs, techniques and devices may not be introduced before extensive evaluation of efficacy or safety, and the true impact of new technologies can be appreciated only over time. As a result, there is always a risk that serious complications or suboptimal outcomes are being overlooked when the technique is not properly assessed.

CONCLUSION

Sixty months after initial therapy, a reintervention was necessary in 12.2% after myomectomy, in 7% after hysteroscopic myomectomy, and in 14.4% after UAE, although infertility as indication for treatment may have influenced outcomes. For HIFU, long-term results were not necessarily encouraging (54%), though based on limited evidence. For the other studied interventions, no long-term data were available at all. In terms of patient satisfaction, improvement of symptoms and quality of life was observed at 12 months after all approaches regardless of the technique applied. The HIFU treatment option showed the least improvement.

Despite the substantial heterogeneity of the study population, this meta-analysis provides valuable information on relative treatment efficacy of various uterine-sparing interventions for fibroids. Our results are important to consider when counseling patients in daily surgical practice. Furthermore, although most uterine-sparing treatment options for fibroids are FDA approved, long-term data regarding their efficacy are limited and therefore urgently needed.

REFERENCES

1. Ryan GL, Syrop CH, van Voorhis BJ. Role, epidemiology, and natural history of benign uterine mass lesions. Clin Obstet Gynecol 2005;48:312–24.
2. Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev 2014: CD005073.
3. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. Obstet Gynecol 2008;112:387–400.
4. Royal College of Obstetricians and Gynaecologists. Uterine artery embolisation in the management of fibroids. December 23, 2013. Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/uterine-artery-embolisation-in-the-management-of-fibroids/
5. Vilos GA, Allaire C, Laberge PY, Leyland N, Vilos AG, Murji A, et al. The management of uterine leiomyomas. J Obstet Gynaecol Can 2015;37:157–81.
6. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Open Med 2009;3:e123–30.
7. Coyne KS, Margolis MK, Murphy J, Spies J. Validation of the UFS-QOL-hysterectomy questionnaire: modifying an existing measure for comparative effectiveness research. Value Health 2012;15:674–9.
8. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
9. Edwards RD, Moss JG, Lumsden MA, Wu O, Murray LS, Twaddle S, et al. Uterine-artery embolization versus surgery for symptomatic uterine fibroids. N Engl J Med 2007;356:360–70.
10. Hahn M, Brucker S, Kraemer D, Wallwiener M, Taran FA, Wallwiener CW, et al. Radiofrequency volumetric thermal ablation of fibroids and laparoscopic myomectomy: long-term follow-up from a randomized trial. Geburtshilfe Frauenheilkd 2015;75:442–9.
11. Jacoby VL, Kohi MP, Poder L, Jacoby A, Lager J, Schembri M, et al. PROMISE trial: a pilot, randomized, placebo-controlled trial of magnetic resonance guided focused ultrasound for uterine fibroids. Fertil Steril 2016;105:773–80.
12. Kramer B, Hahn M, Taran FA, Kraemer D, Isaacson KB, Brucker SY. Interim analysis of a randomized controlled trial comparing laparoscopic radiofrequency volumetric thermal ablation of uterine fibroids with laparoscopic myomectomy. Int J Gynaecol Obstet 2016;133:206–11.
13. Manyonda IT, Bratby M, Horst JS, Banu N, Gorti M, Belli AM. Uterine artery embolization versus myomectomy: impact on quality of life—results of the FUME (Fibroids of the Uterus: Myomectomy versus Embolization) trial. Cardiovasc Intervent Radiol 2012;35:530–6.
14. Mara M, Fucikova Z, Maskova J, Kuzel D, Haakova L. Uterine fibroid embolization versus myomectomy in women wishing to preserve fertility: preliminary results of a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2006;126:226–33.
15. Moss JG, Cooper KG, Khaund A, Murray LS, Murray GD, Wu O, et al. Randomised comparison of uterine artery embolisation (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5-year results. BJOG 2011;118:936–44.
16. van der Kooij SM, Hehenkamp WJ, Volkers NA, Birnie E, Ankum WM, Reekers JA. Uterine artery embolization vs. hysterectomy in the treatment of symptomatic uterine fibroids: 5-year outcome from the randomized EMMY trial. Am J Obstet Gynecol 2010;203:105–13.
17. Tropeano G, di Stasi C, Amoroso S, Vizzielli G, Mascilini F, Scambia G. Incidence and risk factors for clinical failure of uterine leiomyoma embolization. Obstet Gynecol 2012;120:269–76.
18. Rossetti A, Sizzi O, Soranna L, Cucinelli F, Mancuso S, Lanzone A. Long-term results of laparoscopic myomectomy: recurrence rate in comparison with abdominal myomectomy. Hum Reprod 2001;16:770–4.
19. Pelage JP, le Dref O, Beregi JP, Nonent M, Robert Y, Cosson M, et al. Limited uterine artery embolization with tris-acryl gelatin microspheres for uterine fibroids. J Vasc Interv Radiol 2003;14:15–20.
20. Joffre F, Tubiana JM, Pelage JP. FEMIC (Fibromes Embolises aux Microspheres Calibrées): uterine fibroid embolization using tris-acryl microspheres. A French multicenter study. Cardiovasc Intervent Radiol 2004;27:600–6.
21. Ikink ME, Nijenhuis RJ, Verkooijen HM, Voogt MJ, Reuwer PJ, Smeets AJ, et al. Volumetric MR-guided high-intensity focused ultrasound versus uterine artery embolisation for treatment of symptomatic uterine fibroids: comparison of symptom improvement and reintervention rates. Eur Radiol 2014;24:2649–57.
22. Ghezzi F, Cromi A, Bergamini V, Scarperi S, Bolis P, Franchi M. Midterm outcome of radiofrequency thermal ablation for symptomatic uterine myomas. Surg Endosc 2007;21:2081–5.

23. Akinola OI, Fabamwo AO, Akinola RA, Ottun TA, Akinniyi A, Akpan AE. Uterine artery ligation for the treatment of fibroids. Acta Obstet Gynecol Scand 2009;88:59–62.
24. Berman JM, Guido RS, Garza Leal JG, Pemueller RR, Whaley FS, Chudnoff SG. Three-year outcome of the Halt trial: a prospective analysis of radiofrequency volumetric thermal ablation of myomas. J Minim Invasive Gynecol 2014;21:767–74.
25. Brolmann H, Bongers M, Garza-Leal JG, Gupta J, Veersema S, Quartero R, et al. The FAST-EU trial: 12-month clinical outcomes of women after intrauterine sonography–guided transcervical radiofrequency ablation of uterine fibroids. Gynecol Surg 2016;13:27–35.
26. Chrisman HB, West D, Corpuz B, Ryu RK, Salem R, Carr J, et al. Primary failure of uterine artery embolization: use of magnetic resonance imaging to select patients for repeated embolization. J Vasc Interv Radiol 2005;16:1143–7.
27. Garza Leal JG, Hernandez Leon I, Castillo Saenz L, Lee BB. Laparoscopic ultrasound–guided radiofrequency volumetric thermal ablation of symptomatic uterine leiomyomas: feasibility study using the Halt 2000 Ablation System. J Minim Invasive Gynecol 2011;18:364–71.
28. Goodwin SC, Spies JB, Worthington-Kirsch R, Peterson E, Pron G, Li S, et al. Uterine artery embolization for treatment of leiomyomata: long-term outcomes from the FIBROID registry. Obstet Gynecol 2008;111:22–33.
29. Hamoda H, Pepas L, Tasker F, Reidy J, Khalaf Y. Intermediate and long-term outcomes following uterine artery fibroid embolization. Eur J Obstet Gynecol Reprod Biol 2015;191:33–8.
30. Jiang N, Xie B, Zhang X, He M, Li K, Bai J, et al. Enhancing ablation effects of a microbubble-enhancing contrast agent ("Sonovue") in the treatment of uterine fibroids with high-intensity focused ultrasound: a randomized controlled trial. Cardiovasc Intervent Radiol 2014;37:1321–8.
31. Kim HS, Baik JH, Pham LD, Jacobs MA. MR-guided high-intensity focused ultrasound treatment for symptomatic uterine leiomyomata: long-term outcomes. Acad Radiol 2011;18:970–6.
32. Kroencke TJ, Scheurig C, Lampmann LE, Boekkooi PF, Kissner L, Kluner C, et al. Acrylamido polyvinyl alcohol microspheres for uterine artery embolization: 12-month clinical and MR imaging results. J Vasc Interv Radiol 2008;19:47–57.
33. Liang E, Brown B, Kirsop R, Stewart P, Stuart A. Efficacy of uterine artery embolisation for treatment of symptomatic fibroids and adenomyosis—an interim report on an Australian experience. Aust N Z J Obstet Gynaecol 2012;52:106–12.
34. Lohle PN, Voogt MJ, de Vries J, Smeets AJ, Vervest HA, Lampmann LE, et al. Long-term outcome of uterine artery embolization for symptomatic uterine leiomyomas. J Vasc Interv Radiol 2008;19:319–26.
35. Machtinger R, Fennessy FM, Stewart EA, Missmer SA, Correia KF, Tempany CM. MR-guided focused ultrasound (MRgFUS) is effective for the distinct pattern of uterine fibroids seen in African-American women: data from phase III/IV, nonrandomized, multicenter clinical trials. J Ther Ultrasound 2013;1:23.
36. Mohan PC, Tan BS, Kwek BH, Abu J, Koh D, Tay KH, et al. Uterine artery embolisation for symptomatic fibroids in a tertiary hospital in Singapore. Ann Acad Med Singapore 2005;34:78–83.
37. Morita Y, Ito N, Hikida H, Takeuchi S, Nakamura K, Ohashi H. Noninvasive magnetic resonance imaging–guided focused ultrasound treatment for uterine fibroids—early experience. Eur J Obstet Gynecol Reprod Biol 2008;139:199–203.
38. Obed JY, Bako B, Usman JD, Moruppa JY, Kadas S. Uterine fibroids: risk of recurrence after myomectomy in a Nigerian population. Arch Gynecol Obstet 2011;283:311–5.
39. Pansky M, Cowan BD, Frank M, Hampton HL, Zimberg S. Laparoscopically assisted uterine fibroid cryoablation. Am J Obstet Gynecol 2009;201:571–7.
40. Prollius A, de Vries C, Loggenberg E, Nel M, du Plessis A, van Rensburg DJ, et al. Uterine artery embolization for symptomatic fibroids. Int J Gynaecol Obstet 2004;84:236–40.
41. Robles R, Aguirre VA, Argueta AI, Guerrero MR. Laparoscopic radiofrequency volumetric thermal ablation of uterine myomas with 12 months of follow-up. Int J Gynaecol Obstet 2013;120:65–9.
42. Scheurig-Muenkler C, Koesters C, Powerski MJ, Grieser C, Froeling V, Kroencke TJ. Clinical long-term outcome after uterine artery embolization: sustained symptom control and improvement of quality of life. J Vasc Interv Radiol 2013;24:765–71.
43. Sinha R, Hegde A, Mahajan C, Dubey N, Sundaram M. Laparoscopic myomectomy: do size, number, and location of the myomas form limiting factors for laparoscopic myomectomy? J Minim Invasive Gynecol 2008;15:292–300.
44. Siskin G. New treatments for uterine fibroids. Tech Vasc Interv Radiol 2006;9:12–8.
45. Sone M, Arai Y, Shimizu T, Takeuchi Y, Higashihara H, Ohgi S, et al. Phase I/II multiinstitutional study of uterine artery embolization with gelatin sponge for symptomatic uterine leiomyomata: Japan Interventional Radiology in Oncology Study Group study. J Vasc Interv Radiol 2010;21:1665–71.
46. Spies JB, Bruno J, Czeyda-Pommersheim F, Magee ST, Ascher SA, Jha RC. Long-term outcome of uterine artery embolization of leiomyomata. Obstet Gynecol 2005;106:933–9.
47. Spies JB, Bradley LD, Guido R, Maxwell GL, Levine BA, Coyne K. Outcomes from leiomyoma therapies: comparison with normal controls. Obstet Gynecol 2010;116:641–52.
48. Stewart EA, Faur AV, Wise LA, Reilly RJ, Harlow BL. Predictors of subsequent surgery for uterine leiomyomata after abdominal myomectomy. Obstet Gynecol 2002;99:426–32.
49. Tranquart F, Brunereau L, Cottier JP, Marret H, Gallas S, Lebrun JL, et al. Prospective sonographic assessment of uterine artery embolization for the treatment of fibroids. Ultrasound Obstet Gynecol 2002;19:81–7.
50. Walker WJ, Barton-Smith P. Long-term follow up of uterine artery embolisation—an effective alternative in the treatment of fibroids. BJOG 2006;113:464–8.
51. Wang F, Zhang J, Han ZY, Cheng ZG, Zhou HY, Feng L, et al. Imaging manifestation of conventional and contrast-enhanced ultrasonography in percutaneous microwave ablation for the treatment of uterine fibroids. Eur J Radiol 2012;81:2947–52.
52. Wen KC, Chen YJ, Sung PL, Wang PH. Comparing uterine fibroids treated by myomectomy through traditional laparotomy and 2 modified approaches: ultraminilaparotomy and laparoscopically assisted ultraminilaparotomy. Am J Obstet Gynecol 2010;202:144–8.
53. Yang Y, Zhang J, Han ZY, Yu MA, Ma X, Zhou HY, et al. Ultrasound-guided percutaneous microwave ablation for submucosal uterine fibroids. J Minim Invasive Gynecol 2014;21:436–41.
54. Watson GM, Walker WJ. Uterine artery embolisation for the treatment of symptomatic fibroids in 114 women: reduction in size of the fibroids and women's views of the success of the treatment. BJOG 2002;109:129–35.
55. Radosa MP, Owsianowski Z, Mothes A, Weisheit A, Vorwergk J, Asskaryar FA, et al. Long-term risk of fibroid recurrence after laparoscopic myomectomy. Eur J Obstet Gynecol Reprod Biol 2014;180:35–9.
56. Poulsen B, Munk T, Ravn P. Long-term follow up after uterine artery embolization for symptomatic uterine leiomyomas. Acta Obstet Gynecol Scand 2011;90:1281–3.
57. Gabriel-Cox K, Jacobson GF, Armstrong MA, Hung YY, Learman LA. Predictors of hysterectomy after uterine artery embolization for leiomyoma. Am J Obstet Gynecol 2007;196:588.e1–6.
58. Lee JS, Hong GY, Park BJ, Kim TE. Ultrasound-guided high-intensity focused ultrasound treatment for uterine fibroid and adenomyosis: a single center experience from the Republic of Korea. Ultrason Sonochem 2015;27:682–7.
59. Froeling V, Meckelburg K, Schreiter NF, Scheurig-Muenkler C, Kamp J, Maurer MH, et al. Outcome of uterine artery embolization versus MR-guided high-intensity focused ultrasound treatment for uterine fibroids: long-term results. Eur J Radiol 2013;82:2265–9.
60. Duvnjak S, Ravn P, Green A, Andersen PE. Clinical long-term outcome and reinterventional rate after uterine fibroid embolization with nonspherical versus spherical polyvinyl alcohol particles. Cardiovasc Intervent Radiol 2016;39:204–9.

61. Chang CY, Chang YT, Chien SC, Yu SS, Hung YC, Lin WC. Factors associated with operative hysteroscopy outcome in patients with uterine adhesions or submucosal myomas. Int J Gynaecol Obstet 2010;109:125–7.
62. Birinyi L, Kalamasz N, Juhasz AG, Major T, Borsos A, Bacsko G. Follow-up study on the effectiveness of transcervical myoma resection (TCRM). Eur J Obstet Gynecol Reprod Biol 2004;113:78–82.
63. Bucek RA, Puchner S, Lammer J. Mid- and long-term quality-of-life assessment in patients undergoing uterine fibroid embolization. AJR Am J Roentgenol 2006;186:877–82.
64. Choi HJ, Jeon GS, Kim MD, Lee JT, Yoon JH. Is uterine artery embolization for patients with large myomas safe and effective? A retrospective comparative study in 323 patients. J Vasc Interv Radiol 2013;24:772–8.
65. Cho HH, Kim MR, Kim JH. Outpatient multimodality management of large submucosal myomas using transvaginal radiofrequency myolysis. J Minim Invasive Gynecol 2014;21:1049–54.
66. Dobrotwir A, Pun E. Clinical 24 month experience of the first MRgFUS unit for treatment of uterine fibroids in Australia. J Med Imaging Radiat Oncol 2012;56:409–16.
67. Feng ZC, Shi YP, Liu SP. Hysteroscopic resection of submucous fibroids: clinical analysis of 99 cases. Gynaecol Endosc 2002;11:127–30.
68. Funaki K, Fukunishi H, Sawada K. Clinical outcomes of magnetic resonance–guided focused ultrasound surgery for uterine myomas: 24-month follow-up. Ultrasound Obstet Gynecol 2009;34:584–9.
69. Galen DI, Pemueller RR, Leal JG, Abbott KR, Falls JL, Macer J. Laparoscopic radiofrequency fibroid ablation: phase II and phase III results. JSLS 2014;18:182–90.
70. Glasser MH. Minilaparotomy myomectomy: a minimally invasive alternative for the large fibroid uterus. J Minim Invasive Gynecol 2005;12:275–83.
71. Laios A, Baharuddin N, Iliou K, Gubara E, O'Sullivan G. Uterine artery embolization for treatment of symptomatic fibroids; a single institution experience. Hippokratia 2014;18:258–61.
72. Lenard ZM, McDannold NJ, Fennessy FM, Stewart EA, Jolesz FA, Hynynen K, et al. Uterine leiomyomas: MR imaging–guided focused ultrasound surgery—imaging predictors of success. Radiology 2008;249:187–94.
73. McLucas B, Voorhees WD III. Results of UAE in women under 40 years of age. Minim Invasive Ther Allied Technol 2014;23:179–83.
74. Mindjuk I, Trumm CG, Herzog P, Stahl R, Matzko M. MRI predictors of clinical success in MR-guided focused ultrasound (MRgFUS) treatments of uterine fibroids: results from a single centre. Eur Radiol 2015;25:1317–28.
75. Narayan A, Lee AS, Kuo GP, Powe N, Kim HS. Uterine artery embolization versus abdominal myomectomy: a long-term clinical outcome comparison. J Vasc Interv Radiol 2010;21:1011–7.
76. Polena V, Mergui JL, Perrot N, Poncelet C, Barranger E, Uzan S. Long-term results of hysteroscopic myomectomy in 235 patients. Eur J Obstet Gynecol Reprod Biol 2007;130:232–7.
77. Popovic M, Berzaczy D, Puchner S, Zadina A, Lammer J, Bucek RA. Long-term quality of life assessment among patients undergoing uterine fibroid embolization. AJR Am J Roentgenol 2009;193:267–71.
78. Quinn SD, Vedelago J, Gedroyc W, Regan L. Safety and five-year re-intervention following magnetic resonance–guided focused ultrasound (MRgFUS) for uterine fibroids. Eur J Obstet Gynecol Reprod Biol 2014;182:247–51.
79. Shiota M, Kotani Y, Umemoto M, Tobiume T, Shimaoka M, Hoshiai H. Total abdominal hysterectomy versus laparoscopically-assisted vaginal hysterectomy versus total vaginal hysterectomy. Asian J Endosc Surg 2011;4:161–5.
80. Walid MS, Heaton RL. Laparoscopic myomectomy: an intent-to-treat study. Arch Gynecol Obstet 2010;281:645–9.
81. Yoo EH, Lee PI, Huh CY, Kim DH, Lee BS, Lee JK, et al. Predictors of leiomyoma recurrence after laparoscopic myomectomy. J Minim Invasive Gynecol 2007;14:690–7.
82. Yoon SW, Cha SH, Ji YG, Kim HC, Lee MH, Cho JH. Magnetic resonance imaging–guided focused ultrasound surgery for symptomatic uterine fibroids: estimation of treatment efficacy using thermal dose calculations. Eur J Obstet Gynecol Reprod Biol 2013;169:304–8.
83. Capmas P, Voulgaropoulos A, Legendre G, Pourcelot A-G, Fernandez H. Hysteroscopic resection of type 3 myoma: a new challenge? Eur J Obstet Gynecol Reprod Biol 2016;205:165–9.
84. Flyckt R, Soto E, Nutter B, Falcone T. Comparison of long-term fertility and bleeding outcomes after robotic-assisted, laparoscopic, and abdominal myomectomy. Obstet Gynecol Int 2016;2016:2789201.
85. Han NL, Ong CL. Magnetic resonance–guided focused ultrasound surgery (MRgFUS) of uterine fibroids in Singapore. Ann Acad Med Singapore 2014;43:550–8.
86. Liu H, Zhang J, Han Z-Y, Zhang B-S, Zhang W, Qi C-S, et al. Effectiveness of ultrasound-guided percutaneous microwave ablation for symptomatic uterine fibroids: a multicentre study in China. Int J Hyperthermia 2016;32:876–80.
87. Marigliano C, Panzironi G, Molisso L, Pizzuto A, Ciolina F, Napoli A, et al. First experience of real-time elastography with transvaginal approach in assessing response to MRgFUS treatment of uterine fibroids. Radiol Med 2016;121:926–34.
88. Rischbieter P, Sinclair C, Lawson A, Ahmad S. Uterine artery embolisation as an effective choice for symptomatic fibroids: five-year outcome. S Afr J Radiol 2016;20:1–5.
89. Salehi M, Jalilian N, Salehi A, Ayazi M. Clinical efficacy and complications of uterine artery embolization in symptomatic uterine fibroids. Glob J Health Sci 2015;8:245–50.
90. Sangha R, Katukuri V, Palmer M, Khangura RK. Recurrence after robotic myomectomy: is it associated with use of GnRH agonist? J Robot Surg 2016;10:245–9.
91. Song YG, Woo YJ, Kim CW. Uterine artery embolization using progressively larger calibrated gelatin sponge particles. Minim Invasive Ther Allied Technol 2016;25:35–42.
92. Spies JB, Myers ER, Worthington-Kirsch R, Mulgund J, Goodwin S, Mauro M. The FIBROID registry: Symptom and quality-of-life status 1 year after therapy. Obstet Gynecol 2005;106:1309–18.
93. Subramanian S, Clark MA, Isaacson K. Outcome and resource use associated with myomectomy. Obstet Gynecol 2001;98:583–7.
94. Berman JM, Puscheck EE, Diamond MP. Full-term vaginal live birth after laparoscopic radiofrequency ablation of a large, symptomatic intramural fibroid: a case report. J Reprod Med 2012;57:159–63.
95. Gorny KR, Borah BJ, Brown DL, Woodrum DA, Stewart EA, Hesley GK. Incidence of additional treatments in women treated with MR-guided focused US for symptomatic uterine fibroids: review of 138 patients with an average follow-up of 2.8 years. J Vasc Interv Radiol 2014;25:1506–12.
96. Shiota M, Kotani Y, Umemoto M, Tobiume T, Hoshiai H. Indication for laparoscopically assisted vaginal hysterectomy. JSLS 2011;15:343–5.
97. Galen DI, Isaacson KB, Lee BB. Does menstrual bleeding decrease after ablation of intramural myomas? A retrospective study. J Minim Invasive Gynecol 2013;20:830–5.
98. Wang PH, Liu WM, Fuh JL, Chao HT, Chao KC, Yuan CC. Laparoscopic uterine vessel occlusion in the treatment of women with symptomatic uterine myomas with and without adding laparoscopic myomectomy: 4-year results. J Minim Invasive Gynecol 2008;15:712–8.
99. Hald K, Noreng HJ, Istre O, Klow NE. Uterine artery embolization versus laparoscopic occlusion of uterine arteries for leiomyomas: long-term results of a randomized comparative trial. J Vasc Interv Radiol 2009;20:1303–10.
100. Lee WL, Liu WM, Cheng MH, Chao HT, Fuh JL, Wang PH. Uterine vascular occlusion in management of leiomyomas: laparoscopy vs. laparotomy. J Minim Invasive Gynecol 2009;16:562–8.
101. Kim YS, Lim HK, Kim JH, Rhim H, Park BK, Keserci B, et al. Dynamic contrast-enhanced magnetic resonance imaging predicts immediate therapeutic response of magnetic resonance–guided high-intensity focused ultrasound ablation of symptomatic uterine fibroids. Invest Radiol 2011;46:639–47.
102. Smeets AJ, Nijenhuis RJ, van Rooij WJ, Weimar EA, Boekkooi PF, Lampmann LE, et al. Uterine artery embolization in patients with a large fibroid burden: long-term clinical and MR follow-up. Cardiovasc Intervent Radiol 2010;33:943–8.

103. U.S. Food and Drug Administration. Premarket approval: Exablate 2100 System. December 22, 2009. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P040003S006. Accessed September 2017.
104. Zupi E, Centini G, Sabbioni L, Lazzeri L, Argay IM, Petraglia F. Nonsurgical alternatives for uterine fibroids. Best Pract Res Clin Obstet Gynaecol 2016;34:122–31.
105. Mara M, Maskova J, Fucikova Z, Kuzel D, Belsan T, Sosna O. Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. Cardiovasc Intervent Radiol 2008;31:73–85.
106. Goldberg J, Pereira L. Pregnancy outcomes following treatment for fibroids: uterine fibroid embolization versus laparoscopic myomectomy. Curr Opin Obstet Gynecol 2006;18:402–6.
107. Amato P, Roberts AC. Transient ovarian failure: a complication of uterine artery embolization. Fertil Steril 2001;75:438–9.
108. Kroon B, Johnson N, Chapman M, Yazdani A, Hart R. Fibroids in infertility—consensus statement from ACCEPT (Australasian CREI Consensus Expert Panel on Trial Evidence). Aust N Z J Obstet Gynaecol 2011;51:289–95.
109. Rabinovici J, David M, Fukunishi H, Morita Y, Gostout BS, Stewart EA. Pregnancy outcome after magnetic resonance–guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. Fertil Steril 2010;93:199–209.
110. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009;91:1215–23.
111. Thiburce AC, Frulio N, Hocquelet A, Maire F, Salut C, Balageas P, et al. Magnetic resonance–guided high-intensity focused ultrasound for uterine fibroids: mid-term outcomes of 36 patients treated with the Sonalleve system. Int J Hyperthermia 2015;31:764–70.
112. Volkers NA, Hehenkamp WJ, Smit P, Ankum WM, Reekers JA, Birnie E. Economic evaluation of uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: results from the randomized EMMY trial. J Vasc Interv Radiol 2008;19:1007–16.
113. Olive DL, Rutherford T, Zreik T, Palter S. Cryomyolysis in the conservative treatment of uterine fibroids. J Am Assoc Gynecol Laparosc 1996;3(4 Suppl):S36.

1 **Reintervention risk and quality of life outcomes after uterine-sparing interventions for fibroids: a systematic review and meta-analysis**

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Data regarding the efficacy of uterine-sparing interventions are limited. Sixty months after therapy, reintervention risks were 12.2% for myomectomy, 14% for embolization, 53.9% for high-intensity focused ultrasound, and 7% for hysteroscopic myomectomy.

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