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# Ultrasound-guided high-intensity focused ultrasound in the treatment of uterine fibroids

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**Abstract**

The aim of the present study was to investigate factors affecting ablation effect and safety of ultrasound-guided high-intensity focused ultrasound (USgHIFU) for uterine fibroids (UFs).

A retrospective analysis of 346 patients with symptomatic UFs who were treated with USgHIFU was performed. All UFs was grouped based on magnetic resonance imaging (MRI) characteristics before HIFU; all adverse events and treatment data were recorded during and after HIFU. One-way analysis of variance and multiple linear regression analysis were used to evaluate the effect of USgHIFU treatment and affecting factors.

The results showed that the mean age of patients was 38.3±6.1 years, with the mean nonperfusion volume rate of 74.4±14.7% and the mean energy efficiency factor (EEF) of 7.2±4.8 J/mm$^3$. Except for the size group, the ablation rate was significantly different ($P<.001$); and the anterior, intramural, hypointense (T2WI), and mild enhancement (T1WI contrast enhancement) UFs had the highest ablation rate. The EEF of the anterior, intramural, hypointense (T2WI), mild enhancement (T1WI contrast enhancement), and >5 cm UFs had minimum value, with a statistically significant difference ($P<.01$). According to multiple linear regression model, the distance from the UFs ventral side to the skin, enhancement type on T1WI, size of UFs, signal intensity on T2WI, location of UFs, type and volume of fibroids all had a line relationship with EEF, and the enhancement type on T1WI was the greatest factor affecting the ablation effect. Some patients (37.6%) had thermal injury of the sacrum on MRI, but no serious adverse events were observed.

Our results suggest that USgHIFU can be safely used and have a promising prospect for treating UFs, even though its effect may be affected by anatomical features, tissue characteristics, and blood supply.

**Abbreviations:** AEs = adverse events, EEF = energy efficiency factor, MRI = magnetic resonance imaging, NPV = nonperfusion volume, NPVR = nonperfusion volume rate, UFs = uterine fibroids, USgHIFU = ultrasound-guided high-intensity focused ultrasound.

**Keywords:** adverse events, energy efficiency factor, magnetic resonance imaging, ultrasound-guided high-intensity focused ultrasound, uterine fibroids

## 1. Introduction

Uterine fibroids (UFs) are the most common type of benign pelvic tumor in women of reproductive age, with a high prevalence of 20% to 40% over the age of 30.[1] The common symptoms of UFs are abnormal menstrual bleeding, urinary or pelvic discomfort, dysmenorrhea, dyspareunia, infertility, and repeated miscarriages, seriously affecting the quality of patients' life.[1,2] At present, comprehensive application of traditional surgery (myomectomy or hysterectomy), drug treatment,[3] radiofrequency ablation,[4,5] microwave ablation,[6,7] and uterine artery embolization[8–10] greatly improves the treatment outcome of UFs. Even so, these methods have some traumatic and limitations, including the risk of infection, postembolization syndrome and permanent amenorrhea.[10] High-intensity focused ultrasound (HIFU) can gather in vitro scattered ultrasound in lesions and instantly produce high temperatures of 60°C to 100°C, causing coagulation necrosis to achieve noninvasive ablation of tumors. As a new technique of local physiotherapy, HIFU has been widely used in the ablation of UFs and has become an option for young patients who have a strong desire to keep their uterus.

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## 2. Materials and methods

### 2.1. Patients

A total of 346 patients with symptomatic UFs from November 2011 to January 2017 were treated with USgHIFU in our hospital and were enrolled in this study. Before USgHIFU treatment, all patients underwent plain and enhanced magnetic resonance imaging (MRI) with a standardized protocol. Based on clinical evaluation and MRI, 2 experienced radiologists made the diagnosis of UFs and measured the UFs volume $V_0$ ($V=0.5233abc$; $a$, $b$, and $c$ indicated the longitudinal, anteroposterior, and transverse diameter, respectively, of the targeted UFs in 3 dimensions),[11,12] distance from the UFs ventral side to the skin and distance from the dorsal side of UFs to the sacrum. UFs were grouped into anterior, posterior, lateral and fundus according to positions, intramural, subserous, submucosal, and transmural according to types, and <3 cm, 3 to 5 cm, or >5 cm based on the size. Based on the MRI characteristics, UFs can also be classified into mild (lower than the myometrium) and moderate/significant (similar to or higher than that of the myometrium) based on enhancement on T1WI,[13] or hypointense (equal to the skeletal muscle signal), isointense (higher than the skeletal muscle signal but lower than myometrium signal), hyperintense (equal to or higher than the myometrium signal), and mixed signal (2 or 3 signal intensity [SI] types exist at the same time on T2WI)[14,15] according to SI on T2WI. Baseline characteristics of all patients were recorded (Table 1).

### 2.2. Equipment

The HIFU treatment was performed by using a Chongqing JC200 (Chongqing HAIFU, Chongqing, China) focused ultrasound tumor treatment system (frequency, 0.5–2 MHz; electric power, 8.5 kVA; output energy, ≤400 W). The B-mode ultrasound used for monitoring was Mylab70 (Esaote, Genoa, Italy). Imaging was performed with Achieva 3.0T MR system (Philips, Best, the Netherlands) or Signa HDxt 3.0T MR system (GE, Waukesha, WI). The contrast agent was Gd-DTPA.

### 2.3. HIFU treatment

This study was approved by the hospital ethics committee with all patients given written informed consent for the study. Preoperative preparation was performed for all patients including bowel preparation, skin preparation, and catheterization.[16] Patients were in the prone position on the HIFU treatment bed, with their anterior abdominal wall in direct contact with a degassed water sac to push the intestine. The position of the HIFU treatment head and the water sac was adjusted to ensure safe ultrasound passage. According to the patient's weight, fentanyl citrate and midazolam hydrochloride were used for intravenous injection. According to the standard of visual analog scale and the Ramsey grading, the depth of sedation effect was required to reach 3 to 4 levels, and the analgesic effect reached the pain score <4. During HIFU treatment, patient vital signs such as heart rate, respiration rate, blood pressure, and oxygen saturation were monitored. All patients were asked to promptly inform any discomfort. If adverse reactions occurred in this process, the treatment parameters or (and) region will be adjusted according to the severity, and if necessary, the treatment would be terminated immediately. Antibiotics were routinely used to prevent postoperative infection, and MRI was performed to assess the therapeutic effect within 3 days after treatment. The 3-dimensional diameter of the ablation area was measured by MRI, and the nonperfused volume $V_1$ (NPV) was calculated.

**Table 1**

**Baseline characteristics.**

| Characteristics | Values* |
|---|---|
| Number of patients | 346 |
| Age, yrs | 38.3 ± 6.1 (23–53) |
| Number of fibroids | |
| 1 | 207 |
| 2 | 61 |
| 3 | 28 |
| ≥4 | 50 |
| Size of UFs, cm | 5.6 ± 1.6 (2.6–10.4) |
| Volume of UFs, cm$^3$ | 66.39 (36.2–111.8), (7.6–544.2)† |
| Distance from UFs ventral side to skin, cm | 5.3 ± 2.1 (1.6–10.9) |
| Distance from UFs dorsal side to sacrum, cm | 2.7 ± 1.5 (0.5–9.4) |

Unless otherwise noted, values are mean ± standard deviation.
SI = signal intensity, T1WI = T1-weighted image, T2WI = T2-weighted image, UFs = uterine fibroids.
* Values in parentheses represent ranges.
† Values are median and interquartile range.

### 2.4. Data collection

The HIFU treatment parameters included sonication time ($t$), treatment time ($T$), and sonication power ($P$). The $V_0$ and $V_1$ were used to calculate the nonperfusion volume rate (NPVR, defined as the nonperfused volume divided by the target UFs volume); the treatment parameters and $V_1$ were used to calculate the energy efficiency factor (EEF, defined as the ultrasound energy delivered for ablating 1 mm$^3$ of the UFs lesion tissue).[17] All calculation equations were as follows: $NPVR = V_1/V_0 \times 100\%$; $EEF = \eta Pt/1000\ V_1$ ($\eta = 0.7$, represents focusing coefficient).

### 2.5. Statistical analysis

In this study, normally distributed data were expressed as mean ± standard deviation, and skewly distributed data were represented by median and interquartile range. One-way analysis of variance was used to evaluate HIFU ablation among different groups, followed by an SNK-q test. In addition, we defined the dummy variables separately for the multi-category variables. A stepwise method was selected for multiple linear regression analysis treating EEF as the dependent variable and the following parameters as independent variables including the dummy variable, distance from the UFs dorsal side to the sacrum, distance from the UFs ventral side to the skin, enhancement type on T1WI, age, and fibroids volume. The SPSS 17.0 software (IBM, Armonk, NY) was used for all statistical analysis. A $P$-value of <.05 was considered a significant difference.

## 3. Result

### 3.1. Evaluation of USgHIFU ablation

***3.1.1. Treatment parameters.*** The average sonication time and sonication power were 1250.1 ± 879.1 seconds (range, 64–3940 seconds) and 381.2 ± 29.9 W (range, 216–400 W), and the mean treatment time was 127.9 ± 61.4 minutes (range, 15–306 minutes). The mean NPV immediately after HIFU was 61.0 ± 53.0 cm$^3$ (range, 3.6–443.3 cm$^3$), accounting for 74.4 ± 14.7% (range 16.7–98.4%) of the mean baseline volume of treated fibroids. The mean EEF was 7.2 ± 4.8 J/mm$^3$ (range 0.1–30.4 J/mm$^3$).

***3.1.2. Evaluation of USgHIFU ablation at different locations.*** There was a significant difference in the NPVR between different locations ($P < .001$) (Table 2). Compared with anterior, lateral, and uterine fundus fibroids, the fibroids in the posterior part of uterus had the lowest NPVR ($P < .01$). The EEF of the posterior fibroids was statistically significant ($P < .01$) larger than fibroids at all the other locations, but no significant ($P > .05$) difference existed between fibroids at all the other locations. The anterior UFs had the highest NPVR (79.9 ± 11.9%) while the UFs in fundus had the smallest EEF (6.0 ± 4.6 J/mm$^3$).

***3.1.3. USgHIFU ablation assessment of UFs of different types.*** Different UFs of different types had significant ($P < .001$) differences in NPVR and EEF. A statistically significant ($P < .01$)

**Table 2**

**Evaluation of ultrasound-guided high-intensity focused ultrasound ablation in different locations.**

| | Anterior | Posterior | Lateral | Fundus | P |
|---|---|---|---|---|---|
| N | 110 | 95 | 97 | 44 | |
| NPVR, % | 79.9±11.9 | 67.2±14.9 | 74.4±14.5 | 76.5±15.2 | .000 |
| EEF, J/mm$^3$ | 6.5±4.3 | 9.0±5.6 | 6.7±4.3 | 6.0±4.6 | .000 |

EEF=energy efficiency factor, NPVR=nonperfusion volume rate.

**Table 3**

**Evaluation of ultrasound-guided high-intensity focused ultrasound ablation in different types.**

| | Intramural | Submucosal | Subserous | Transmural | P |
|---|---|---|---|---|---|
| N | 156 | 76 | 66 | 48 | |
| NPVR, % | 78.3±11.3 | 70.4±16.0 | 77.5±11.4 | 62.1±19.0 | .000 |
| EEF, J/mm$^3$ | 6.3±3.7 | 8.6±5.8 | 6.3±4.3 | 9.3±6.1 | .000 |

EEF=energy efficiency factor, NPVR=nonperfusion volume rate.

difference existed in NPVR in the intramural vs submucosal fibroids, intramural vs transmural fibroids, subserous vs submucosal fibroids, subserous vs transmural fibroids, and submucosal vs transmural fibroids. The mean EEF of transmural UFs was 9.3±6.1 J/mm$^3$, significantly ($P<.01$) higher than intramural and subserous fibroids. No significant ($P>.05$) difference existed in the EEF between intramural and subserous fibroids or between submucosal and transmural fibroids (Table 3).

*3.1.4. Evaluation of USgHIFU ablation in different T2WI and T1WI enhancement types.* There was a significant difference in ablation results in different T2WI types and T1WI enhancement types ($P<.01$). The highest NPVR existed in the T2WI hypointense group (80.1±11.4%) and mild enhancement T1WI group (83.5±9.6%). A significant difference existed in the EEF in the T1WI mild enhancement vs moderate/significant enhancement, T2WI hypointense vs isointense group ($P=.005$), T2WI hypointense vs mixed signal group ($P=.011$), and T2WI hypointense vs hyperintense group ($P=.000$). The UFs of the hypointense group and mild enhancement T1WI group had the highest NPVR and lowest EEF (Table 4).

*3.1.5. Evaluation of USgHIFU ablation in different size.* There was a significant ($P=.025$) difference in NPVR between 3 to 5 cm and <3 cm fibroids, but no statistical difference existed in 3 to 5 cm vs >5 cm group ($P=.217$) and <3 cm vs >5 cm group ($P=.084$). A significant ($P<.05$) difference existed in EEF in the group <3 cm vs 3 to 5 cm, <3 cm vs >5 cm, and 3 to 5 cm vs >5 cm. Fibroids ranging 3 to 5 cm had the greatest NPVR (76.1± 13.8%) while fibroids > 5 cm had smallest EEF (6.1±4.0 J/mm$^3$) (Table 5).

### 3.2. Multifactor linear regression model

Seven independent variables were selected for the multifactor linear regression model: distance from the UFs ventral side to the skin, T1WI enhancement type, SI on T2WI, size, location, type, and volume. Since Model 7 fitted better than the other models (adjusted $R^2=0.308$), we chose it for analysis (Tables 6 and 7). The multiple linear regression equation was: $y=1.516+0.443X_1+2.897X_2-1.813X_3-1.926X_4+1.482X_5+2.015X_6-0.009X_7$ ($y$=dependent variable: EEF; $X_1$=distance from the UFs ventral side to the skin; $X_2$=enhancement type on T1WI; $X_3$=size of UFs [>5 cm]; $X_4$=SI on T2WI [hypointense]; $X_5$=location of UFs [posterior]; $X_6$=type of UFs [transmural]; $X_7$=volume of fibroids). We also conducted a hypothesis test on this regression model, and it had an F value equal to 22.261 ($P<.001$), indicating that at least 1 independent variable had a nonzero regression coefficient. This model was statistically significant. In the standard partial regression coefficients in this model, the values of enhancement type on T1WI (0.243) and the distance from the UFs ventral side to the skin (0.194) were larger than that of the other, and they could be considered to have a greater impact on EEF. However, nonstandard or standard partial regression coefficients of the groups of SI on T2WI (hypointense), size (>5 cm), and volume were negative, and we could conclude that the lower T2WI signal or the larger size and volume of fibroids, the smaller the EEF required for HIFU ablation.

### 3.3. Adverse events

In the overall study population, the major adverse events (AEs) during and after HIFU were lower abdominal pain, with a rate of 67.3%. About 37.6% of patients had sacrococcygeal signal changes, and 6.4% of patients had transient leg pain/numbness. Except for 1 patient whose operation was terminated due to a shallow 2nd skin burns with surgical scars in the treated area, the intraoperative AEs in all patients disappeared after changing the treatment parameters and areas. No serious AEs were observed.

## 4. Discussion

Many factors may affect HIFU ablation in the treatment of UFs. Gong et al[17] showed that the NPVR was associated with the locations of UFs and the uterus, because the attenuation of the ultrasound beam was less when the ultrasonic beam travelled through the shorter acoustic pathway. The NPVR and ablative efficiency may be significantly different between various types of UFs, and Cheng et al[18] found that the NPVR of submucosal and intramural UFs was both significantly lower than that of the subserosal ones. In addition, the blood supply can absorb HIFU

**Table 4**

**Evaluation of ultrasound-guided high-intensity focused ultrasound ablation in different signal intensity on T2WI and enhancement type on T1WI.**

| | A* | B* | P | Hypo- | Isoin- | Hyper- | Mixed | P |
|---|---|---|---|---|---|---|---|---|
| N | 79 | 267 | | 109 | 114 | 67 | 56 | |
| NPVR, % | 83.5±9.6 | 71.7±14.9 | .000 | 80.1±11.4 | 74.3±15.3 | 64.2±15.8 | 72.1±15.5 | .000 |
| EEF, J/mm$^3$ | 4.4±2.5 | 8.0±5.1 | .000 | 5.7±3.0 | 7.5±4.8 | 8.6±5.4 | 7.7±6.2 | .001 |

EEF=energy efficiency factor, NPVR=nonperfusion volume rate.
* A=mild enhancement, B=moderate or significant enhancement, Hypo-=hypointense, Iso-=isointense, Hyper-=hyperintense.

**Table 5**

**Evaluation of ultrasound-guided high-intensity focused ultrasound ablation in different sizes.**

| | <3 cm | 3–5 cm | >5 cm | P |
|---|---|---|---|---|
| N | 19 | 121 | 206 | |
| NPVR, % | 67.9±14.8 | 76.1±13.8 | 74.0±15.1 | .067 |
| EEF, J/mm$^3$ | 10.9±6.6 | 8.5±5.2 | 6.1±4.0 | .000 |

EEF=energy efficiency factor, NPVR=nonperfusion volume rate.

**Table 6**

**Multivariable regression model.**

| Model | R | $R^2$ | Adjusted $R^2$ | SE of the estimate |
|---|---|---|---|---|
| 1 | 0.331* | 0.109 | 0.107 | 4.6283482 |
| 2 | 0.439† | 0.193 | 0.188 | 4.4121698 |
| 3 | 0.487‡ | 0.237 | 0.230 | 4.2971915 |
| 4 | 0.523§ | 0.273 | 0.264 | 4.2000856 |
| 5 | 0.543|| | 0.295 | 0.284 | 4.1428436 |
| 6 | 0.559¶ | 0.313 | 0.300 | 4.0967088 |
| 7 | 0.568# | 0.323 | 0.308 | 4.0730604 |

SE=standard error, SI=signal intensity, T1WI=T1-weighted image, T2WI=T2-weighted image, UFs=uterine fibroids.

* Predictors: (Constant), distance from UFs ventral side to skin.

† Predictors: (Constant), distance from UFs ventral side to skin, enhancement type on T1WI.

‡ Predictors: (Constant), distance from UFs ventral side to skin, enhancement type on T1WI, size of UFs (>5 cm).

§ Predictors: (Constant), distance from UFs ventral side to skin, enhancement type on T1WI, size of UFs (>5 cm), SI on T2WI (hypointense).

|| Predictors: (Constant), distance from UFs ventral side to skin, enhancement type on T1WI, size of UFs (>5 cm), SI on T2WI (hypointense), location of UFs (posterior).

¶ Predictors: (Constant), distance from UFs ventral side to skin, enhancement type on T1WI, size of UFs (>5 cm), SI on T2WI (hypointense), location of UFs (posterior), type of UFs (transmural).

# Predictors: (Constant), distance from UFs ventral side to skin, enhancement type on T1WI, size of UFs (>5 cm), SI on T2WI (hypointense), location of UFs (posterior), type of UFs (transmural), volume of fibroids.

energy and leave the treatment area with circulation movement, resulting in low energy deposition efficiency; therefore, T1WI contrast enhancement can reflect the blood perfusion status of UFs to predict the effect of ablation.[19] In addition, many studies have shown that the efficacy of HIFU correlates with the SI on T2WI and that the low SI can be more easily ablated, compared with the high SI UFs. This may be due to the fact that numerous nuclear areas, higher smooth muscle density and lower extracellular matrix per unit volume lead to less energy deposition required at the focal point.[15,18,20–22] Gong et al[17] also found that the volume of the UFs was positively correlated with the NPVR, but negatively correlated with EEF, which may be explained by "damage–dame interference effects": the acoustic environment of the surrounding focusing tissue can be dynamically affected by the expansion of the necrotic region and ascent of temperature on the focal point, thus making the ultrasonic energy more easily deposited.[23] The smaller the EEF value, the less energy is required to ablate a certain volume of UFs with the higher HIFU ablation efficiency.[24]

In our study, the posterior UFs had more pronounced attenuation of ultrasonic energy and a larger EEF ($P<.01$) compared with UFs at the lateral, fundus, and anterior positions, which is supported by findings of other studies.[16,17] In the UFs of different types, the transmural UFs were more difficult to ablate, and their EEF was significantly greater than in the other types ($P<.01$); the ablation rate and energy deposition efficiency of intramural and subserosal UFs were significantly higher ($P<.01$) than submucosal and transmural UFs. The energy deposition efficiency of hypointense T2WI and mild enhancement group was significantly better than that of the isointense/hyperintense and moderate/significant enhancement group ($P<.01$), which was consistent with the previous research results.[15,16] The NPVR in the hypointense T2WI group was significantly higher than in the hyperintense group, and the NPVR of the mild enhancement on T1WI contrast enhancement was significantly higher than that of the moderate or significant group. Based on the results of multiple linear regression analysis, it can be considered that the proportion of the total variation in the EEF of the dependent variable that can be explained by the independent variables in the regression model is 32.3% (Table 6). According to Table 7, we can consider T1WI moderate/significant enhancement, long target skin distance, posterior and transmural fibroids more difficult to ablate, and the energy deposition efficiency is more affected by the former two. We can also assume that energy deposition efficiency of UFs with the hypointense T2WI is higher than UFs with isointense, hyperintense, and mixed signal, and >5 cm UFs are more efficiently ablated than those of <3 cm, 3 to 5 cm. Therefore, our study confirmed again that the blood supply (T1WI enhancement) was the major factor affecting energy deposition efficiency.

It should be noted that some patients had skin burns, lower abdominal pain, lower extremity numbness, and sacrococcygeal pain during this progress. Due to sedation or analgesia, the patient's tolerance to pain may be enhanced, which makes skin burns more likely to occur. Lower abdominal pain may be the body's response to intraoperative energy deposition, postoperative aseptic necrosis, or edema. The numbness of the lower limbs may also be related to the patient's prolonged prone position (127.9±61.4 minutes), and the sciatic/buttock pain may result from the back-field effects of ultrasound. Furthermore, we found

**Table 7**

**Coefficients*.**

| Model 7 | Unstandardized coefficients | Standardized coefficients | t | P |
|---|---|---|---|---|
| Constant | 1.516 | | 1.192 | .234 |
| Distance from UFs ventral side to skin | 0.443 | 0.194 | 3.879 | .000 |
| Enhancement type on T1WI | 2.897 | 0.243 | 5.200 | .000 |
| Size of UFs (>5 cm) | −1.813 | −0.180 | −3.043 | .003 |
| SI on T2WI (hypointense) | −1.926 | −0.184 | −3.922 | .000 |
| Location of UFs (posterior) | 1.482 | 0.135 | 2.885 | .004 |
| Type of UFs (transmural) | 2.015 | 0.144 | 3.106 | .002 |
| Volume of fibroids | −0.009 | −0.130 | −2.195 | .029 |

SI=signal intensity, T1WI=T1-weighted image, T2WI=T2-weighted image, UFs=uterine fibroids.

* Dependent variable: energy efficiency factor.

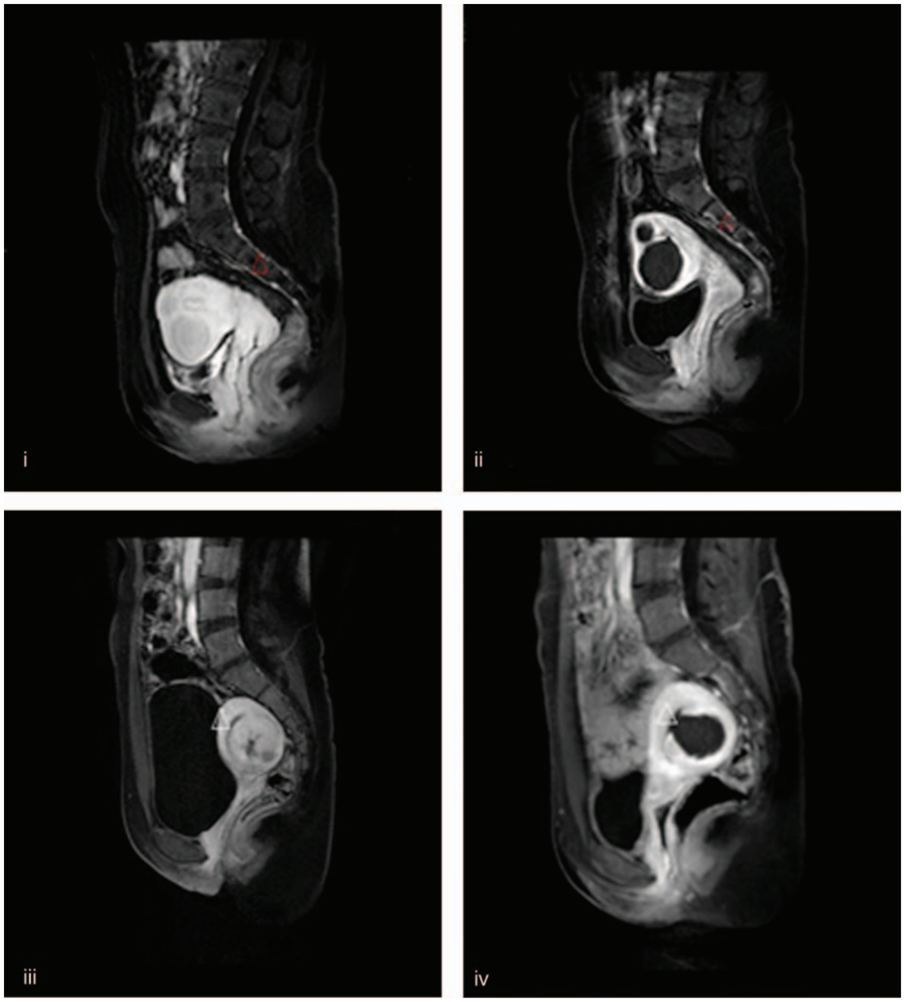


**Figure 1.** The abnormal signal of sacrum and endometrium (I–IV). (I) Before high-intensity focused ultrasound (HIFU), the signals of each vertebral body was consistent. (II) After HIFU, the signal of the anterior segment of each vertebral body in the posterior acoustic field was significantly changed, which was manifested as the nonstrengthening area. (III) The endometrium was intact and continuous before HIFU treatment. (IV) After HIFU, the continuity of the endometrium was interrupted. (As shown by triangle arrow.)

that some patients had endometrial interruption sign after HIFU (Fig. 1), which may increase the risk of endometrial impairment.[25] In 130 patients, abnormal signal (37.6%) of sacrum bone caused by thermal damage was detected after surgery, and MRI showed no enhanced region in the sacrum vertebral body (Fig. 1). This phenomenon may be caused by large acoustic impedance of the sacrum, which absorbs the ultrasonic energy of the posterior acoustic field, resulting in occlusion of small blood vessels in the vascular bed, but no relevant studies have been reported so far.

Our study has some limitations. First, we did not record the patient's BMI and the location of the uterus which may affect NPVR and ablation efficiency of HIFU therapy.[17] Second, our study was a retrospective analysis with the possibility of selection bias. In future studies, these limitations have to be addressed properly.

In conclusion, USgHIFU can be safely used and have a promising prospect for treating UFs even though its effect may be affected by anatomical features, tissue characteristics, and blood supply.

## Author contributions

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