Accepted Manuscript

High-intensity focused ultrasound therapy

Vincent Y.T. Cheung, MBBS, FRCOG, FRCSC

PII: S1521-6934(17)30135-9

DOI: 10.1016/j.bpobgyn.2017.09.002

Reference: YBEOG 1750

To appear in: Best Practice & Research Clinical Obstetrics & Gynaecology

Received Date: 29 July 2017

Accepted Date: 11 September 2017

Please cite this article as: Cheung VYT, High-intensity focused ultrasound therapy, *Best Practice & Research Clinical Obstetrics & Gynaecology* (2017), doi: 10.1016/j.bpobgyn.2017.09.002.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



High-intensity focused ultrasound therapy

Vincent Y.T. Cheung, MBBS, FRCOG, FRCSC

Department of Obstetrics and Gynaecology, Queen Mary Hospital, The University of Hong Kong, Hong Kong.

Corresponding author: Vincent Y.T. Cheung

Address: Department of Obstetrics and Gynaecology, Queen Mary Hospital,

102 Pokfulam Road, Hong Kong

E-mail: vytc@hku.hk
Telephone: 852-22553914
Facsimile: 852-25173278

Abstract

High-intensity focused ultrasound therapy has received increasing interest in the management of benign uterine tumors. Either magnetic resonance or ultrasound imaging has been used to target and monitor the ablation process. This article provides an overview of the background, clinical use, treatment outcomes and safety of high-intensity focused ultrasound in the treatment of uterine fibroids and adenomyosis; including a summary of clinical trials comparing magnetic resonance- or ultrasound-guided high-intensity focused ultrasound, with other minimally invasive or surgical interventions. The potential of this treatment modality as an alternative uterine-sparing option for women with fibroids and adenomyosis is discussed.

Keywords

adenomyosis fibroid high-intensity focused ultrasound magnetic resonance-guided ultrasound-guided

Introduction

High-intensity focused ultrasound (HIFU) is a relatively new minimally invasive modality for treating benign tumors. In gynaecology, it has been considered a uterine-sparing option for women seeking alternatives to hysterectomy for uterine fibroids and adenomyosis. It is a technology that focuses beams of ultrasound wave at one point, where the highest magnitude of energy is deposited. The principle of using this extracorporeal source of focused ultrasound energy to induce coagulative necrosis in the target tissue without damaging the overlying and surrounding vital structures was introduced by Lynn et al in 1942 [1]. However, this technique did not progressed rapidly because of inadequate targeting methods. Since the 1980s, HIFU has started to receive considerable interest in the management of solid tumors; and more recently, HIFU has been applied in the management of uterine fibroids and adenomyosis. Results obtained by various research groups have shown that HIFU in the treatment of fibroids and adenomyosis is safe, effective and highly acceptable to patients [2,3,4]. This article reviews the background, clinical application, and treatment outcomes of HIFU in the treatment of uterine fibroids and adenomyosis.

Principles of HIFU therapy

HIFU incorporates multiple ultrasound beams produced by piezoelectric or piezoceramic transducers directed into a three-dimensional focal point of typically a small volume of 5 mm in diameter and 10 mm in length. The intention is to raise and maintain at the target tissue a temperature of above 60°C for more than 1 second or longer, in order to cause coagulative necrosis and cell death. Synergistically, mechanical effect mostly by cavitation (intracellular water expands and contracts under the influence of acoustic pressure and develops microbubbles, which suddenly collapse and produce shock waves), and damaging effect to tumor blood vessels, also contribute to tissue destruction. During the ablation process, the HIFU beam has to be targetted and monitored under image guidance either by magnetic resonance or ultrasound.

Magnetic resonance-guided imaging allows excellent anatomic resolution and accurate localization of treatment targets. It evaluates treatment adequacy by real-time temperature mapping changes. Currently, the only United States Food and Drug Administration (FDA) approved magnetic resonance-guided high intensity focused ultrasound (MRgHIFU) system for fibroid treatment is the ExAblate device (Insightec, Tirat Carmel, Israel). Another system, Sonalleve, which is developed by Philips Healthcare (Guildford, Surrey, United Kingdom) has received Conformité Européene (CE) marking for fibroid treatment.

In 2002, Wang et al. reported their initial experience of ultrasound-guided HIFU (USgHIFU) on 6 patients, and concluded that it was safe and effective in treating uterine fibroids [5]. USgHIFU utilizes greyscale or echogenicity changes to determine the adequacy of fibroid ablation, and although it has been suggested to be cheaper [6] and require shorter treatment time than MRgHIFU [2], these have never been confirmed in any studies. The JC HIFU system (Chongqing Haifu Technology, Chongqing, China; Fig. 1) has been installed at Queen Mary Hospital since 2006 mainly for the treatment of hepatocellular carcinoma [7]; and since 2012 for the treatment of uterine fibroid [2]. This HIFU system consists of a real-time 3.5-MHz diagnostic ultrasound scanner integrated into the center of a 12-cm in diameter, 15-cm in focal length, 0.8-MHz therapeutic ultrasound transducer (Fig. 2). The therapeutic system can attain an acoustic output power of up to 400 W. The ultrasound transducer system which is emerged in a degassed water circulation system, has a capability of 6directional motion, and is controlled by a master computer unit. During treatment, the entire lesion is divided into slices of 5 mm. The acoustic output power is set between 350 and 400 W, and with successive sweeps from the deep to the shallow region, the entire volume of the lesion is ablated. Other similar USgHIFU systems, including the HIFU-2001 (SJTU Suntec Industry, Shanghai, China), HIFUNIT9000 (Shanghai A&S Science and Technology, Shanghai, China), and FEP-BY Series (China Medical Technologies, Beijing, China) are also currently used clinically for the treatment of fibroids. However, none of these systems described have received FDA approval. More recently, the new Mirabilis

HIFU system Prototype (Analogic Corporation, Peabody, MA) pilot trial has demonstrated an effective and safe profile and a short treatment time [8].

Patient selection

The selection criteria for HIFU therapy vary depending on the experience of individual centers. Generally, this treatment is applicable for premenopausal women with symptomatic fibroids and/or adenomyosis. However, women with pedunculated fibroid, fibroid suspicious of malignancy, known or suspected extensive pelvic adhesions such as a history of acute pelvic inflammatory disease, severe pelvic endometriosis, or major lower abdominal surgery are generally considered contraindications for the treatment [2,3,4]. Women who desire future fertility are used to be inappropriate candidates for the treatment but with expanded experience and knowledge of pregnancy outcomes following treatment, some centers may allow women who desire future fertility to undergo HIFU treatment [4]. In 2009, the FDA changed the labeling of MRgHIFU to take into account the desire for future pregnancy and not to have this as an absolute contraindication [9]. Women with thick abdominal wall are considered relative contraindication particularly in relation to MRgHIFU when obese women may have difficulty in positioning within the bore of the magnetic resonance machine. It is possible that once a center has accumulated more experience, these criteria can be loosened, which can accommodate more patients who are eligible for the therapy.

HIFU procedure

In most centers, selected patients are screened with pretreatment magnetic resonance imaging to establish the size, number, and exact location of fibroids, and to exclude other associated conditions such as adenomyosis and adnexal lesions. Pretreatment planning provides an opportunity to mimic the treatment process and is performed with the patient lying prone on the treatment table. The path of sonication, the depth of the target, the proximity of the target to the sacrum, and the likelihood of the presence of a bowel loop along

the path of sonication are evaluated.

The HIFU procedure, both magnetic resonance- and ultrasound-guided, are performed with the patient under intravenous conscious sedation, which allows for continuous patient feedback and reduces patient movement to a minimum. With a Foley catheter placed in the urinary bladder, the patient is carefully placed in the prone position so that the skin overlying the fibroid to be treated is in contact with degassed water. During treatment, the fibroid is ablated systemically, under magnetic resonance or ultrasound guided imaging, using temperature mapping or greyscale changes respectively to determine the adequacy of fibroid ablation.

Post-treatment management consists of maintaining the patient in prone position for about 1 hour and cooling the urinary bladder with the use of cold normal saline solution. Analgesics such as diclofenac and acetaminophen are given for pain relief. Magnetic resonance imaging can be performed within the first 24 hours to determine the amount of the nonperfused volume (NPV), which is an indicator of tissue necrosis and a marker of subsequent treatment success.

Treatment outcomes

In most studies, treatment effectiveness of HIFU for fibroid is evaluated by the degree of fibroid volume reduction, subsequent symptom resolution, and the rate of reintervention for persistent or recurrent symptoms. Fibroid volume is measured in longitudinal, anteroposterior, and transverse dimensions and was calculated using the following formula: V = 0.5233 X D1 X D2 X D3, where V indicates fibroid volume; D1, longitudinal dimension; D2, anteroposterior dimension; and D3, transverse dimension. Improvement of menorrhagia is usually measured by the symptom severity score, using a validated health- and symptom-related quality of life questionnaire specific to fibroids, known as the Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QOL) [10].

In patients with adenomyosis, the improvement of menorrhagia is reported using the symptom severity score as applied to fibroids and/or the menorrhagia scale which is scored according to patients' descriptions on a 5-point scale or using a menstrual score chart as described by Sharp et al. in 1995 [11]. The reduction of dysmenorrhea is determined based on the menstrual pain score using a visual analog scale.

Indicator of treatment efficacy also includes the NPV, which is the percentage of the fibroid or adenomyotic volume being ablated and is shown as a nonenhancing area on contrast-enhanced T1-weighed magnetic resonance imaging after the treatment. This NPV has been shown to be associated with the degree of symptom improvement and fibroid volume reduction [12,13].

MRgHIFU and fibroids

Despite using the restricted protocols as limited by the FDA, early results demonstrated promising results. Hindley et al. in 2004 reported that 79.3% of 109 patients had significant improvement in their fibroid symptoms after treatment, with a mean decrease in the fibroid volume of 13.5% at 6 months [14]. Rabinovici et al. also reported similar results in 35 treated women, with 69% of patients reporting significant or partial improvement in symptoms. In addition, there was a 12% and a 15% reduction in fibroid volume 1 month and 6 months after treatment respectively [15]. Longer follow up studies at 12–24 months' follow-up after MRgFUS provide some information about the durability of treatment. Stewart et al. evaluated 82 patients at 12 months' followup and noted an average of 10% fibroid volume reduction and sustained symptom relief in 51% of the patients [16]. In a review of 359 patients from the data of multiple clinical trials, Stewart et al. demonstrated that the maximal decrease in fibroid volume was approximately 25% at 12 months after treatment, which is related to the treated volumes [12]. In a 4-year series of 130 women published in 2011, Gorny et al reported symptomatic improvement in 85.7%, 92.9%, and 87.6% of patients at 3, 6 and 12 months' follow up, respectively [13].

A more recent literature reivew by Pron in 2015 demonstrated a clinically significant reduction in fibroid-related symptoms after MRgHIFU in studies conducted in 10 countries, although few involved follow-up longer than 1 year [17]. Nine studies involving the restricted protocols and seven studies involving protocols that allowed complete or near-complete ablation. All studies reported significant reduction in mean symptom severity scores, over baseline values at 3 month to up to 36 months after treatment [17]. The ranges of fibroid volume reduction from the 5 studies reviewed were 12.6-18.1% (3-month, from 2 studies), 12.6-25.0% (6-month, from 4 studies), 9.3-30.0% (12-month, from 3 studies), and 32.3% (36-month, from 1 study) [17]. Retreatment rates ranged from 4.9-33.3% at 12 months after treatment in early clinical studies involving the restricted protocols, and 38.0-50.0% at 12 months after treatment in later reports involving near-complete ablation [17]. The most common retreatment was hysterectomy (50%; 47/94) [17]. In a recently published PROMISe trial, the MRgHIFU group had more improved symptom severity scores by 12 weeks when compared to the placebo group (mean 31 points and 13 points, respectively) [18]. The mean fibroid volume decreased 18% in the MRgHIFU group with no decrease in the placebo group at 12 weeks. Two years after MRgHIFU, 4 of 12 women who had a follow-up evaluation, had undergone another fibroid surgery or procedure [18].

USgHIFU and fibroids

In 2002, Wang et al. reported their preliminary results of using USgHIFU in treating 6 fibroids in 6 patients, and showed a 63.2% reduction in fibroid volume over 4 to 12 months, with significant improvement of symptoms in 5 patients [5]. With further development of imaging monitoring technology and the therapeutic technique, HIFU has been clinically considered an alternative treatment for uterine fibroids in China [19]. In an earlier review of 8 articles published from 2005 to 2012 on USgHIFU, the percentage of patients who showed improvement after the procedure was 48.2% at 3 months after treatment to up to 89.5% at 6 months; with a 38.5% and 48.8% reduction of symptom severity scores at 6 and 12 months after treatment respectively [2].

The percentages of fibroid volume reduction at 3, 6, and 12 months were 27.2-47.1%, 47.9-73.1% and 50.3-78.9% respectively [2]. In a more recent reviw of the cases that were treated in 10 centres in China between 2006 and 2013 using an NPV ratio of over 25% as a technical success, 98.4% (7319/7439) of the uterine fibroids had successful ablation with a mean NPV ratio of $83.1 \pm 15.6\%$ (range 25-100%). The NPV ratio was greater than 70% in more than 80% of the treated fibroids. On the basis of these NPV ratios achieved, the re-intervention rate was less than 10% after 24-month follow-up [19].

HIFU and adenomyosis

In 2007, Fan et al. tested the feasibility of using MRgHIFU for the treatment of adenomyosis [20]. Ten patients with symptomatic adenomyosis were treated with MRgHIFU. An average NPV ratio of 62.5 ± 21.6% were achieved. All patients experienced symptom relief with no complications occurred [20]. The results of this study, together with those from 10 other studies on adenomyosis treatment were reviewed in a recent article [3]. Five studies were on MRgHIFU treatment and 6 were on USgHIFU treatment, consisting of 84 and 1066 patients respectively. The degree of menorrhagia reduction after treatment were reported in 10 studies and ranged from 12.4-33.3% (1-month), 25.3-80.8% (3-month), 16.4-52.4% (6-month), 24.9-66.4% (12-month), 44.0% (18-month), and 44.8% (24-month) [3]. The reduction of dysmenorrhea, as determined based on the menstrual pain score, was evaluated in seven studies; all showed a reduction of dysmenorrhea at 3 months (range, 25.0-83.3%), 6 months (44.7-100%), 12 months (64.0-72.1%), 18 months (54.2%), and 24 months (56.0%) [3]. Five studies reported the degree of uterine volume reduction after HIFU therapy, with values ranging from 12.7-54.0% over follow-up periods of 1 to 12 months [3]. The NPV was reported in 7 studies, with mean values ranging from 24.4-62.5% [3].

Safety

Although, studies had demonstrated that HIFU is safe in treating uterine

fibroids and adenomyosis, when HIFU was first introduced, adverse effects such as skin burn and nerve injury had been reported [14,16,19]. With the improvement of this technique and increase of physicians' experience, the rate of adverse effects has decreased dramatically [19]. Complications reported in most clinical or comparative cohort studies are evaluated based on the standards as defined by the Society of Interventional Radiology Standards of Practice Committee Classification of Complications by Outcome [21]. Major complications were defined as those requiring therapy or minor hospitalization of less than 48 hours (Class C); requiring major therapy, unplanned increase in the level of care, or prolonged hospitalization of more than 48 hours (Class D); having permanent adverse sequelae (Class E); or resulting in death (Class F).

From the recent Ontario Health Technology Assessment Series publication, reviewing 21 studies on MRgHIFU comprising 1,594 patients, 26 major complications (1.6%) were reported [17]. The rate was higher with the restricted protocol (4.1%; 22/534) when compared to the complete or near-complete ablation protocol (0.4%; 4/1,060). The major adverse events included deep venous thrombosis; non-target thermal injury such as sciatic nerve palsy or skin burn; transfusions; and re-hospitalizations for various conditions including fever, removal of discharging ablated fibroid products, urinary tract infection, endometritis, and yeast infection [17].

At the First international symposium devoted to MRgHIFU, "MRgFUS 2008" (October 6–7, 2008, Washington, DC), the participants reported a total of 17 adverse events, which were not previously reported in the published literature: 5 neuropathies, 4 grade 1–2 skin burns, performance of 2 emergency hysterectomies, 2 abdominal wall edemas, 1 bowel injury, 1 bladder injury, 1 deep vein thrombosis, and 1 fat necrosis [22].

In a large retrospective review on 9988 patients with USgHIFU treatments, 1062 patients (10.6%) presented with 1305 adverse events; of which only 24 events (1.8%) were Class C and 8 (0.6%) were Class D [23]. The most common complications were vaginal discharge (8.7%) and lower

abdominal pain (2.3%). Twenty-six patients had skin burn (0.3%) and 2 patients had intestinal perforation (0.02%) [23].

The most commonly reported complication of HIFU therapy for fibroids is skin burn [24]. In a retrospective analysis of 115 women with symptomatic fibroids who underwent MRgHIFU, 2 cases (1.7%) of first-degree skin burn were reported [25]. Lee et al. reported their experience on 618 patients who had USgHIFU for fibroids and adenomyosis, and the incidence of skin burn was 1.3% (8/618, 5 cases of first degree and 3 cases of second degree) [26]. Other complications in the same series included foot drop (1 case), transient unilateral leg weakness (5 cases), tumor lysis syndrome with transient acute prerenal failure (1 case), sleep apnea due to a sedative agent (1 case) and transient hematuria (10 cases) [26]. In a recently published prospective multicentre patient choice cohort study (IDEAL Exploratory study), the incidence of second degree skin burn was 0.2% (3/1353) [27].

There has been concern on the potential impact of hysterectomy and uterine artery embolization on ovarian reserve for the treatment of fibroids, mainly due to their effects on ovarian perfusion [28-30]. Ovarian dysfunction can lead to accelerated onset of menopause and diminished fertility. During HIFU, therapeutic ultrasound waves travel between the transducer and the targets. Therefore, there is a possibility that HIFU may adversely affect ovarian reserve if one or both ovaries are located along the course of sonication. Using anti-Mullerian hormone as a marker, our preliminary findings suggest that ovarian reserve is not affected by USgHIFU therapy in premenopausal women over age 40 [31]. Whether this is an advantage of HIFU over hysterectomy or uterine artery embolization in the treatment of fibroids, will need to be confirmed by further studies.

Comparative studies

A summary of the clinical trials comparing between MRgHIFU or USgHIFU, with other minimally invasive or surgical interventions, is outlined in Table 1 [27, 32-

40]. All studies are on fibroid treatment and none on adenomyosis. There is no randomized trial comparing MRgHIFU to other interventions except for the recently published periprocedural outcomes comparing MRgHIFU and fibroid embolization [36]. However, there are randomized trials comparing USgHIFU to myomectomy and to radiofrequency ablation. There is no comparison between MRgHIFU and USgHIFU. Study findings suggest that HIFU treatment of fibroids is associated with fewer complications, and shorter hospital stay, when compared with hysterectomy, but MRgHIFU is associated but more reinterventions, when compared with uterine artery embolization and hysterectomy. The long-term results of the FIRSTT Trial comparing MRgHIFU and uterine artery embolization on the effectiveness for symptom relief, economic utilization, and ovarian reserve after treatment, when available, will add to our knowledge [41].

Pregnancy after HIFU

When the ExAblate System was initially introduced as a uterine sparing procedure for fibroids, it was only FDA approved for women who had no desire for future childbearing. The reason was the uncertainty on the impact of HIFU on reproductive and pregnancy outcomes. However, with increased number of apparently favourable experience from women who conceived successfully after HIFU, the FDA in 2009 stated that "patients should have completed child bearing" to be eligible for the procedure [9].

Most evidences on pregnancies after HIFU are from case reports and series. Rabinovici et al. reported the largest series of 54 pregnancies in 51 women after MRgHIFU [42]. Live births occurred in 41% of pregnancies, with a 28% spontaneous abortion rate, an 11% rate of elective pregnancy termination, and a 20% (11/54) ongoing pregnancies beyond 20 gestational weeks [42]. In another review of 35 published reports of live birth following MRgHIFU, 54% (19 of 35) of pregnancies resulted in vaginal delivery [43]. However, the heterogeneity of these data is great, and the power of this case series is too low to detect rare but serious outcomes, such as uterine rupture and placenta accreta.

In a case series, which followed 24 women with unintended pregnancy following USgHIFU, 7 women carried their pregnancies to term and all were delivered by cesarean section. Of the remaining pregnancies, 2 had spontaneous miscarriage and 15 had elective termination [44]. In a recently completed follow up of 68 HIFU-treated adenomyosis patients who wished to conceive, 54 patients conceived at a median of 10 months (range 1–31 months) post-HIFU, and 21 of them delivered healthy babies. No uterine rupture occurred during gestation or delivery. However, 20 of the 54 patients had spontaneous miscarriage, and the outcomes of the remaining 13 patients were not reported [45].

The minimally invasive nature of HIFU, together with its ability to ablate fibroids or adenomyoma with less uterine scarring when compared with surgery, suggests that HIFU could be a well tolerated approach for patients desiring fertility and may not increase obstetric risk [6]. In addition, it was observed that patients with submucous fibroids and adenomyosis who had infertility, conceived after HIFU treatment and delivered term babies [46-48]. The results suggested that HIFU seems to be a safe treatment option for patients desiring future fertility. It is also reassuring that studies are underway to further evaluate the use of HIFU in patients desiring future fertility [41].

Conclusions

HIFU appears to be effective and safe in the management of symptomatic fibroids and adenomyosis. However, more information on long-term outcomes and safety are essential to enable continual expansion of its clinical applications. Although emerging evidence of successful pregnancy outcomes in patients after HIFU treatment are available, further studies are needed to ensure this therapy a safe uterine-sparing modality in women who desire future fertility.

Conflict of interest statement

The author has no conflict of interest to declare; in particular no financial interest with any HIFU system maufacturing company.

Practice Points

- HIFU seems to be a promising minimally invasive, uterine sparing treatment for uterine fibroids and adenomyosis, resulting in improved quality of life and diminished fibroid size.
- Studies have suggested that HIFU is relatively safe in treating uterine fibroids and adenomyosis with a small risk of advise effects notably skin burn.
- Existing data suggested that HIFU seems to be a safe treatment option for patients desiring future fertility and may not increase obstetric risk.

Research Agenda

- Further randomized controlled trials to determine the efficacy, safety and fertility outcome of HIFU versus other minimally invasive or conventional treatment modality for fibroids and adenomyosis.
- Trials to compare between MRgHIFU and USgHIFU.
- More data is needed on the fertility and pregnancy outcomes following HIFU treatment.

References

- 1. Lynn JG, Zwemer RL, Chick AJ, Miller AE. A new method for the generation and use of focused ultrasound in experimental biology. Gen Physiol 1942;26:179–93.
- *2. Cheung VY. Sonographically guided high-intensity focused ultrasound for the management of uterine fibroids. J Ultrasound Med 2013;32:1353-8.
- *3. Cheung VY. Current status of high-intensity focused ultrasound for the management of uterine adenomyosis. Ultrasonography 2017;36:95-102.

- *4. Al Hilli MM, Stewart EA. Magnetic resonance-guided focused ultrasound surgery. Semin Reprod Med 2010;28:242-9.
- 5. Wang W, Liu WY, Zhou J, Xu JM, Gai LH, Huang CJ. Treatment of symptomatic uterine leiomyomata with high intensity focused ultrasound: a preliminary clinical study [in Chinese]. Chinese Journal of Ultrasonography 2002;11:161-3.
- *6. Zhang L, Rao F, Setzen R. High intensity focused ultrasound for the treatment of adenomyosis: selection criteria, efficacy, safety and fertility. Acta Obstet Gynecol Scand 2017;96:707-14.
- 7. Ng KK, Poon RT, Chan SC, Chok KS, Cheung TT, Tung H, et al. High-intensity focused ultrasound for hepatocellular carcinoma: a single-center experience. Ann Surg 2011;253:981–87.
- 8. Parsons JE, Lau MPH, Martin PJ, Islas Lagos JJ, Aguilar Aguirre JM, Garza Leal JG. Pilot Study of the Mirabilis System Prototype for Rapid Noninvasive Uterine Myoma Treatment Using an Ultrasound-Guided Volumetric Shell Ablation Technique. J Minim Invasive Gynecol 2017;24:579-91.
- 9. U.S. Food and Drug Administration https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P0400 03S006 [accessed 29.07.17]
- 10. Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol 2002;99:290–300.
- 11. Sharp NC, Cronin N, Feldberg I, Evans M, Hodgson D, Ellis S. Microwaves for menorrhagia: a new fast technique for endometrial ablation. Lancet 1995;346:1003–4.
- 12. Stewart EA, Gostout B, Rabinovici J, Kim HS, Regan L, Tempany CM. Sustained relief of leiomyoma symptoms by using focused ultrasound surgery. Obstet Gynecol 2007;110:279–87.
- 13. Gorny KR, Woodrum DA, Brown DL, Henrichsen TL, Weaver AL, Amrami KK, 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; 22:857–64.
- 14. Hindley J, Gedroyc WM, Regan L, Stewart E, Tempany C, Hynyen K, et al. MRI guidance of focused ultrasound therapy of uterine fibroids: early results. Am J Roentgenol 2004;183:1713-9.
- 15. Rabinovici J, Inbar Y, Revel A, Zalel Y, Gomori JM, Itzchak Y, et al. Clinical improvement and shrinkage of uterine fibroids after thermal ablation by

- magnetic resonance-guided focused ultrasound surgery. Ultrasound Obstet Gynecol 2007;30:771–7.
- 16. Stewart EA, Rabinovici J, Tempany CM, Inbar Y, Regan L, Gostout B, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. Fertil Steril 2006;85:22-9.
- *17. Pron G. Magnetic Resonance-Guided High-Intensity Focused Ultrasound (MRgHIFU) Treatment of Symptomatic Uterine Fibroids: An Evidence-Based Analysis. Ont Health Technol Assess Ser 2015;15:1-86.
- 18. Jacoby VL, Kohi MP, Poder L, Jacoby A, Lager J, Schembri M, et al. PROMISe trial: a pilot, randomized, placebo-controlled trial of magnetic resonance guided focused ultrasound for uterine fibroids. Fertil Steril 2016;105:773-80.
- *19. Zhang L, Zhang W, Orsi F, Chen W, Wang Z. Ultrasound-guided high intensity focused ultrasound for the treatment of gynaecological diseases: A review of safety and efficacy. Int J Hyperthermia 2015;31:280-4.
- 20. Fan TY, Zhang L, Chen W, Liu Y, He M, Huang X, et al. Feasibility of MRIguided high intensity focused ultrasound treatment for adenomyosis. Eur J Radiol 2012;81:3624–30.
- 21. Omary RA, Bettmann MA, Cardella JF, Bakal CW, Schwartzberg MS, Sacks D, et al. Quality improvement guidelines for the reporting and archiving of interventional radiology procedures. J Vasc Interv Radiol 2002;13(9 Pt 1):879-81.
- 22. Taran FA, Hesley GK, Gorny KR, Stewart EA. What factors currently limit magnetic resonance-guided focused ultrasound of leiomyomas? a survey conducted at the first international symposium devoted to clinical magnetic resonance-guided focused ultrasound. Fertil Steril 2010;94: 331–4.
- *23. Chen J, Chen W, Zhang L, Li K, Peng S, He M, Hu L. Safety of ultrasound-guided ultrasound ablation for uterine fibroids and adenomyosis: A review of 9988 cases. Ultrason Sonochem 2015;27:671-6.
- 24. Gizzo S, Saccardi C, Patrelli TS, Ancona E, Noventa M, Fagherazzi S, et al. Magnetic resonance-guided focused ultrasound myomectomy: safety, efficacy, subsequent fertility and quality-of-life improvements, a systematic review Reprod Sci 2014;21:465-76.
- 25. Trumm CG, Stahl R, Clevert DA, Herzog P, Mindjuk I, Kornprobst S, 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;48:359-65.

- *26. Lee JS, Hong GY, Park BJ, Kim TE. Ultrasound-guided high-intensity focused ultrasound treatment for uterine fibroid & adenomyosis: A single center experience from the Republic of Korea. Ultrason Sonochem 2015;27:682-7.
- *27. Chen J, Li Y, Wang Z, McCulloch P, Hu L, Chen W, et al; Committee of the Clinical Trial of HIFU versus Surgical Treatment for Fibroids. Evaluation of high-intensity focused ultrasound ablation for uterine fibroids: an IDEAL prospective exploration study. BJOG 2017 Apr 19.
- 28. Farquhar CM, Sadler L, Harvey SA, Stewart AW. The association of hysterectomy and menopause: a prospective cohort study. BJOG 2005;112:956-62.
- 29. Hehenkamp WJ, Volkers NA, Broekmans FJ, de Jong FH, Themmen AP, Birnie E, et al. Loss of ovarian reserve after uterine artery embolization: a randomized comparison with hysterectomy. Hum Reprod 2007;22:1996-2005.
- 30. Tulandi T, Sammour A, Valenti D, Child TJ, Seti L, Tan SL. Ovarian reserve after uterine artery embolization for leiomyomata. Fertil Steril 2002;78:197-8.
- 31. Cheung VY, Lam TP, Jenkins CR, Cheung GK, Chan SS, Choi WK. Ovarian Reserve After Ultrasound-Guided High-Intensity Focused Ultrasound for Uterine Fibroids: Preliminary Experience. J Obstet Gynaecol Can 2016;38:357-61.
- 32. Taran FA, Tempany CMC, Regan L, Inbar Y, Revel A, Stewart EA. Magnetic resonance-guided focused ultrasound (MRgFUS) compared with abdominal hysterectomy for treatment of uterine leiomyomas. Ultrasound Obstet Gynecol 2009;34:572–8.
- 33. Froeling V, Meckelburg K, Scheurig-Muenkler C, Schreiter NF, Kamp J, Maurer MH, et al. Midterm results after uterine artery embolization versus MR-guided high-intensity focused ultrasound treatment for symptomatic uterine fibroids. Cardiovasc Interv Radiol 2013;36:1508–13.
- 34. Froeling V, Meckelburg K, Schreiter NF, Scheurig-Muenkler C, Kamp J, Maurer MH, et al. Outcome of uterine artery embolization versus MR-guided high-intensity focused ultrasound treatment for uterine fibroids: long-term results. Eur J Radiol 2013;82:2265–9.
- 35. Ikink ME, Nijenhuis RJ, Verkooijen HM, Voogt MJ, Reuwer PJ, Smeets AJ, et al. Volumetric MR-guided high-intensity focused ultrasound versus uterine artery embolisation for treatment of symptomatic uterine fibroids: comparison of symptom improvement and reintervention rates. Eur Radiol 2014;24:2649-57.
- 36. Barnard EP, AbdElmagied AM, Vaughan LE, Weaver AL, Laughlin-Tommaso SK, Hesley GK, et al. Periprocedural outcomes comparing fibroid embolization and focused ultrasound: a randomized controlled trial and comprehensive cohort analysis. Am J Obstet Gynecol 2017;216:500.e1-500.e11.

- 37. Wang X, Qin J, Chen J, Wang L, Chen W, Tang L. The effect of high-intensity focused ultrasound treatment on immune function in patients with uterine fibroids. Int J Hyperthermia 2013;29:225–33.
- 38. Wang X, Qin J, Wang L, Chen J, Chen W, Tang L. Effect of high-intensity focused ultrasound on sexual function in the treatment of uterine fibroids: comparison to conventional myomectomy. Arch Gynecol Obstet 2013;288:851–8.
- *39. Wang F, Tang L, Wang L, Wang X, Chen J, Liu X, et al. Ultrasound-guided high-intensity focused ultrasound vs laparoscopic myomectomy for symptomatic uterine myomas. J Minim Invasive Gynecol 2014;21:279–84.
- 40. Meng X, He G, Zhang J, Han Z, Yu M, Zhang M, et al. A comparative study of fibroid ablation rates using radio frequency or high-intensity focused ultrasound. Cardiovasc Intervent Radiol 2010;33:794–9.
- 41. Bouwsma EV, Hesley GK, Woodrum DA, Weaver AL, Leppert PC, Peterson LG, et al. Comparing focused ultrasound and uterine artery embolization for uterine fibroids-rationale and design of the Fibroid Interventions: reducing symptoms today and tomorrow (FIRSTT) trial. Fertil Steril 2011;96:704-10.
- *42. Rabinovici J, David M, Fukunishi H, Morita Y, Gostout BS, Stewart EA. Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. Fertil Steril 2010;93:199–209.
- 43. Clark NA, Mumford SL, Segars JH. Reproductive impact of MRI-guided focused ultrasound surgery for fibroids: a systematic review of the evidence. Curr Opin Obstet Gynecol 2014;26:151-61.
- 44. Qin J, Chen JY, Zhao WP, Hu L, Chen WZ, Wang ZB. Outcome of unintended pregnancy after ultrasound-guided high-intensity focused ultrasound ablation of uterine fibroids. Int J Gynaecol Obstet 2012;117:273–7.
- 45. Zhou CY, Xu XJ, He J. Pregnancy outcomes and symptom improvement of patients with adenomyosis treated with high intensity focused ultrasound ablation (in Chinese). Zhonghua Fu Chan Ke Za Zhi 2016;51:845–9.
- 46. Zaher S, Lyons D, Regan L. Successful in vitro fertilization pregnancy following magnetic resonance-guided focused ultrasound surgery for uterine fibroids. J Obstet Gynaecol Res 2011;37:370–3.
- 47. Bouwsma EV, Gorny KR, Hesley GK, Jensen JR, Peterson LG, Stewart EA. et al. Magnetic resonance-guided focused ultrasound surgery for leiomyoma-associated infertility. Fertil Steril 2011;96:e9–e12.

48. Ricabinovi J, Inbar Y, Eylon SC, Schiff E, Hananel A, Freundlich D. Pregnancy and live birth after focused ultrasound surgery for symptomatic focal adenomyosis: a case report. Hum Reprod 2006;21:1255-9.

Figure Legends

- Figure 1. JC high-intensity focused ultrasound system.
- Figure 2. Real-time diagnostic ultrasound scanner integrated in the center of the therapeutic ultrasound transducer.

Table 1. Summary of the clinical trials comparing between MRgHIFU or USgHIFU, with other minimally invasive or surgical interventions.

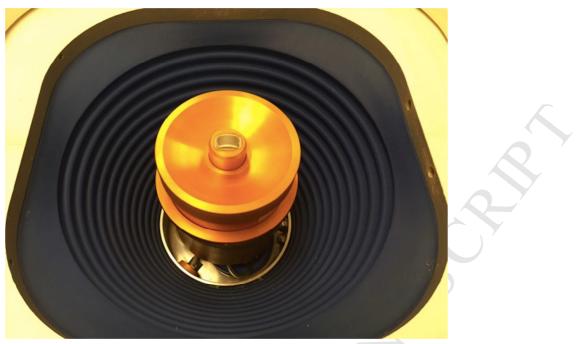
Author, Year (Country)	Study Design	Number of participants	Outcomes		
MRgHIFU versus abdomin	al hysterectomy (AH)				
Taran et al, 2009 (USA, Israel, UK, Germany) [32]	Prospective cohort	109 MRgHIFU; 83 AH	MRgHIFU had faster recevery, less clinical complications and adverse events (12.8%) than AH (39.8%); SF-36 subscale scores in MRgHIFU was worse at 6 months and had 4 treatment failures.		
MRgHIFU versus uterine artery embolization (UAE)					
Froeling et al, 2013 (Germany) [33]	Prospective cohort (mid-term results)	50 MRgHIFU; 30 UAE	MRgHIFU had less improvement in total HRQoL score, with higher reintervention rate (30.0%) than UAE (6.7%)		
Froeling et al, 2013 (Germany) [34]	Prospective cohort (long-term results)	36 MRgHIFU; 41 UAE	MRgHIFU had less improvement in symptom severity and total HRQoL scores, with higher reintervention rate (66.7%) than UAE (12.2%)		
Ikink et al, 2014 (Netherlands) [35]	Prospective cohort	51 MRgHIFU; 68 UAE	MRg-HIFU had less effect on symptom relief and HRQoL improvement than UAE. Reintervention rate after MR-HIFU (35.3%) was 7.1 times higher than after UAE (4.4)		
Barnard et al, 2017 (USA) [36]	randomized trial and comprehensive cohort (Periprocedural outcomes)	43 MRgHIFU; 40 UAE	MRgHIFU had longer treatment times, but UAE had longer recovery times and used more prescription medications		

USgHIFU versus hysterectomy and myomectomy

Chen et al, 2017 (China) [27]	Prospective cohort	1353 USgHIFU; 472 hysterectomy; 586 myomectomy	HIFU caused substantially less morbidity than surgery, with similar longer-term QoL	
USgHIFU versus myomect	omy			
Wang et al, 2013 (China) [37]	Randomized trial	60 USgHIFU; 60 AM*	USgHIFU had fewer post-operative complications, and shorter hospital stay	
Wang et al, 2013 (China) [38]	Randomized trial	48 USgHIFU; 52 AM*	No differences in sexual function between USgHIFU and AM at 3 and 6 months after treatment	
Wang et al, 2014 (China) [39]	Prospective cohort	83 USgHIFU; 39 LM*	USgHIFU led to comparable QoL and symptom improvement, fewer clinical complications and adverse events, shorter hospital stay, and faster recovery	
USgHIFU versus radiofrequency ablation (RFA)				
Meng et al, 2010 (China) [40]	Randomized trial	50 USgHIFU; 50 RFA	Complete ablation rate of USgHIFU was lower than that of RFA. No severe complications noted in both groups	

^{*} AM = abdominal myomectomy; LM = laparoscopic myomectomy





Highlights

- An overview of the background, clinical use, treatment outcomes and safety of high-intensity focused ultrasound (HIFU) in the treatment of uterine fibroids and adenomyosis is provided.
- HIFU seems to be a promising minimally invasive, uterine sparing treatment for uterine fibroids and adenomyosis, resulting in improved quality of life and diminished fibroid size.
- Studies have suggested that HIFU is relatively safe in treating uterine fibroids and adenomyosis with a small risk of advise effects notably skin burn.