International Journal of Hyperthermia

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ihyt20

Adverse events and complications after magnetic resonance-guided focused ultrasound (MRgFUS) therapy in uterine fibroids – a systematic review and future perspectives

Jakub Kociuba, Tomasz Łoziński, Magdalena Zgliczyńska, Maciej Byrczak, Salvatore Giovanni Vitale, Maciej Skrzypczak, Kornelia Zaręba & Michał Ciebiera

To cite this article: Jakub Kociuba, Tomasz Łoziński, Magdalena Zgliczyńska, Maciej Byrczak, Salvatore Giovanni Vitale, Maciej Skrzypczak, Kornelia Zaręba & Michał Ciebiera (2023) Adverse events and complications after magnetic resonance-guided focused ultrasound (MRgFUS) therapy in uterine fibroids – a systematic review and future perspectives, International Journal of Hyperthermia, 40:1, 2174274, DOI: 10.1080/02656736.2023.2174274

To link to this article: https://doi.org/10.1080/02656736.2023.2174274

INTERNATIONAL JOURNAL OF HYPERTHERMIA
2023, VOL. 40, NO. 1, 2174274
https://doi.org/10.1080/02656736.2023.2174274

Taylor & Francis
Taylor & Francis Group

REVIEW

Adverse events and complications after magnetic resonance-guided focused ultrasound (MRgFUS) therapy in uterine fibroids – a systematic review and future perspectives

Jakub Kociuba[a], Tomasz Łoziński[b,c], Magdalena Zgliczyńska[d], Maciej Byrczak[a], Salvatore Giovanni Vitale[e], Maciej Skrzypczak[f], Kornelia Zaręba[g] and Michał Ciebiera[a]

[a]Second Department of Obstetrics and Gynecology, Center of Postgraduate Medical Education, Warsaw, Poland; [b]Department of Obstetrics and Gynecology, Pro-Familia Hospital, Rzeszow, Poland; [c]Department of Gynecology and Obstetrics, Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszow, Poland; [d]Department of Obstetrics, Perinatology and Neonatology, Centre of Postgraduate Medical Education, Warsaw, Poland; [e]Obstetrics and Gynecology Unit, Department of General Surgery and Medical Surgical Specialties, University of Catania, Italy; [f]Second Department of Gynecology, Medical University of Lublin, Lublin, Poland; [g]Obstetrics and Gynecology Department, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates

ABSTRACT

Objectives: The aim of this review was to analyze and summarize the most common adverse events (AEs) and complications after magnetic resonance-guided focused ultrasound (MRgFUS) therapy in uterine fibroids (UFs) and to establish the risk factors of their occurrence.

Methods: We searched for original research studies evaluating MRgFUS therapy in UFs with outcomes containing AEs and/or complications in different databases (PubMed/MEDLINE, SCOPUS, COCHRANE) until March 2022. Reviews, editorials, opinions or letters, case studies, conference papers and abstracts were excluded from the analysis. The systematic literature search identified 446 articles, 43 of which were analyzed.

Results: According to available evidence, the overall incidence of serious complications in MRgFUS therapy is relatively low. No AEs/complications were reported in 11 out of 43 analyzed studies. The mean occurrence of all AEs in the analyzed material was 24.67%. The most commonly described AEs included pain, skin burns, urinary tract infections and sciatic neuropraxia. Major AEs, such as skin ulcerations or deep vein thrombosis, occurred in 0.41% of cases in the analyzed material.

Conclusion: MRgFUS seems to be safe in UF therapy. The occurrence of AEs, especially major ones, is relatively low in comparison with other methods. The new devices and more experience of their users seem to reduce AE rate. The lack of unification in AE reporting and missing data are the main issues in this area. More prospective, randomized studies with unified reporting and long follow-up are needed to determine the safety in a long-term perspective.

ARTICLE HISTORY
Received 29 August 2022
Revised 18 January 2023
Accepted 24 January 2023

KEYWORDS
Magnetic resonance-guided focused ultrasound; MR-HIFU; uterine fibroid; adverse event; complication

Introduction

Uterine fibroids (UFs) are benign tumors of the female genital tract originating from the uterine smooth muscle cells and fibroblasts. Despite quite a simple structure, their pathophysiology is unquestionably complicated [1]. According to currently available data, the development of UFs is associated with a change from a normal myometrial cell to a mutated cell with the potential for further division. Estrogen and progesterone seem to play an essential role in the induction of paracrine reaction, which promotes tumor stem cell division and growth [1,2]. Genetics was also mentioned to have an influence on the incidence of UFs, as these tumors are much more commonly seen in certain populations, e.g., Afro-American women [3].

UFs constitute a common social problem affecting up to 70–80% women under 50 years of age, 15–30% of whom develop severe symptoms [1]. According to a recent epidemiological systematic review by Stewart et al. [3], the most common risk factors include: African-American ethnicity, advanced age, perimenopausal status, hypertension, family history, time from the last delivery, food additives and soybean milk in the diet. Obesity has also been recently mentioned to be a serious risk factor [4].

The most common clinical manifestations of UFs include excessive uterine bleeding, anemia, pelvic discomfort, urinary incontinence, recurrent pregnancy loss or preterm labor. Currently available data concerning the percentage of women with symptomatic UFs vary. According to the literature, the symptoms occurred in about 25–50% of affected patients, which was the reason why the majority of them did not need any therapy, but only observation [5,6]. Health care

CONTACT Jakub Kociuba jakubkociuba@gmail.com Second Department of Obstetrics and Gynecology, Center of Postgraduate Medical Education, Inflancka 6, 00-189, Warsaw, Poland

Supplemental data for this article can be accessed online at https://doi.org/10.1080/02656736.2023.2174274

providers should pay particular attention to symptomatic women, as clinical manifestations constitute the main indication for UF therapy. The criteria of selecting appropriate treatment largely depends on the age, clinical manifestations and patient's expectations concerning the preservation of fertility [7]. As UFs are benign tumors and the symptoms are the main indication for treatment initiation, it is very important to choose the best option, which is as adjusted to the patient's preferences and individualized as possible. Information about the advantages and disadvantages, effectiveness and possible adverse events (AEs) or complications of a treatment should be presented to the patient in order to allow aware patient-shared decision making, which would positively influence patient compliance and trust [8].

Different types of UF therapy are available. They are most often divided into conservative treatment and invasive (surgical) methods. The conservative option includes pharmacotherapy aims at reducing symptom severity (e.g., menorrhagia). It may involve the use of analgesics, oral contraceptives, antihemorrhagic drugs, levonorgestrel-releasing intrauterine devices, gonadotropin-releasing hormone (GnRH) analogs or ulipristal acetate (UPA) – a selective progesterone receptor modulator [9]. GnRH analogs and UPA seemed to be the most effective in symptom reduction [10,11], but the possible adverse effects of these drugs (such as risk of osteoporosis and menopausal symptoms) may be unacceptable for some women [12]. Furthermore, a recently published randomized trial investigating relugolix therapy combined with estradiol, and norethindrone acetate in symptomatic UFs showed the effectiveness of the therapy and the incidence of AEs similar to that of placebo [13]. These are certainly methods to be considered for patient-tailored therapy.

Hysterectomy is the most common surgical procedure performed to treat UFs. However, it was proved to be connected with significant morbidity, mortality and a great economic and social impact on health care systems around the world [14,15]. Moreover, this therapeutic option excludes further reproductive plans, so many women at reproductive age look for less invasive procedures. Due to technological development, new surgical and non-surgical modalities have been introduced that meet patients' expectations for less invasive treatment. Laparoscopic or hysteroscopic myomectomy, uterine artery embolization (UAE), ultrasound-guided or magnetic resonance-guided focused ultrasound (USgFUS or MRgFUS) should be considered by women who do not accept the risk of AEs connected with open surgery, especially with hysterectomy.

MRgFUS is a noninvasive thermal ablation technique, which enables the treatment of UFs through concentrated ultrasound beam. Heating the tissue is the main mechanism triggering the necrosis of targeted fibroid tissue area. Magnetic resonance imaging (MRI) enables planning the treatment and controlling the real-time temperature map. Directly after the procedure, contrast-enhanced MRI is performed to visualize the ablated area, referred to as non-perfused volume (NPV). The result of treatment is most often described as NPV%, which means NPV divided by the volume of the targeted fibroid.

The purpose of our systematic review was to reassess all available literature and to conduct a thorough investigation of the type and frequency of AEs and complications occurring after MRgFUS therapy in UFs, basing on current data regardless of the device used, fibroid type, inclusion and exclusion criteria, and the protocol used. We also investigated the risk factors of particular complications, discussed potential methods to avoid them in the future and analyzed how to plan further studies in the context of AE reporting.

Material and methods

The review was created pursuant to the Updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) 2020 [16]. The following databases were used as sources: PubMed/MEDLINE, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) and the detailed search strategy is presented below. The last search was run on 4 March 2022.

Database	Number of retrieved articles	Search strategy
PubMed	202	("Leiomyoma"[Mesh] OR myom* OR leiomyom* OR fibromyom* OR (uterine AND fibroid*) OR (uterine AND fibrom*)) AND (mrgfus OR mrg-fus OR (magnetic AND resonance AND guided AND focused AND ultrasound*) OR (MRI AND guided AND focused AND ultrasound*) OR (magnetic AND resonance AND guided AND high AND intensity AND Focused AND Ultrasound) OR (magnetic AND resonance AND guided AND focus AND ultrasonograph*) OR mrhifu OR mr-hifu OR mrghifu OR hifu OR (MRI AND guided AND focus AND ultrasonograph*) OR termoablation* OR thermoablation*) AND (complication* OR (adverse AND event*))
Scopus	208	TITLE-ABS-KEY ((myom* OR leiomyom* OR fibromyom* OR (uterine AND fibroid*) OR (uterine AND fibrom*)) AND (mrgfus OR mrg-fus OR (magnetic AND resonance AND guided AND focused AND ultrasound*) OR (MRI AND guided AND focused AND ultrasound*) OR (magnetic AND resonance AND guided AND high AND intensity AND Focused AND Ultrasound) OR (magnetic AND resonance AND guided AND focus AND ultrasonograph*) OR mrhifu OR mr-hifu OR mrghifu OR hifu OR (MRI AND guided AND focus AND ultrasonograph*) OR termoablation* OR thermoablation*) AND (complication* OR (adverse AND event*))) AND (LIMIT-TO (LANGUAGE,"English"))
Cochrane	36	#1 "Leiomyoma"[Mesh] #2 myom* OR leiomyom* OR fibromyom* OR (uterine AND fibroid*) OR (uterine AND fibrom*) #3 mrgfus OR mrg-fus OR (magnetic AND resonance AND guided AND focused AND ultrasound*) OR (MRI AND guided AND focused AND ultrasound*) OR (magnetic AND resonance AND guided AND high AND intensity AND Focused AND Ultrasound) OR (magnetic AND resonance AND guided AND focus AND ultrasonograph*) OR mrhifu OR mr-hifu OR mrghifu OR hifu OR (MRI AND guided ANG focus AND ultrasonograph*) OR termoablation* OR thermoablation* #4 complication* OR (adverse AND event*) #5 (#1 OR #2) AND #3 AND #4 + Trials
Total	446	

We retrieved 446 references using the above-mentioned search strategy. The automatic search function in EndNote X9 (Clarivate Analytics, London, UK) was used to delete 154 duplicates. Additional 39 were manually identified. The remaining 255 manuscripts were screened by two study authors (J.K., M.B.) using the earlier established inclusion and exclusion criteria.

The analysis included complete English-language manuscripts containing randomized and nonrandomized control trials, cohort and case-control studies with information about AEs/complications related to MRgFUS therapy. Studies with no data regarding AEs/complications and those concerning ablative techniques other than MRgFUS were excluded. Non-English and animal studies, ongoing trials, reviews, case reports, case series, letters to editors, expert opinions and conference papers were also eliminated.

In the next step, two other study authors reviewed the complete manuscripts in detail (M.Z., M.C.). Disagreements at any step were resolved through discussion with all study authors. Ultimately, 43 papers were included in the systematic review. The selection process is outlined in the PRISMA Flow Diagram (Figure 1).

We used a pilot-tested original extraction sheet for the collection of the following information from selected manuscripts: authorship, year of publication, type of study, main aim, demographics, inclusion and exclusion criteria, UF characteristics, treatment parameters, outcomes, AEs and the time of follow-up.

The risk of bias of cohort studies was assessed independently by two study authors (M.Z, J.K.) using the Newcastle–Ottawa Quality Assessment Scale, modified by the authors for the needs of this manuscript [18]. Each article could be awarded one star for each star-rated feature within the 'Selection' category and one or two stars within the 'Outcomes' and 'Comparability' categories. Specific criteria for star awarding are included in the first column of Supplementary Table S3. Finally, an article was rated as having a low risk of bias if it reached: 2/3 or 3/3 or 3/4 or 4/4 stars in 'Selection' AND 1 or 2 stars in 'Comparability' AND 3 or 4 stars in 'Outcome'; moderate risk of bias with 2/4 or 1/3 stars in 'Selection' AND 1 or 2 stars in 'Comparability' AND 2 stars in 'Outcome'; high risk of bias with 0 or 1 star in 'Selection' OR 0 stars in 'Comparability' OR 0 or 1 stars in 'Outcome'.

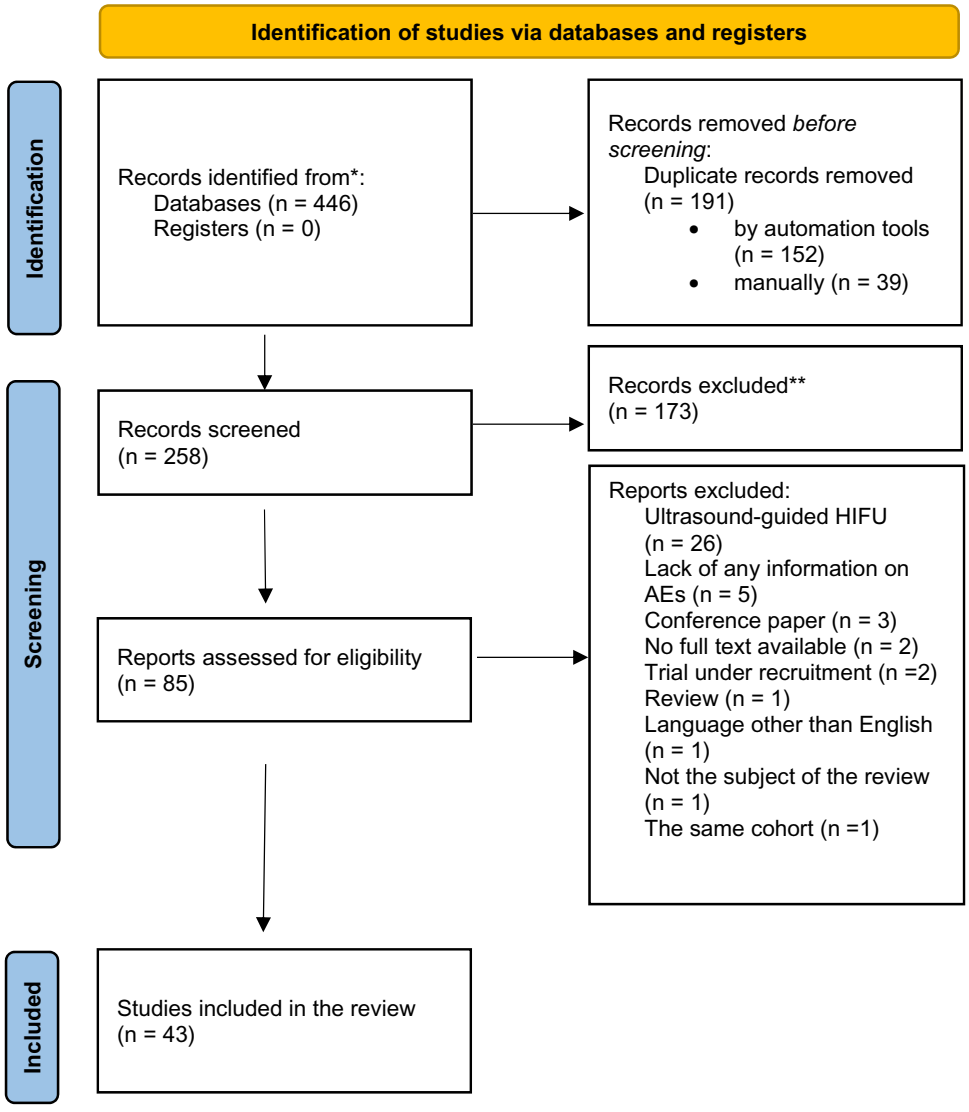

Figure 1. PRISMA flow diagram [17]. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

The Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was used for the assessment of the risk of bias in randomized control trials [19]. The following five domains were assessed in the studies: 'Risk of bias arising from the randomization process', 'Risk of bias due to deviations from the intended interventions', 'Missing outcome data', 'Risk of bias in the measurement of the outcome' and 'Risk of bias in the selection of the reported result'. In each domain, the risk of bias could be assessed as 'low', raising 'some concerns' and 'high'. The study was evaluated to be: at a low risk of bias for all domains for this result; to raise some concerns in at least one domain for this result, but not to be at a high risk of bias for any domain; to be at a high risk of bias in at least one domain for this result OR to have some concerns for multiple domains in a way that substantially lowers confidence in the result. Similarly, any disagreements were resolved through consensus with all study authors.

Results

The systematic literature search resulted in the retrieval of 43 articles that met the inclusion criteria [20–62]. The total number of patients treated in all analyzed manuscripts was 3102. Prospective cohort studies were the most common type (22 out of 43), followed by retrospective cohort analyses (19 out of 43). Only two studies were randomized control trials [27,29]. As the MRgFUS is a relatively new method of UF treatment, the oldest study was dated from 2003, whereas the most recent one was from 2021. The follow-up time of 3–6 months was most commonly reported. One-year or longer follow-up was found in 17 out of 43 retrieved studies. The main characteristics of analyzed manuscripts are collected in Supplementary Table S1.

The risk of bias assessment classified 23 studies as being at a low, 8 at a moderate and 12 at a high risk of bias based on the reported AEs. Small sample size and short follow-up time were the most common sources of bias in the reviewed studies. The details of the evaluation of each manuscript are presented in Supplementary Tables S2 and S3.

We analyzed the occurrence of AEs in 39 papers. No information concerning the number of patients with AEs out of the whole cohort was included in four manuscripts [34,44,58,62]. The number of patients in 39 papers equaled 2919. All kinds of AEs were reported in 720 patients, whereas major AEs occurred in only 12 patients. The mean occurrence of AEs in the analyzed material was 24.67% (major and minor ones), while the major AE rate was 0.41%. Our review showed that 10 out of 43 studies described no AEs [20,22,25,28,29,45,49,51,56,59]. The details of AEs from 33 studies which reported at least one AE are summarized in Table 1.

We performed additional analysis for the occurrence of AEs in relation to the device used in the procedure. According to available data, three types of devices were used for UF therapy during analyzed period of time (ExAblate, Sonalleve and Chongqing Haifu). All devices were used in two versions (ExAblate 2000/2100, Sonalleve V1/V2 and Chongqing Haifu JM 2.5 C/JM 5100). ExAblate 2000 was used the most commonly. It was listed in 25, mostly older, papers [21,27–29,34,35,39,40,42,45,47–49,51–63], among which the number of patients with AEs was missing in three manuscripts [34,58,62]. The mean occurrence of AEs was 18.03% in 22 studies with the use of ExAblate 2000. Sonalleve was the second most popular device. It was described in 11 studies [22–24,30,32,36,38,41,43,44,46]. In most cases, the authors did not publish information about the version of the used system. Only four studies provided information concerning the version (three papers mentioned Sonalleve V1 and 1 – V2) [22–24,30]. The number of patients with AEs was missing in one manuscript [44]. The mean occurrence of AEs was 40.3% in 10 studies without distinguishing the version of the device. ExAblate 2100 was the third most common system. It was mentioned in four manuscripts [20,21,33,37]. The mean occurrence of AEs was 5.25% with this system. Chongqing Haifu devices were less popular. JM 2.5 C appeared in only one study (mean occurrence of AEs was 19.05%) [50], whereas JM 5100 was mentioned in two papers (the mean occurrence rate of AEs was 35.45%) [26,31]. The comparison of AEs rate in particular devices are summarized in Table 2.

Discussion

AE reporting seems to be the most serious limitation of almost all relevant original studies and reviews about ultrasound ablation in UF therapy. Discrepancy may be due to the lack of unification in AE reporting in the majority of studies. The absence of a clear definition of AE makes it difficult to compare the results. As an example, some authors included post-treatment pregnancy or post-treatment fibroid surgery into AEs [30]. This issue was also mentioned by other authors [64].

Despite the already mentioned limitations, we tried to compare the occurrence of AEs with reference to different devices. The highest rate of AEs was noted in patients treated with the Sonalleve system, followed by ExAblate 2000, Chongqing and ExAblate 2100. Similar results were also observed by other authors [64]. One of the analyzed studies compared two versions of the ExAblate device [21]. The occurrence of AEs was 5.5% in case of ExAblate 2100 versus 13.1% with ExAblate 2000. The introduction of new technology and more experience of their users seem to have influenced AE rates. However, no clear definition of AE, over- and underreporting are serious limitations when performing a reliable statistical analysis. In our opinion, this is a key issue that requires experts to address the problem and come up with appropriate conclusions and create recommendations based on them.

Pain is one of the most common AEs connected with this method of treatment. This complication was reported in 22 out of 43 analyzed studies [21,23,24,26,27,30,31,34–36,38,40,43,44,46,47,52,53,57,60–63]. The majority of the studies described pelvic/abdominal pain or discomfort in the pelvic area. Some studies described leg, buttock, or sacral area pain, which mostly resolved several hours following the treatment [21,24,30,31,34,35,38,40,43,44,47,53,59,61,63]. No

Table 1. Adverse events in details.

Author and year	Overall AEs in patients % (number of patients)	Frequency of adverse events/complication % (number of patients)														
		Pain/discomfort														
		Abdominal	Pelvic	Lower back	Buttock	Legs	Skin burns	Skin redness/ rash	Abdominal edema	Deep vein thrombosis	Neuropraxia	Urinary tract infection/urine retention	Hematuria	Vaginal bleeding/ discharge	Nausea/Dizziness/ Malaise/Fatigue/ Lethargy	Others
1. (Browne, Gorny et al. 2021)	*ExAblate 2000* 13.1 (11/130) *ExAblate 2100* 5.5 (4/71)			3.8 (5) *ExAblate 2000*					8.5 (11) *ExAblate 2000* 5.4 (4) *ExAblate 2100*	0.8 (1) *ExAblate 2000*						
2. (Verpalen, de Boer et al. 2020)	13.7 (17/124)	2.4 (3)					3.2 (4)	2.4 (3)			1.6 (2)	0.8 (1)	0.8 (1)	2.4 (3)	0.8 (1)	
3. (Keserci, Duc et al. 2020)	69,7 (23/33)		9.1 (3)	9.1 (3)	9.1 (3)		3 (1)					3 (1)		3 (1)	9.1 (3)	24.2 (8) heating sensation
4. (Wang, Wang et al. 2018)	50 (5/10)		30 (3/10)											20 (2)		
5. (Barnard, AbdElmagied et al. 2017)	43 (20/43)			11,6 (5)				7 (3)			7 (3)	11.6 (5)				7 (3) SIR class C-E, vaginal passage of fibroid tissue 4.7 (2)
6. (Barnard, AbdElmagied et al. 2017)	44 (12/27)															7 (2) SIR class C-E
7. (Chen, Keserci et al. 2016)	77.6 (83/107)	56.1 (60)		12.1 (13)	3.7 (4)	19.6 (21)	0.9 (1)	2.8 (3)	4.7 (5)		2.8 (3)					32.7 (35) skin heating/pain, 0.9 (1) pubic bone pain
8. (Xu, Fu et al. 2015)	20.9 (9/43)	16.3 (7)		2.3 (1)			2.3 (1)		9 (12)							
9. (Thiburce, Frulio et al. 2015)	8.3 (3/36)						2.8 (1)					2.8 (1) pyelonephritis				2.8 (1) infection of the necrotic treated fibroid
10. (Mindjuk, Trumm et al. 2015)	11.9 (30/252)						1.2 (3)		10.4 (20)					0.4 (1)		
11. (Ikink, Van Breugel et al. 2015)	8 no data	37.5 (3)		37.5 (3)							25 (2)				37.5 (3) dizziness, 25 (2) lethargy	25 (2) abdominal tenderness, 25 (2) dyspepsia and constipation
12. (Quinn, Vedelago et al. 2014)	11.1 (31/280)	6.43 (18)		1.4 (4)			1.4 (4)				1.1 (3)	1.4 (4) UTI 0.4 (1) urine retention		0.4 (1)	0.4 (1) nausea	0.4 (1) fibroid expulsion
13. (Park, Kim et al. 2014)	67.6 (50/74)		26 (19)				3 (2)		12 (9)		1 (1)	3 (2)		3 (2)	16 (12) 1 (1) nausea	3 (2) abdominal bloating
14. (Trumm, Stahl et al. 2013)	3.5 (4/115)						2.6 (3)	0.9 (1)								
15. (Ruhnke, Eckey et al. 2013)	33.3 (6/18)		28 (5) [5.6 (1) sacral area, 5.6 (1) area of c-section scar]											5.6 (1) increased post-therapeutic menstrual bleeding		
16. (Machtinger, Fennessy et al. 2013)	53.3 (65/122)	21.1 (NA)			21.9 (NA) back/ leg pain			7 (NA)				11.7 (N/A)		6.3		11.7 (N/A) gastrointestinal complaints
17. (Dorenberg, Courivaud et al. 2013)	14.3 (1/7)						14.3 (1)									
18. (Brown, Hesley et al. 2013)	18.2 (2/11)										9.1 (1)	9.1 (1)				

(*continued*)

Table 1. Continued.

Author and year	Overall AEs in patients % (number of patients)	Frequency of adverse events/complication % (number of patients)														
		Pain/discomfort														
		Abdominal	Pelvic	Lower back	Buttock	Legs	Skin burns	Skin redness/ rash	Abdominal edema	Deep vein thrombosis	Neuropraxia	Urinary tract infection/urine retention	Hematuria	Vaginal bleeding/ discharge	Nausea/Dizziness/ Malaise/Fatigue/ Lethargy	Others
19. (Voogt, Trillaud et al. 2012)	100 (31/31)	55 (17) pain, 42 (13) discomfort			3 (1) sciatic nerve pain			10 (3)				23 (7)	3 (1)	10 (3) bleeding, 3 (1) vaginal irritation	19 (6) fatigue, 13 (4) headache, 10 (3) fever >38, 10 (3) nausea	32 (10) position-related pain, 19 (6) other non-specified
20. (Venkatesan, Partanen et al. 2012)	11 no data	(9) abdominal cramping	(1) suprapubic pain			(2)										
21. (Kim, Kim et al. 2012)	18.5 (5/27) (cystitis, numbness, burn)	48.1 (13)					11 (3)				3.7 (1)	3.7 (1)			33.3 (9)	
22. (Desai, Patil et al. 2012)	28 (14/50)	2 (1)				20 (10)	2 (1)					2 (1) UTI, 2 (1) urine retention				
23. (Yoon, Seong et al. 2011)	25 (5/20)						10 (2)		15 (3)							
24. (Zhang, Chen et al. 2010)	19 (4/21)						9.5 (2)	9.5 (2)								
25. (Taran, Tempany et al. 2009)	80.7 (88/109)			62 (68) pain/discomfort			16 (17) dermatological AEs				7 (8)	24 (26)			17 (19) systemic events	28 (30) gynecological, 20 (22) gastrointestinal, 3 (3) cardiovascular
26. (Okada, Morita et al. 2009)	30.7 (88/287)	11.5 (33/287)			7 (20/287) leg or lower back pain		4.2 (12/287)							8 (23/287)		
27. (Morita, Takeuchi et al. 2009)	6 (5/83)						4.8 (4)				1.2 (1)					
28. (Morita, Ito et al. 2008)	10.4 (5/48)						8.3% (4)				2.1% (1)					
29. (Fennessy, Tempany et al. 2007)	51.9 (83/160)	18.1% (29)	10.6% (17)											6.9% (11) vaginal discharge, 6.9% heavy menses	16.3% (26) nausea or vomiting	
30. (Stewart, Rabinovici et al. 2006)	N/A						5% (N/A)				0.9% (1) sciatic nerve palsy				6% (NA) fever 0.9% (1) nausea	
31. (Hindley, Gedroyc et al. 2004)	8.25 (9/109)				0.9% (1) leg and buttock pain							0.9% (1) UTI		4.6% (5) heavy bleeding, 0.9% (1) pain and bleeding	0.9% (1) nausea	
32. (Smart, Hindley et al. 2006)	14.3 (7/49)			4% (2)			4% (2) superficial, 2% (1) serious				2% (1) sensory loss to a small area of the skin in the right groin				2% (1) fainting	2% (1) urticarial reaction to IV meperidine
33. (Stewart, Gedroyc et al. 2003)	N/A			25% (N/A) discomfort, 14% (N/A) pain and abdominal tenderness			3.6% (2)							3.6% (2) increased vaginal bleeding	10% (N/A) nausea and pain	

N/A: not available; UTI: urinary tract infection.

Table 2. Comparison of AEs rate in particular devices.

Device type	Mean AEs rate (%)
ExAblate 2000	18.03
Sonalleve	40.3
ExAblate 2100	5.25
JM 2.5C	19.05
JM 5100	35.45

unification in reporting pain intensity after treatment was observed in the analyzed data. The authors of only three studies performed post-treatment pain rating with a scale as a study outcome [27,34,43]. In order to unify reporting and enable data comparison it would be justified to use any of the commonly used scales of pain intensity in further studies, e.g., the Visual Analog Scale (VAS), the Verbal Rating Scale (VRS) or the Numerical Rating Scale (NRS) [65]. There is no clear definition of pain used by the authors which may cause under- or overreporting of this AE. Using a pain assessment scale, e.g., the VAS scale, in every follow-up could improve the interpretation and comparison of data.

Other commonly reported AEs included skin burns and other dermatological issues such as rash or skin ulcerations. Such AEs were reported in 22 studies [23,24,27,30–33,35–37,40,41,43,47,48,50,52–55,58,60]. First- and second-degree skin burns and redness in the suprapubic area constituted the majority of the described cases. Major dermatological AEs were reported in only two cases (skin burn requiring surgical repair and skin ulceration [35,58]). Due to the fact that almost all skin burns were described as first- and second-degree, the lack of data regarding the size or location of a skin burn was a limitation in reporting this AE.

Our systematic review showed that nerve damage was another clinical problem that should be considered as a potentially serious AE of MRgFUS treatment. Neuropraxia and sciatic nerve palsy occurred rarely and were reported in 13 studies [23,27,30,34–36,42,46,52,54,55,58,60,63]. According to the authors, sciatic nerve palsy (being an AE of the procedure) resolved in most of cases shortly without any further complications. One study described a possible etiology of this AE-treated UFs were located on the posterior wall of the uterus, which could cause heat transfer to the sacral area causing transient neuropathy [58]. Other authors did not report the exact location of treated UFs with reference to particular AEs, so it is impossible to deduce which UF location might predispose to this AE. More studies are needed to investigate the relationship between the location of UFs and the occurrence of AEs. Currently, due to the paucity of data, it is only possible to infer from the anatomical location.

Other reported AEs included urinary tract infections or hematuria. Their potential pathophysiology is unknown. The authors of one analyzed study reported pyelonephritis that needed antibiotic therapy [32]. Some authors suggested cystitis related to Foley catheterization during the procedure, but the opinion was not supported by evidence [24,36]. Further investigation is needed to establish which patients are in the risk group for this AE and should receive prophylactic antibiotic therapy before the procedure. Vaginal discharge and bleeding or fibroid expulsion after the procedure were also mentioned in several cases (Table 1). Moreover, abdominal subcutaneous tissue and muscle edema were reported. However, they were only an MRI finding after the procedure without any or with minimal symptoms in almost all cases [33].

All the reviewed studies described only 12 serious complications related to the procedure (C-F on the Society of Interventional Radiology scale or major AEs due to the Standard Code of Federal Regulation) [35,52,58,60,61,63,66]. They were mostly reported in older (2004–2014) studies. The major AEs included fibroid expulsion, a major skin burn requiring surgical repair, and one case of persistent neuropathy [35]. These serious AEs occurred in only 0.41% of the total cohort. No deaths related to the procedure were reported. Deep vein thrombosis seems to be the most serious AE reported. It occurred in only one case [21,63]. MRgFUS seemed to be associated with the lowest risk of DVT incidence in comparison with other UF treatment methods. A meta-analysis dated from 2012 regarding the complications of a UAE procedure revealed that DVT occurred in 0.2% of cases [67]. With regard to hysterectomy, the incidence of DVT varied from a clinical diagnosis rate of 1% to events detected by more sensitive laboratory methods of up to 12% [68]. Therefore, MRgFUS treatment might be offered to patients with an increased risk of thromboembolic events.

Subsequently, it is worth considering AEs in comparison with other treatment methods. Two studies (2003 and 2009) clearly described a significantly lower incidence of AEs in MRgFUS compared to open surgery [52,62]. AEs related to pain or discomfort, the gastrointestinal tract, skin and nervous system were reported significantly less frequently by women from the MRgFUS cohort compared to women from the hysterectomy group. A limited number of studies compared all UF treatment methods with reference to the occurrence of AEs in particular patients. Further research is needed in this area to provide patients with the best treatment option, adjusted to their expectations in terms of the safety and efficiency. In 2017, a randomized control trial was conducted with one of the aims being the comparison of AEs in patients treated with UAE [27]. The overall incidence of AEs was similar and not significant in both methods (MRgFUS, UAE) in this RCT. However, another study concerning AEs in UAE and MRgFUS revealed no AEs in MRgFUS group, whereas in the UAE group, the overall incidence of AEs was 19% [69]. Those studies were limited by a small sample size. Further investigation is needed.

Another limitation is the diversity in follow-up time among investigated studies. The most common reported observation time was 3–6 months (Supplementary Table S1). Only few studies with the follow-up of over 3 years were identified in the analyzed material [20,21,23,25,35,42].

Conclusions

Our review suggests that MRgFUS is becoming more popular these days and is a relatively safe choice in UF therapy. The occurrence of AEs, especially major ones, is rather low. The new devices and more experience of their users in MRgFUS therapy seem to reduce AE rates. The lack of a clear

definition of AE, poor unification and missing data in the reporting of AEs and other complications related to MRgFUS therapy in UFs are some of the main issues. More prospective, randomized studies on larger populations with unified reporting and long follow-up records are necessary to accurately determine the safety of the procedure.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The study was funded by the Center of Postgraduate Medical Education, Warsaw, Poland, grant number 501-1-022-26-22.

ORCID

Jakub Kociuba http://orcid.org/0000-0001-7959-3707
Tomasz Łoziński http://orcid.org/0000-0002-5129-5262
Magdalena Zgliczyńska http://orcid.org/0000-0003-4957-4921
Maciej Byrczak http://orcid.org/0000-0002-8476-8759
Salvatore Giovanni Vitale http://orcid.org/0000-0001-6871-6097
Maciej Skrzypczak http://orcid.org/0000-0002-1289-5900
Kornelia Zaręba http://orcid.org/0000-0002-8262-4380
Michał Ciebiera http://orcid.org/0000-0001-5780-5983

References

[1] Bulun SE. Uterine fibroids. N Engl J Med. 2013;369(14):1344–1355.
[2] Ciarmela P, Islam MS, Reis FM, et al. Growth factors and myometrium: biological effects in uterine fibroid and possible clinical implications. Hum Reprod Update. 2011;17(6):772–790.
[3] Stewart EA, Cookson CL, Gandolfo RA, et al. Epidemiology of uterine fibroids: a systematic review. BJOG. 2017;124(10):1501–1512.
[4] Qin H, Lin Z, Vásquez E, et al. Association between obesity and the risk of uterine fibroids: a systematic review and meta-analysis. J Epidemiol Community Health. 2021;75(2):197–204.
[5] Parker WH. Etiology, symptomatology, and diagnosis of uterine myomas. Fertil Steril. 2007;87(4):725–736.
[6] Zimmermann A, Bernuit D, Gerlinger C, et al. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. BMC Womens Health. 2012;12:6.
[7] Al-Hendy A, Myers ER, Stewart E. Uterine fibroids: burden and unmet medical need. Semin Reprod Med. 2017;35(6):473–480.
[8] Riggan KA, Stewart EA, Balls-Berry JE, et al. Patient recommendations for shared decision-making in uterine fibroid treatment decisions. J Patient Exp. 2021;8:23743735211049655.
[9] Dolmans MM, Donnez J, Fellah L. Uterine fibroid management: today and tomorrow. J Obstet Gynaecol Res. 2019;45(7):1222–1229.
[10] West CP, Lumsden MA, Lawson S, et al. Shrinkage of uterine fibroids during therapy with goserelin (Zoladex): a luteinizing hormone-releasing hormone agonist administered as a monthly subcutaneous depot. Fertil Steril. 1987;48(1):45–51.
[11] Farris M, Bastianelli C, Rosato E, et al. Uterine fibroids: an update on current and emerging medical treatment options. Ther Clin Risk Manag. 2019;15:157–178.
[12] Donnez J, Arriagada P, Marciniak M, et al. Liver safety parameters of ulipristal acetate for the treatment of uterine fibroids: a comprehensive review of the clinical development program. Expert Opin Drug Saf. 2018;17(12):1225–1232.
[13] Al-Hendy A, Lukes AS, Poindexter AN, 3rd, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. N Engl J Med. 2021;384(7):630–642.
[14] Vilos GA, Allaire C, Laberge PY, et al. The management of uterine leiomyomas. J Obstet Gynaecol Can. 2015;37(2):157–178.
[15] Boyd LR, Novetsky AP, Curtin JP. Effect of surgical volume on route of hysterectomy and short-term morbidity. Obstet Gynecol. 2010;116(4):909–915.
[16] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol. 2021;134:178–189.
[17] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
[18] Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. 2000.
[19] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
[20] Inbar Y, Machtinger R, Barnett-Itzhaki Z, et al. MRI guided focused ultrasound (MRgFUS) treatment for uterine fibroids among women with and without abdominal scars. Int J Hyperthermia. 2021;38(1):1672–1676.
[21] Browne JE, Gorny KR, Hangiandreou NJ, et al. Comparison of clinical performance between two generations of magnetic resonance-guided focused ultrasound systems in treatments of uterine leiomyomas. Acad Radiol. 2021;28(10):1361–1367.
[22] Verpalen IM, van 't Veer-Ten Kate M, de Boer E, et al. Development and clinical evaluation of a 3-step modified manipulation protocol for MRI-guided high-intensity focused ultrasound of uterine fibroids. Eur Radiol. 2020;30(7):3869–3878.
[23] Verpalen IM, de Boer JP, Linstra M, et al. The focused ultrasound myoma outcome study (FUMOS); a retrospective cohort study on long-term outcomes of MR-HIFU therapy. Eur Radiol. 2020;30(5):2473–2482.
[24] Keserci B, Duc NM, Nadarajan C, et al. Volumetric MRI-guided, high-intensity focused ultrasound ablation of uterine leiomyomas: ASEAN preliminary experience. Diagn Interv Radiol. 2020;26(3):207–215.
[25] Sinha V, Mehta S, Kalantzis G, et al. Artifact from myomectomy/C-Section on MRI images - what does this mean for MR-guided focused ultrasound candidacy for uterine fibroids? Int J Hyperthermia. 2019;36(1):1079–1083.
[26] Wang Y, Wang ZB, Xu YH. Efficacy, efficiency, and safety of magnetic resonance-guided high-intensity focused ultrasound for ablation of uterine fibroids: comparison with ultrasound-Guided method. Korean J Radiol. 2018;19(4):724–732.
[27] Barnard EP, AbdElmagied AM, Vaughan LE, et al. Periprocedural outcomes comparing fibroid embolization and focused ultrasound: a randomized controlled trial and comprehensive cohort analysis. Am J Obstet Gynecol. 2017;216(5):500.e1–500.e11.
[28] Tung SL, Chou TY, Tseng HS, et al. A retrospective study of magnetic resonance-guided focused ultrasound ablation for uterine myoma in Taiwan. Taiwan J Obstet Gynecol. 2016;55(5):646–649.
[29] Jacoby VL, Kohi MP, Poder L, et al. PROMISe trial: a pilot, randomized, placebo-controlled trial of magnetic resonance guided focused ultrasound for uterine fibroids. Fertil Steril. 2016;105(3):773–780.
[30] Chen R, Keserci B, Bi H, et al. The safety and effectiveness of volumetric magnetic resonance-guided high-intensity focused ultrasound treatment of symptomatic uterine fibroids: early clinical experience in China. J Ther Ultrasound. 2016;4:27.
[31] Xu Y, Fu Z, Yang L, et al. Feasibility, safety, and efficacy of accurate uterine fibroid ablation using magnetic resonance imaging-guided high-intensity focused ultrasound with shot sonication. J Ultrasound Med. 2015;34(12):2293–2303.
[32] Thiburce AC, Frulio N, Hocquelet A, 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(7):764–770.
[33] Mindjuk I, Trumm CG, Herzog P, et al. MRI predictors of clinical success in MR-guided focused ultrasound (MRgFUS) treatments of uterine fibroids: results from a single centre. Eur Radiol. 2015;25(5):1317–1328.

[34] Ikink ME, Van Breugel JMM, Schubert G, et al. Volumetric MR-guided high-intensity focused ultrasound with direct skin cooling for the treatment of symptomatic uterine fibroids: proof-of-Concept study. Biomed Res Int. 2015;2015:684250.
[35] Quinn SD, Vedelago J, Gedroyc W, et al. Safety and five-year re-intervention following magnetic resonance-guided focused ultrasound (MRgFUS) for uterine fibroids. Eur J Obstet Gynecol Reprod Biol. 2014;182:247–251.
[36] Park MJ, Kim YS, Rhim H, et al. Safety and therapeutic efficacy of complete or near-complete ablation of symptomatic uterine fibroid tumors by MR imaging-guided high-intensity focused US therapy. J Vasc Interv Radiol. 2014;25(2):231–239.
[37] Trumm CG, Stahl R, Clevert DA, et al. Magnetic resonance imaging-guided focused ultrasound treatment of symptomatic uterine fibroids: impact of technology advancement on ablation volumes in 115 patients. Invest Radiol. 2013;48(6):359–365.
[38] Ruhnke H, Eckey T, Bohlmann MK, et al. MR-guided HIFU treatment of symptomatic uterine fibroids using novel feedback-regulated volumetric ablation: effectiveness and clinical practice. Rofo. 2013;184(10):983–991.
[39] Quinn SD, Vedelago J, Regan L, et al. Safety and treatment volumes achieved following new developments of the magnetic resonance-guided focused ultrasound system in the treatment of uterine fibroids: a cohort study. J Ther Ultrasound. 2013;1:20.
[40] Machtinger R, Fennessy FM, Stewart EA, et al. MR-guided focused ultrasound (MRgFUS) is effective for the distinct pattern of uterine fibroids seen in African-American women: data from phase III/IV, non-randomized, multicenter clinical trials. J Ther Ultrasound. 2013;1:23.
[41] Dorenberg EJ, Courivaud F, Ring E, et al. Volumetric ablation of uterine fibroids using Sonalleve high-intensity focused ultrasound in a 3 Tesla scanner-first clinical assessment. Minim Invasive Ther Allied Technol. 2013;22(2):73–79.
[42] Brown DL, Hesley GK, Gorny KR, et al. Safety of MR-guided focused ultrasound treatment of pedunculated subserosal uterine leiomyomas. J Ther Ultrasound. 2013;1(1):19.
[43] Voogt MJ, Trillaud H, Kim YS, et al. Volumetric feedback ablation of uterine fibroids using magnetic resonance-guided high intensity focused ultrasound therapy. Eur Radiol. 2012;22(2):411–417.
[44] Venkatesan AM, Partanen A, Pulanic TK, et al. Magnetic resonance imaging-guided volumetric ablation of symptomatic leiomyomata: correlation of imaging with histology. J Vasc Interv Radiol. 2012;23(6):786–794.e4.
[45] Park H, Yoon SW, Kim KA, et al. Magnetic resonance imaging-guided focused ultrasound treatment of pedunculated subserosal uterine fibroids: a preliminary report. J Vasc Interv Radiol. 2012; 23(12):1589–1593.
[46] Kim YS, Kim JH, Rhim H, et al. Volumetric MR-guided high-intensity focused ultrasound ablation with a one-layer strategy to treat large uterine fibroids: initial clinical outcomes. Radiology. 2012; 263(2):600–609.
[47] Desai SB, Patil AA, Nikam R, et al. Magnetic resonance-guided focused ultrasound treatment for uterine fibroids: first study in Indian women. J Clin Imaging Sci. 2012;2:74.
[48] Yoon SW, Seong SJ, Jung SG, et al. Mitigation of abdominal scars during MR-guided focused ultrasound treatment of uterine leiomyomas with the use of an energy-blocking scar patch. J Vasc Interv Radiol. 2011;22(12):1747–1750.
[49] Kim HS, Baik JH, Pham LD, et al. MR-guided high-intensity focused ultrasound treatment for symptomatic uterine leiomyomata: long-term outcomes. Acad Radiol. 2011;18(8):970–976.
[50] Zhang L, Chen WZ, Liu YJ, et al. Feasibility of magnetic resonance imaging-guided high intensity focused ultrasound therapy for ablating uterine fibroids in patients with bowel lies anterior to uterus. Eur J Radiol. 2010;73(2):396–403.
[51] Zaher S, Gedroyc W, Lyons D, et al. A novel method to aid in the visualisation and treatment of uterine fibroids with MRgFUS in patients with abdominal scars. Eur J Radiol. 2010;76(2):269–273.
[52] Taran FA, Tempany CM, Regan L, MRgFUS Group, et al. Magnetic resonance-guided focused ultrasound (MRgFUS) compared with abdominal hysterectomy for treatment of uterine leiomyomas. Ultrasound Obstet Gynecol. 2009;34(5):572–578.
[53] Okada A, Morita Y, Fukunishi H, et al. Non-invasive magnetic resonance-guided focused ultrasound treatment of uterine fibroids in a large Japanese population: impact of the learning curve on patient outcome. Ultrasound Obstet Gynecol. 2009;34(5):579–583.
[54] Morita Y, Takeuchi S, Hikida H, et al. Decreasing margins to the uterine serosa as a method for increasing the volume of fibroids ablated with magnetic resonance-guided focused ultrasound surgery. Eur J Obstet Gynecol Reprod Biol. 2009;146(1):92–95.
[55] Morita Y, Ito N, Hikida H, et al. Non-invasive magnetic resonance imaging-guided focused ultrasound treatment for uterine fibroids - early experience. Eur J Obstet Gynecol Reprod Biol. 2008;139(2): 199–203.
[56] Funaki K, Sawada K, Maeda F, et al. Subjective effect of magnetic resonance-guided focused ultrasound surgery for uterine fibroids. J Obstet Gynaecol Res. 2007;33(6):834–839.
[57] Fennessy FM, Tempany CM, McDannold NJ, et al. Uterine leiomyomas: MR imaging-guided focused ultrasound surgery–results of different treatment protocols. Radiology. 2007;243(3):885–893.
[58] Stewart EA, Rabinovici J, Tempany CM, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. Fertil Steril. 2006;85(1):22–29.
[59] Smart OC, Hindley JT, Regan L, et al. Magnetic resonance guided focused ultrasound surgery of uterine fibroids–the tissue effects of GnRH agonist pre-treatment. Eur J Radiol. 2006;59(2):163–167.
[60] Smart OC, Hindley JT, Regan L, et al. Gonadotrophin-releasing hormone and magnetic-resonance-guided ultrasound surgery for uterine leiomyomata. Obstet Gynecol. 2006;108(1):49–54.
[61] Hindley J, Gedroyc WM, Regan L, et al. MRI guidance of focused ultrasound therapy of uterine fibroids: early results. Am J Roentgenol. 2004;183(6):1713–1719.
[62] Stewart EA, Gedroyc WM, Tempany CM, et al. Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique. Am J Obstet Gynecol. 2003;189(1):48–54.
[63] Gorny KR, Woodrum DA, Brown DL, et al. Magnetic resonance-guided focused ultrasound of uterine leiomyomas: review of a 12-month outcome of 130 clinical patients. J Vasc Interv Radiol. 2011;22(6):857–864.
[64] Verpalen IM, Anneveldt KJ, Nijholt IM, et al. Magnetic resonance-high intensity focused ultrasound (MR-HIFU) therapy of symptomatic uterine fibroids with unrestrictive treatment protocols: a systematic review and meta-analysis. Eur J Radiol. 2019;120:108700.
[65] Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14(7):798–804.
[66] Khalilzadeh O, Baerlocher MO, Shyn PB, et al. Proposal of a new adverse event classification by the society of interventional radiology standards of practice committee. J Vasc Interv Radiol. 2017; 28(10):1432–1437.e3.
[67] Toor SS, Jaberi A, Macdonald DB, et al. Complication rates and effectiveness of uterine artery embolization in the treatment of symptomatic leiomyomas: a systematic review and meta-analysis. Am J Roentgenol. 2012;199(5):1153–1163.
[68] Clarke-Pearson DL, Geller EJ. Complications of hysterectomy. Obstet Gynecol. 2013;121(3):654–673.
[69] Ikink ME, Nijenhuis RJ, Verkooijen HM, 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(10):2649–2657.