

## Original Article

# Efficacy and safety of magnetic resonance-guided focused ultrasound surgery (MRgFUS) ablation in the management of abnormal uterine bleeding due to uterine leiomyoma or adenomyosis

Yaoqu Huang<sup>1\*</sup>, Shouguo Zhou<sup>1\*</sup>, Juan Wang<sup>1\*</sup>, Zhuochao Pang<sup>2\*</sup>

<sup>1</sup>Department of MRI and MRgFUS, Affiliated Foshan Hospital of Traditional Chinese Medicine, Guangzhou University of Chinese Medicine, Qinren Road, Chancheng District, Foshan 528000, Guangdong Province, P. R. China;

<sup>2</sup>Department of Gynecology, Affiliated Foshan Hospital of Traditional Chinese Medicine, Guangzhou University of Chinese Medicine, Qinren Road, Chancheng District, Foshan 528000, Guangdong Province, P. R. China. \*Equal contributors.

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**Abstract:** Purpose: To investigate the efficacy and safety of magnetic resonance-guided focused ultrasound surgery (MRgFUS) ablation for abnormal uterine bleeding (AUB) due to uterine leiomyoma or adenomyosis. Methods: In total, thirty patients with AUB due to uterine leiomyoma (AUB-L group) or adenomyosis (AUB-A group) were treated by MRgFUS ablation. After MRgFUS ablation, the short-term clinical efficacy within one year was assessed. Results: Sixteen patients were classified into the AUB-L group and 14 patients into the AUB-A group. The average nonperfused volume (NPV) ratios of the AUB-L and AUB-A groups were  $82.7\% \pm 13.6\%$  and  $83.3\% \pm 11.1\%$ , respectively. Compared with the baseline, the lesion volumes in the AUB-L and AUB-A groups were reduced by 45.6% and 34.6%, respectively, at 3 months after MRgFUS ablation. The hemoglobin concentration was increased by 22.4% in the AUB-L group and 15.3% in the AUB-A group at 3 months posttreatment. No amenorrhea occurred during the 12-month follow-up. The duration of bleeding decreased significantly in the AUB-A group. The mean PBAC scores at 3, 6 and 12 months posttreatment were reduced by 50.8%, 48.4% and 42.8%, respectively, in the AUB-L group and by 50.9%, 53.8% and 47.9%, respectively, in the AUB-A group. Compared with the baseline, at 3, 6 and 12 months posttreatment, the HRQL score increased by 41.5%, 43.3% and 33.3%, respectively, in the AUB-L group and by 24.7%, 31.1% and 28.2%, respectively, in the AUB-A group. Conclusion: MRgFUS is an effective and safe noninvasive uterine-sparing treatment modality in the management of AUB-L and AUB-A. MRgFUS can target lesion for ablation effectively, remove the factors that lead to AUB, retain a normal menstrual cycle, relieve AUB symptoms significantly and improve quality of life.

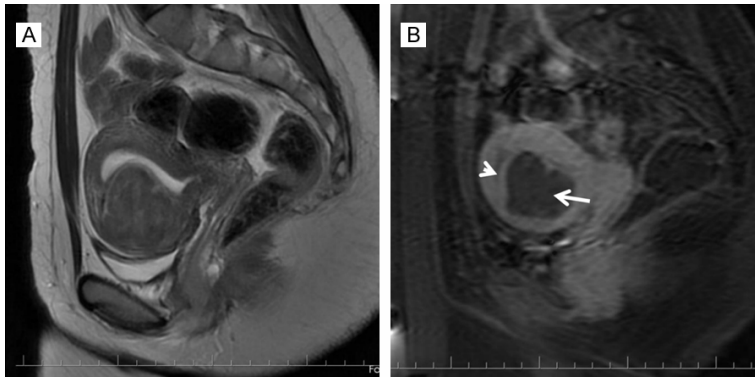
**Keywords:** Magnetic resonance-guided focused ultrasound surgery, abnormal uterine bleeding, uterine, leiomyoma, adenomyosis

## Introduction

Abnormal uterine bleeding (AUB) is a common problem in women of every age group from adolescence to menopause [1, 2]. Approximately 10-35% of women report symptoms of AUB during their lifetime [3]. AUB negatively affects health by causing anemia, and it impacts the quality of life and activity of women patients.

The International Federation of Gynecology and Obstetrics (FIGO) classification system has divided AUB into 9 categories as with the sys-

tem of acronym PALM-COEIN. PALM refers to structural entities that include polyps (AUB-P), adenomyosis (AUB-A), leiomyoma (AUB-L), and malignancy/hyperplasia (AUB-M) [2]. Adenomyosis and submucous myoma are important structural factors. The methods used to remove these structural factors include medical therapy, the levonorgestrel-releasing intrauterine system, endometrial ablation, uterine artery embolization, and surgical therapy [4-6]. Magnetic resonance-guided focused ultrasound surgery (MRgFUS) is a newer noninvasive ultrasound thermal ablation technique that targets



**Figure 1.** Sagittal magnetic resonance images of a 34-year-old female with AUB and reproductive needs: A. T2-weighted image at baseline showing a solitary submucosal leiomyoma; B. T1-weighted gadolinium-enhanced image after MRgFUS ablation showing that the unenhanced areas (arrow) of the lesions were defined as NPV and showing an NPV ratio of 95.9%. The image also shows that the endometrium is intact (arrowhead).

individual myomas and adenomyosis [7-9]. Here, we hypothesize that by ablating the lesion, MRgFUS will effectively remove the etiology of AUB, resulting in clinical improvement, and that MRgFUS may have some advantages that large-scale endometrial ablation methods such as endometrial ablation may not have. In this study, thirty patients with AUB-L or AUB-A were treated with MRgFUS and followed up for a short time to further clarify the effectiveness and safety of MRgFUS.

### Materials and methods

#### Patients

From March 2017 to September 2019, thirty patients with AUB caused by uterine leiomyoma or adenomyosis received ablation treatment by MRgFUS at the Foshan Hospital of Traditional Chinese Medicine. This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Foshan Hospital of Traditional Chinese Medicine (approval numbers: 2017-001). Before treatment, the details of the treatment were discussed with all patients, who then signed a consent forms.

The inclusion criteria were as follows: (1) Women of childbearing age; (2) AUB, mainly with symptoms of menorrhagia lasting for  $\geq 3$  months; (3) confirmation of AUB-L or AUB-A by gynecological examination, hysteroscopy, laboratory examination and MR examination (**Figure**

**1A**); (4) submucosal myoma as the causal leiomyoma; (5) willingness to undergo MRgFUS treatment; and (6) ability to communicate with the nurse or physician during the treatment.

Patients who met any of the following criteria were excluded from the study: (1) pregnant or lactating; (2) suspected or confirmed uterine malignancy; (3) acute pelvic inflammatory disease; (4) body mass index  $>30.0$  kg/m<sup>2</sup> and/or thickness of the subcutaneous fat of the anterior abdominal wall greater than 4.0 cm;

(5) adhesive bowel and/or extensive abdominal scars in the proposed acoustic pathway; (6) uncontrolled diabetes, abnormal liver or abnormal renal function; or (7) contraindications for MRI.

#### GnRH-a pretreatment

All patients in the AUB-A group were pretreated with two to three injections of gonadotropin-releasing hormone agonist (GnRH-a) (Goserelin Acetate, AstraZeneca, London, UK; or Triptorelin Acetate, Ipsen Pharma Biotech, Boulogne-Billancourt, France) before MRgFUS ablation. The purpose of the treatment was to reduce the blood supply to and signal in the lesions and make the ablation easier [10]. The first course was injected on the 1st or 2nd day of menstruation. The next injection was administered 28 days later.

#### MRgFUS treatment

MRgFUS ablation was performed using a focused ultrasound system (ExAblate2100, InSightec, Haifa, Israel) guided by a 3-T MR system (Discovery 750W, GE Healthcare, Milwaukee, USA). The patient was positioned prone on the treatment table, with the abdominal wall immersed in degassed water. Approximately 200-300 ml of ultrasonic coupling agent was injected into the rectum to protect the intestinal wall. Treatment was performed by two physicians. First, sagittal, axial and coronal T2-weighted imaging sequences were imported into

the workstation. Then, the physician planned the region of treatment with protective markers for the intestine, sacrum and pubis. The computer divided the region of treatment into different spots, which needed to be treated one by one. During the treatment, physicians monitored the temperature changes in major structures and the lesion in the sonication path in real time through dynamic anatomic imaging and temperature mapping and stopped sonication in time when the temperature became abnormal in nontherapeutic areas. The treatment was performed under sedation and analgesia with dexmedetomidine (Hengrui Pharma, Lianyungang, China) and sufentanil (Humanwell Pharma, Yichang, China). During therapy, the patient's pulse and peripheral oxygenation were monitored continuously, and the patients were asked to stay awake and inform the doctor of any abnormal sensations immediately.

### *Magnetic resonance imaging evaluation*

In this study, "baseline" was defined as the initial state in which treatment for myoma or adenomyosis lesions had not been received. All patients underwent pelvic contrast-enhanced MRI with a standardized protocol including T2-weighted imaging (T2WI) and T1-weighted imaging (T1WI) at baseline evaluation, immediately after MRgFUS ablation, and 3 months after MRgFUS treatment. Because MRI is an expensive examination, there is a risk of gadolinium contrast agent deposition. In addition, some of our patients came from other cities or provinces, so it was difficult to return to our hospital for multiple MRI examinations. Therefore, in our follow-up plan, we required only that patients undergo review by MRI three months after treatment to evaluate the early changes in lesions. On the workstation, the volumes of the myoma or adenomyosis lesions were calculated using the cumulative volume method. The unenhanced areas of the lesions were defined as nonperfusion areas (**Figure 1B**). The nonperfused volume (NPV) and lesion volume before MRgFUS ablation were measured, and their ratio was defined as the NPV ratio.

### *Clinical follow-up posttreatment*

The patients were instructed to report any adverse effects in the first month and return for follow-up at 3, 6 and 12 months posttreatment for clinical evaluation. Any complications during

the follow-up period were recorded and graded according to the Society of Interventional Radiology (SIR) [11]. Hemoglobin concentrations were measured at baseline and at the 3-month follow-up. The health-related quality of life (HRQL) assessment included 29 questions and was evaluated via the UFS-QOL questionnaire using a 5-point categorical scale. The subscale scores were summed and transformed into a 0-100 point scale, with a higher HRQL score indicating improved quality of life [12]. Menstrual blood volume was assessed by the pictorial blood loss assessment chart (PBAC) method, and a PBAC score greater than 100 meant a menstrual blood volume >80 ml [13]. Because the main symptom of AUB patients in this study was menorrhagia, recurrence was defined as a PBAC score above baseline that remained high for 2 months or more.

### *Statistical analysis*

Normally distributed data are expressed as the mean  $\pm$  standard deviation. Skewed data are reported using the median and interquartile range. Continuous variables were compared using the t-test or analysis of variance (ANOVA). Statistical analysis was completed with SPSS 19.0 (IBM Corporation, Armonk, NY, USA), and a *P*-value of less than 0.05 was defined as statistically significant.

## Results

### *Patients and lesions*

Based on the lesions related to AUB, thirty patients were divided into the AUB-L group (leiomyoma) and the AUB-A group (adenomyosis). In this study, 16 were classified as the AUB-L group, and 14 were classified as the AUB-A group. **Table 1** shows that the average age was  $40.0 \pm 6.0$  years in the AUB-L group and  $39.9 \pm 4.3$  years in the AUB-A group. The mean durations of disease among patients in the AUB-L and AUB-A groups were  $3.2 \pm 2.9$  years and  $6.1 \pm 3.3$  years, respectively ( $P < 0.05$ ). The average leiomyoma lesion volume was  $128.8 \pm 102.4$  cm<sup>3</sup>, while the average adenomyosis lesion volume was  $102.7 \pm 48.2$  cm<sup>3</sup>. No significant differences in the baseline characteristics, namely, hemoglobin, menstrual length, PBAC score, or HRQL score, were observed between the two groups ( $P > 0.05$ ).

## Management of AUB-L and AUB-A with MRgFUS

**Table 1.** Comparison of baseline characteristics between patients of AUB-L group and AUB-A group

Characteristic	AUB-L (n=16)	AUB-A (n=14)	P-value
Age (years)	40.0 ± 6.0	39.9 ± 4.3	0.971
Duration of disease (years)	3.2 ± 2.9	6.1 ± 3.3	0.014
BMI (Kg/cm <sup>2</sup> )	23.1 ± 2.7	22.3 ± 2.8	0.864
Type of lesion	11/5 (solitary/multiple)	8/6 (focal/diffuse)	-
Volume of lesion (cm <sup>3</sup> )	128.8 ± 102.4 <sup>a</sup>	102.7 ± 48.2	0.373
Hemoglobin (g/L)	95.8 ± 19.9	103.2 ± 20.9	0.330
Menstrual length (days)	7.4 ± 2.8	8.5 ± 2.8	0.266
PBAC score	176.9 ± 45.5	183.2 ± 46.8	0.710
HRQL score	54.7 ± 16.9	57.0 ± 14.4	0.694

BMI: Body mass index; PBAC: Pictorial blood loss assessment chart; HRQL: Health related quality of life. <sup>a</sup>To patient of multiple leiomyoma, calculate the total volume.

**Table 2.** Comparison of MRgFUS treatment results between patients of AUB-L group and AUB-A group

Characteristic	AUB-L (n=16)	AUB-A (n=14)	P-value
Treatment time (min)	200.8 ± 63.6	166.9 ± 56.8	0.137
Total energy used (kJ)	212.8 ± 90.6	183.8 ± 131.9	0.485
NPV ratio (%)	82.7 ± 13.6	83.3 ± 11.1	0.895
Adverse effects (yes/no)	4/12	6/8	0.259

NPV: Nonperfused volume.

### Evaluation of MRgFUS ablation results

As shown in **Table 2**, an average NPV ratio of 82.7 ± 13.6% was achieved in the AUB-L group, and a ratio of 83.3 ± 11.1% was observed in the AUB-A group. There was no patient with a NPV ratio below 55%. No significant difference with regard to the treatment results was observed between the two groups ( $P > 0.05$  for all).

### Adverse effects

After MRgFUS treatment, there were six adverse events among 4 patients in the AUB-L group (4/16, 25.0%) and 10 adverse events among 6 patients in the AUB-A group (6/14, 42.9%) (**Table 2**). According to the SIR classification (**Table 3**), there were seven recorded class A adverse effects, and no clinical intervention was needed. There were also nine class B events, which required nominal therapy. Five cases of skin abnormalities were relieved by local dressing within one week. Four patients complained of lower limb pain or weakness and were given vitamins for neurotrophs and dexamethasone to reduce edema. Treatment was successful within 2 weeks in all but one patient; this patient, who was in the AUB-A group, expe-

rienced leg pain for more than 6 weeks, and oral analgesics were needed for the first week. There were no serious complications (class C-F class by the SIR standard) reported during or after MRgFUS treatment in this study.

### Follow-up results

No hormones or other agents were prescribed to control AUB during the study period. Recurrence in two patients in the AUB-L group was confirmed at the 12-month follow-up. One patient in the AUB-A group was pregnant at 8 months after MRgFUS treatment and gave birth to a female infant. Two patients in the AUB-A group underwent surgical therapy or LNG-IUD treatment 8 months or 11 months after MRgFUS ablation due to recurrence of symptoms.

**Tables 4** and **5** showed that the lesion volume 3 months after MRgFUS ablation was significantly decreased compared with the baseline. The reduction rates of the volumes of the AUB-L and AUB-A groups at 3 months were 45.6% and 34.6% ( $P = 0.001$  and  $0.000$ , respectively, compared with the baseline). The hemoglobin concentration was increased by 22.4% in the AUB-L group and 15.3% in the AUB-A group three months after treatment compared with the baseline ( $P = 0.000$  and  $0.004$ , respectively).

In this study, no amenorrhea occurred after MRgFUS treatment at the 12-month follow-up. **Tables 4** and **5** show that the duration of bleeding was reduced in both groups after ablation but was significant only in the AUB-A group, wherein it decreased from 8.5 days at baseline

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**Table 3.** Summary of complications according to the SIR classification system

SIR class	Description	Complications	No. (leiomyoma/adenomyosis)
A	No therapy, no consequences	Vaginal discharge	2/3
		Lower abdominal pain	1/1
B	Nominal therapy, observation, no consequences	Redness or blisters on the skin	2/2
		Subcutaneous indurations	0/1
		Lower limb pain/weakness	1/3
C~F			0

SIR: Society of Interventional Radiology.

**Table 4.** Variation of lesion volume, hemoglobin, duration of bleeding, PBAC score and HRQL score of AUB-L group in follow-up (n=16)

Characteristic	Baseline	3 months post-treatment	6 months post-treatment	12 months post-treatment	P-value
Volume of lesion, cm <sup>3</sup>	128.8 ± 102.4	70.1 ± 53.6	-	-	0.001
Variation rate <sup>a</sup> (%)		(-45.6)			
Hemoglobin, g/L	95.8 ± 19.9	117.3 ± 14.1	-	-	0.000
Variation rate <sup>a</sup> (%)		(22.4)			
Duration of bleeding, day	7.4 ± 2.8	6.2 ± 1.2	6.6 ± 1.6	7.1 ± 1.5	0.296
Variation rate <sup>a</sup> (%)		(-16.2)	(-10.8)	(-4.1)	
PBAC score	176.9 ± 45.5	87.0 ± 12.7 <sup>b</sup>	91.2 ± 20.7 <sup>b</sup>	101.1 ± 27.4 <sup>b</sup>	0.000
Variation rate <sup>a</sup> (%)		(-50.8)	(-48.4)	(-42.8)	
HRQL score	54.7 ± 16.9	77.4 ± 12.7 <sup>b</sup>	78.4 ± 12.8 <sup>b</sup>	72.9 ± 18.4 <sup>b</sup>	0.010
Variation rate <sup>a</sup> (%)		(41.5)	(43.3)	(33.3)	

PBAC: Pictorial blood loss assessment chart; HRQL: Health related quality of life. <sup>a</sup>compared with baseline value. <sup>b</sup>compared with baseline, *P*<0.05.

**Table 5.** Variation of lesion volume, hemoglobin, duration of bleeding, PBAC score and HRQL score of AUB-A group in follow-up (n=14)

Characteristic	Baseline	3 months post-treatment	6 months post-treatment	12 months post-treatment <sup>a</sup>	P-value
Volume of lesion, cm <sup>3</sup>	102.7 ± 48.2	67.2 ± 35.1	—	—	0.000
Variation rate <sup>b</sup> (%)		(-34.6)			
Hemoglobin, g/L	103.2 ± 20.9	119.0 ± 15.3	—	—	0.004
Variation rate <sup>b</sup> (%)		(15.3)			
Duration of bleeding, day	8.5 ± 2.8	6.4 ± 1.7 <sup>c</sup>	6.9 ± 0.9 <sup>c</sup>	7.2 ± 1.9	0.031
Variation rate <sup>b</sup> (%)		(-24.7)	(-18.8)	(-15.3)	
PBAC score	183.2 ± 46.8	89.9 ± 24.6 <sup>c</sup>	84.6 ± 22.2 <sup>c</sup>	95.4 ± 32.5 <sup>c</sup>	0.000
Variation rate <sup>b</sup> (%)		(-50.9)	(-53.8)	(-47.9)	
HRQL score	57.0 ± 14.4	71.1 ± 13.8 <sup>c</sup>	74.7 ± 11.3 <sup>c</sup>	73.1 ± 15.9 <sup>c</sup>	0.005
Variation rate <sup>b</sup> (%)		(24.7)	(31.1)	(28.2)	

PBAC: Pictorial blood loss assessment chart; HRQL: Health related quality of life. <sup>a</sup>n=11. <sup>b</sup>compared with baseline value. <sup>c</sup>compared with baseline, *P*<0.05.

to 6.4 days after 3 months (*P*=0.005) and to 6.9 days at 6 months after treatment (*P*=0.027). The mean PBAC score was reduced by 50.8%, 48.4% and 42.8% at 3, 6 and 12 months

posttreatment, respectively, in the AUB-L group. In the AUB-A group, the reduction in the mean PBAC was 50.9%, 53.8% and 47.9% at 3, 6 and 12 months posttreatment, respectively



(Tables 4 and 5). The reduction in PBAC score was significant at all time points in both groups compared with the baseline ( $P=0.000$  at all time points).

The HRQL score was significantly improved after MRgFUS treatment in both groups (Tables 4 and 5). Compared with the baseline, at 3, 6 and 12 months posttreatment, the scores increased by 41.5%, 43.3% and 33.3%, respectively ( $P=0.000$ ,  $0.000$  and  $0.001$ , respectively, compared with the baseline) in AUB-L group and by 24.7%, 31.1% and 28.2% in the AUB-A group, respectively ( $P=0.009$ ,  $0.001$  and  $0.006$ , respectively, compared with the baseline).

### Discussion

Among women with heavy menstrual bleeding associated with submucosal leiomyomas or adenomyosis, hysterectomy or endometrial ablation remain the major choices clinically for patients who no longer wish to preserve their fertility [5, 6]. However, due to increased maternal age and delayed pregnancy desire, women suffering from AUB are found more common to wish to preserve the uterus and its functionality to be able to conceive [14]. Therefore, alternative technologies that are less invasive are necessary.

MRgFUS is a thermal ablation technique. During treatment, high-intensity ultrasound waves bypass nontarget structures and are focused on a target to cause thermally induced protein denaturation and coagulative necrosis, leading to cell death [7]. Unlike nontargeted and large-scale endometrial ablation methods, MRgFUS is characterized by targeted and noninvasive local ablation. Its features include the following: first, it can target lesions for ablation effectively and avoid the factors that lead to AUB; second, in patients who no longer wish to preserve their fertility, only a small part of the endometrium is ablated after treatment, and most of the healthy endometrium will be retained [15], so the problems of amenorrhea are avoided, and the patients can maintain a healthy menstrual cycle; third, we can ablate the lesions causing AUB without injuring the endometrium (Figure 1). This advantage is particularly important for women with reproductive needs.

Technical success can be gauged on immediate postprocedure contrast MRI based on the extent of the NPV of the treated fibroids and adenomyosis. Park et al. [16] found that a NPV ratio greater than 80% meant a greater reduction in the lesion at follow-up. As shown in our study, most of the responsible lesions causing the AUB to be successfully ablated, with a mean NPV ratio not less than 80%. This result indicated that MRgFUS could effectively remove the structural entities that led to AUB. Similar to the findings of other reports [17, 18], lesion volume was significantly reduced at 3 months posttreatment. Our results showed that the average reductions in leiomyoma and adenomyosis were 45% and 35%, respectively.

Typically, significant clinical improvement could be obtained soon after the procedure, within three menstrual cycles. Menorrhagia was the most common and major symptom of AUB, affecting all patients in this study. Because patients in our study were younger women of childbearing age, the goal of treatment was to restore normal menstruation rather than promote amenorrhea. MRgFUS could ablate lesions while preserving the endometrium as much as possible; therefore, it was helpful maintaining normal menstruation. In our study, the one-year clinical follow-up showed adequate and sustained symptom relief of menorrhagia in both the leiomyoma and adenomyosis groups. During the first year after treatment, approximately half of the patients had continuously decreasing PBAC scores. These results suggested that after MRgFUS treatment, the menstrual blood volume of patients had returned to the tolerable range and that secondary amenorrhea had been avoided. Because most of the patients' menstrual blood loss was normal or close to normal, their hemoglobin concentration and anemic states were also effectively alleviated. Menostaxis is another common symptom of AUB. Our study showed that although the extent to which the duration of bleeding was shortened after MRgFUS among patients with uterine leiomyoma remained unclear, bleeding could be maintained within a normal range within 6 months after treatment. The follow-up results of the adenomyosis group showed that menstrual prolongation at 3 and 6 months after ablation was significantly improved. Although the 12-month follow-up showed that the average duration of menstrual

bleeding exceeded seven days, the trend in symptom recurrence was slow.

We used HRQL questionnaires to evaluate the quality of life of patients with AUB and observed significant improvements in the HRQL score at the 3-, 6- and 12-month follow-ups. Similar improvements in symptom scores were also observed in a previous report of MRgFUS treatment for leiomyoma or adenomyosis [17], indicating improved short-term quality of life after treatment. We also noticed that the rate of increase in the adenomyosis group was lower, which may be related to the obvious influence of dysmenorrhea on the quality of life of patients with adenomyosis.

Safety is a main concern of MRgFUS treatment. Complications following MRgFUS were usually transient and mild and were categorized into SIR class A or B, and the incidence was similar between the leiomyoma and adenomyosis group. Among the class B adverse effects, it is necessary to pay attention to lower limb pain or weakness, which was observed mostly in the treatment of adenomyosis. This complication suggested sacral nerve damage, but it was usually mild edema, which can subside a short time after treatment. Therefore, MRgFUS is a safe treatment in the management of leiomyoma and adenomyosis.

One challenge that has inhibited mainstream adoption of MRgFUS is the prolonged duration of most procedures, usually being 2-4 hours, which can be prohibitive in many practice settings given the limited availability and high cost of MR scanner time. Therefore, technical improvements are needed to increase the efficiency of treatment. Another challenge is long-term efficacy. All uterine-preserving treatments have a potential risk of reintervention caused by lesion regrowth and symptom recurrence. Some trials have demonstrated higher reintervention rates for MRgFUS at midterm or long-term follow-up than for other treatments [19, 20]. It should be noted that because MRgFUS is a noninvasive treatment method with less damage and fewer complications, it can be used for a second or third time to consolidate the long-term clinical effect of patients. However, the two patients with recurrence in the AUB-A group did not undergo MRgFUS again, which may be related to the patients' understanding and compliance with the new method.

The limitations of our study include the small number of subjects and the short follow-up period. Therefore, a multicenter prospective study with a larger number of patients and longer-term follow-up is needed to validate the results of our study. In particular, the comparison between different types needs more case to study.

In conclusion, MRgFUS is an effective and safe noninvasive uterine-sparing treatment modality in the management of AUB due to uterine leiomyoma or adenomyosis. More importantly, especially for patients who are not willing to undergo hysterectomy or endometrial ablation, MRgFUS can target lesions for ablation effectively, remove the factors that lead to AUB, retain a normal menstrual cycle, improve AUB symptoms significantly and improve quality of life. However, improving its long-term clinical efficacy still needs further investigation.

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### Disclosure of conflict of interest

None.

**Address correspondence to:** Yaoqu Huang, Department of MRI and MRgFUS, Affiliated Foshan Hospital of Traditional Chinese Medicine, Guangzhou University of Chinese Medicine, No. 6 Qinren Road, Chancheng District, Foshan 528000, Guangdong Province, P. R. China. Tel: +86-13630098007; E-mail: doctorhyq@163.com

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