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Review Article

Is High-intensity Focused Ultrasound Effective for the Treatment of Adenomyosis? A Systematic Review and Meta-analysis

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ABSTRACT **Study Objective:** To systematically review the literature regarding the efficacy of high-intensity focused ultrasound (HIFU) in reducing adenomyotic lesions, patients' pain and bleeding symptoms, and the impact on patients' quality of life.

Data Source: A search was performed through PubMed/MEDLINE and Cochrane databases.

Methods of Study Selection: All available studies published in the English language in the last 10 years that evaluated the effects of HIFU for adenomyosis.

Tabulation, Integration, and Results: A systematic review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A meta-analysis was performed on data from homogeneous studies. Pooled results from the meta-analysis showed that after HIFU treatment for adenomyosis, a large effect was observed in reducing the uterine volume at 12 months (standard mean difference [SMD] = 0.85), a significant reduction in dysmenorrhea at 3 months (SMD = 1.83) and 12 months (SMD = 2.37), and a significant improvement in quality of life at 6 months (SMD = 3.0) and 12 months (SMD = 2.75). Adverse reactions after HIFU were reported in 55.9% of patients.

Conclusion: This review suggests a potential benefit for HIFU in the treatment of adenomyosis-related symptoms; however, findings of the meta-analysis were based on fewer, nonuniform studies, which did not equally account for each specific symptom/parameter across the board. Results showed there appears to be a potential of HIFU in the treatment of adenomyosis-related symptoms. To date, there are no comparative and randomized clinical trials comparing the HIFU technique with other conservative treatment options. As yet, there are insufficient data regarding fertility and pregnancy outcomes. Journal of Minimally Invasive Gynecology (2019) 00, 1—12. © 2019 AAGL. All rights reserved.

Keywords: High-intensity focused ultrasound; Adenomyosis; Systematic review

Adenomyosis is defined as the presence of ectopic endometrial tissue within the myometrium. It is a common gynecologic disease, often found in women of childbearing age. The prevalence of adenomyosis is reported to be between 8.8% and 31%, the exact prevalence of which is difficult to determine [1]. With the recent evolution of imaging techniques, such as transvaginal ultrasonography (TVUS) and magnetic resonance imaging (MRI), the accuracy of noninvasive diagnosis of adenomyosis has improved [1].

Adenomyosis brings both an increase in absenteeism rates and a reduction in patients' quality of life. Dysmenorrhea, abnormal uterine bleeding, and infertility are often associated with the disease [2]. Medical therapies, such as progestins, intrauterine levonorgestrel-releasing systems, and gonadotropin-releasing hormone agonists, have been used for the treatment of women with adenomyosis with a desire for uterine preservation [3]. Many studies showed that medical treatment for adenomyosis improve symptoms and promote uterine volume reduction with great satisfaction rates [1]. However, limited data are available on the efficacy of medical treatment for the treatment of adenomyosis-related infertility [4].

High-intensity focused ultrasound (HIFU) was introduced in China in the 1990s as a noninvasive therapeutic technique for the treatment of malignant solid tumors of the liver, breast, pancreas, and bone [5—7]. HIFU works by concentrating ultrasound waves at the desired location using an

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external source of energy to induce thermal ablation of the tumor mass below intact skin [5]. It is a noninvasive technique noted to have low morbidity and is associated with rapid recovery [8].

HIFU has emerged as an alternative uterine-sparing option for the treatment of gynecologic conditions including leiomyomas and, recently, adenomyosis. The main objective of this study was to systematically review the literature regarding the efficacy of HIFU in reducing the adenomyotic lesion patients' pain and bleeding symptoms and the impact on patients' quality of life.

Material and Methods

Selection Criteria and Search Strategy

A thorough search of the literature was performed through PubMed/MEDLINE and Cochrane databases for studies published in the English language in the last 10 years that evaluated the effects of HIFU for adenomyosis. This systematic review was registered in PROSPERO (ID 127533; https://www.crd.york.ac.uk/prospero) and conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [9]. The last literature search was performed in March 2019. The quality of the individual studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria a tool for the quality assessment of studies included in systematic reviews [10].

The following search terms were used: "adenomyosis" and "high intensity focused ultrasound" as keywords to recover all possible publications using the PubMed and Cochrane databases. Medical Subject Headings (MeSH) terms were used as follows: ("focal adenomyosis "[Subheading] OR ("ablation treatment "[All Fields] AND "HIFU" [All Fields]) OR "diffuse adenomyosis"[All Fields] OR "HIFU"[All Fields] OR "surgical"[MeSH Terms] OR "treatment"[All Fields] OR " benign uterine disease"[All Fields] OR "high intensity ultrasound"[MeSH Terms] OR "ultrasound"[All Fields]) OR ("focal adenomyosis"[Subheading] OR ("treatment"[All Fields] AND "surgical"[All Fields]) OR "HIFU"[All Fields] OR "diffuse adenomyosis" [All Fields] OR "effects "[MeSH Terms]) OR ("infertility" [MeSH Terms] OR "HIFU"[All Fields]) OR ("reproductive desire "[Subheading] OR AND "HIFU"[All Fields])) AND ("infertility"[MeSH Terms] OR "adenomyosis therapy" [All Fields]).

The search was conducted by 2 authors (A.L.S.M. and M.P.A.). In cases of conflict, resolution was achieved by discussion with the senior authors (E.B., R.M.K., and M.S.A.). References of articles were also manually reviewed for other relevant articles.

Data Extraction

One author (A.L.S.M.) abstracted the data into tables, and another author (M.P.A.) separately verified the data for accuracy. Data obtained from the studies included the following: first author; publication year; sample size; study design; imaging tools for the diagnosis adenomyosis; and the mean values of HIFU ablation, such as treatment time, sonication time, nonperfused volume, nonperfused volume ratio (NPVR), uterine volume, and adenomyotic lesion volume.

Additional data abstracted included the presence of dysmenorrhea (defined as pelvic pain during menstrual cycle), which is evaluated using the visual analog scale (VAS, 0−10) [11] and Health Related Quality of life (HRQOL) questionnaires when available. HRQOL questionnaires included the Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire (UFS-QOL) [12]. This questionnaire accessed the severity of symptoms using 8 questions (using a 5-point Likert scale) categorized into 7 subscales (increased amount of menstrual blood loss, menstrual blood clotting, prolonged menstruation, menstrual disorders, pelvic tightness/pressure, fatigue, and frequent urination during day and night times) and the HRQOL with 29 questions (5-point Likert scale) and 6 domains (concern, activities, energy/mood, control, self-consciousness, and sexual function). Higher symptom severity scores indicate worse symptoms, whereas higher HRQOL scores denote better HRQOL.

Data on infertility were also retrieved and included the number of patients trying to achieve pregnancy during follow-up after HIFU treatment. The pregnancy rate (defined as 12 weeks pregnant with transvaginal ultrasound) and live birth rate, when available, were also abstracted.

Data regarding adverse reactions were also retrieved according to the Society of Interventional Radiology (SIR) practice guidelines [13], which classified reactions according to the following categories: grade A (no therapy, no consequence), grade B (nominal therapy required, no consequence, including overnight admission for observation only), grade C (therapy required, including minor hospitalization of less than 48 hours), grade D (major therapy required, including an unplanned increase in level of care or prolonged hospitalization for at least 48 hours), grade E (permanent adverse sequelae), and grade F (death).

The main treatment outcome measure after HIFU therapy was assessed by the amount of NPVR, which is defined as the percentage of the adenomyotic lesion without perfusion after treatment evaluated by MRI. The greater the NPVR, the better the long-term symptom relief sustained [14,15]. The duration required for HIFU treatment, defined as the time between the first sonication and the last sonication, was also abstracted from the studies.

Statistical Analysis

The results of the articles were described using mean, standard deviation, and absolute and relative frequency. The mean and standard deviation were abstracted from the studies. When not available, it was calculated from the median and range provided from the existing data [16,17]. Data from graphics were obtained using the

software WebPlot Digitizer (Ankit Rohatgi, San Francisco, CA) [18].

A meta-analysis was performed on pooled data from homogeneous studies, defined as studies that assessed outcomes using the same validated questionnaire(s) with a similar study design (i.e., assessment done pre- and post-treatment) and for the same follow-up period. Treatment outcomes evaluated for meta-analysis included uterine volume, VAS score for dysmenorrhea, and UFS-QOL questionnaire score. Meta-analysis was performed using the generic inverse variant method with random effects using RevMan software (RevMan, Windows, version 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Pooled results comparing before and after treatment outcomes were described as the standardized mean difference (SMD). An SMD of 0 means that there is no difference before and after treatment. An SMD value of 0.2 indicates a small effect of the treatment, a value of 0.5 indicates a medium effect, and a value of 0.8 or larger indicates a large effect [19]. A p value $<.05$ was considered significant.

Results

Selected Study Characteristics

Sixteen full-text studies were evaluated for inclusion, of which 7 were excluded for not reporting clinical outcomes (n = 3), not evaluating patients both before and after treatment (n = 3), and for including results from patients with myoma and adenomyosis. A total of 9 articles were included in the final systematic review for qualitative analysis synthesis [5,6,8,20−25], of which 6 homogeneous studies allowed meta-analysis [5,6,20,22,23,25] (Fig. 1). Only noncomparative studies were identified, 4 of which were retrospective [21−23,25] and 5 were prospective [5,8,20,23,24] (Table 1). There were no randomized controlled trials identified in the literature.

The main diagnostic imaging method for adenomyosis was MRI in 6 studies [5,8,20,21,23,25], TVUS in 1 study [24], and a combination of both methods in 2 studies [6,22]. The imaging criteria used for MRI diagnosis of adenomyosis in these studies were focal or uneven width of the junctional zone, low junctional zone signal, high-signal points in the T2-weighted image, scattered hemorrhagic areas within the junctional zone, and unclear zone margins. Also, junctional zone thickness greater than 30 mm on MRI was defined as diffuse adenomyosis, and an isolated lesion larger than 30 mm was defined as focal adenomyosis. The most common diagnostic imaging criterion used on TVUS was the presence of myometrium cysts. For the evaluation of adenomyosis at follow-up, enhanced MRI was used in 8 studies [5,6,8,21−23,25,26] and TVUS in 1 study [24].

Eight articles [5,6,8,21−25] evaluated the improvement of symptomatology and quality of life of patients with adenomyosis after HIFU ablation. None of the studies included patients with concurrent endometriosis. In 3 studies [6,21,24], the results of HIFU in women with myomas alone were compared with those with adenomyosis alone.

Quality Assessment

Using the QUADAS scoring system, 6 studies were classified as good and 3 as fair (Fig. 2, Table 1). Areas of deficiencies included lack of power calculation [5,6,20], loss of follow-up [23,25], unblinded evaluators [1−5,13−16], and lack of objective outcome measures [5,8,22,24].

Patient Characteristics

Baseline characteristics of patients included for treatment with HIFU are shown in Table 1. A total of 1813 patients with adenomyosis were included, with 1613 (89.0%) noted to have diffuse adenomyosis and 200 (11.0%) with focal adenomyosis. The mean age of the patients was 39.71 ± 2.1 years. The mean uterine volume before HIFU ablation was 263 ± 132 cm^3, and the mean volume of the adenomyotic lesion was 157.8 ± 99 cm^3.

There was a large variation in the mean duration of sonication time that ranged from 971.2 to 1211 seconds (Table 2). The posttreatment NPVR was reported in 6 studies [5,8,20,21,23,25] with a total of 1285 patients and ranged from 34.5% to 72.9%.

Outcome Measures

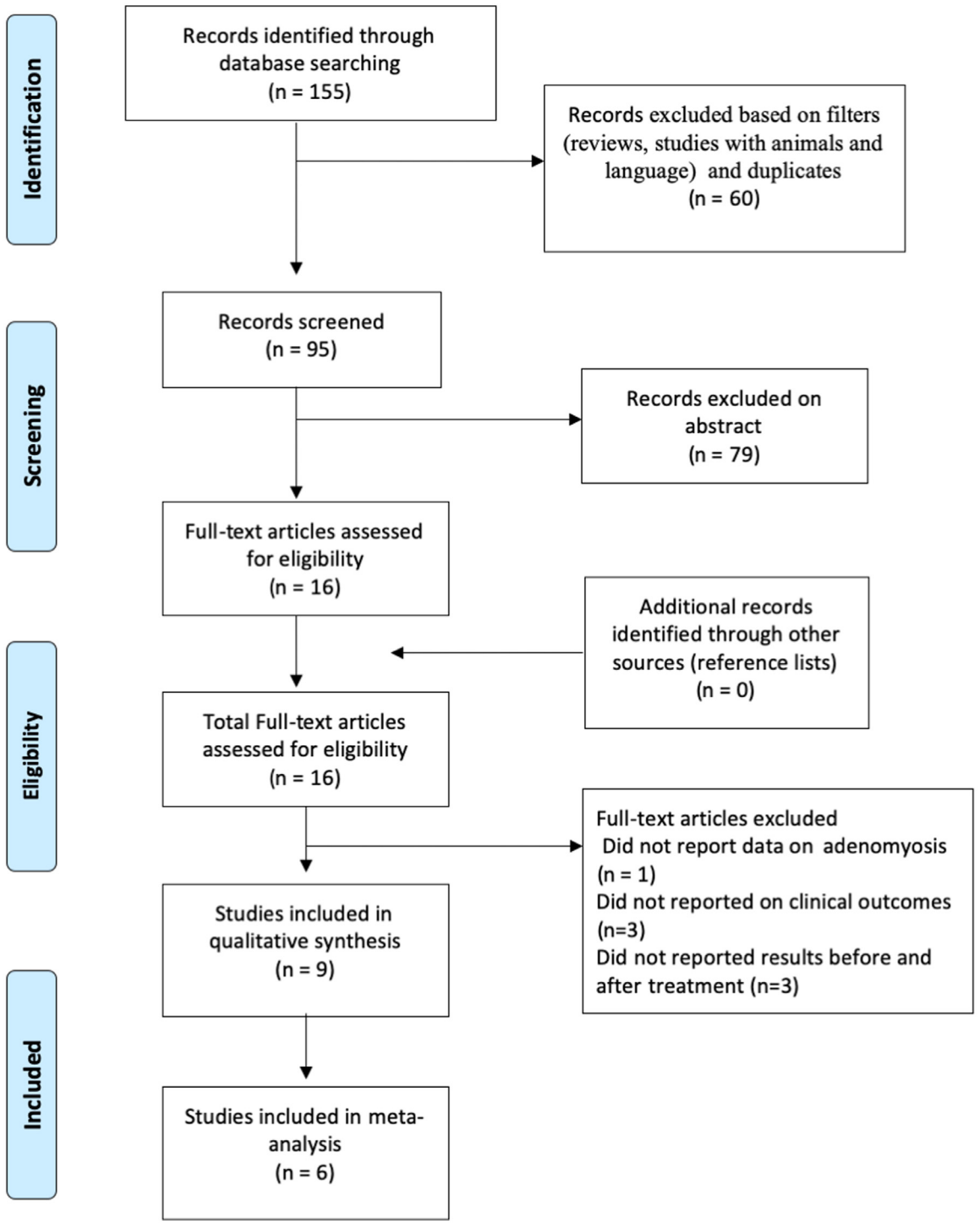
The outcome measures used in the included studies were categorized according to the reduction of uterine and adenomyosis lesion volume, the impact on symptomatology of bleeding and pain, HRQOL, and pregnancy outcomes. Adverse reactions to HIFU are also included later. None of the studies included in this systematic review evaluated for amenorrhea rate and subsequent abnormal uterine bleeding such as bothersome spotting.

Impact on Uterine Volume and Adenomyosis Lesions

Four of 9 of the included studies [5,6,8,22] with a total of 729 patients evaluated the effect of HIFU ablation on the uterine volume measured at 12 months after treatment (Table 3). The pooled results from the meta-analysis showed a significant reduction in uterine volume 12 months after HIFU treatment for adenomyosis (SMD = 0.85; 95% confidence interval [95% CI]: 0.73 −0.96; Fig. 3). Two of 9 studies [5,24] with a total of 464 patients evaluated the reduction in the size of the adenomyotic lesion after HIFU. One study [24] showed a significant reduction in adenomyosis lesion volume at

Fig. 1

A flow diagram showing the selection of articles for systematic review on HIFU treatment for adenomyosis.



3 months (299.28 ± 165.12 cm^3 to 151.25 ± 79.73 cm^3; p <.001) and 6 months (299.28 ± 165.12 cm^3 to 134.45 ± 75.86 cm^3; p <.001), and the other study [4] noted a significant reduction in adenomyotic lesions at 12 months (120.66 ± 90.52 to 84.75 ± 64.56; p <.001; Table 3).

Symptomatology of Dysmenorrhea and Abnormal Uterine Bleeding

Studies included in this systematic review used different outcome measures for the evaluation of dysmenorrhea and abnormal uterine bleeding including the VAS [11],

Table 1

Characteristics and Quality Assessment of Included Studies That Evaluated the Effect of High-intensity Focused Ultrasound for the Treatment of Patients with Adenomyosis

					Adenomyosis			Quality Assessment	
Author, Year	Study Design	Diagnostic Imaging	Age	Total (n)	Diffuse n (%)	Focal n (%)	Myoma n (%)	QUADAS	Bias Risk Assessment
Feng YH, 2017	Retrospective	MRI	38.9 ± 6.33	417	260 (62.3)	157 (37.6)	NA	Good	Not blinded, measures of interest taken one time after intervention
Lee J, 2015	Retrospective	TVUS, MRI	40.43 ± 5.0	618	346 (56.0)	NA	272 (44.0)	Good	Not blinded, p values not reported
Lee JS, 2017	Prospective	TVUS, MRI	40.5 ± 5.25	79	34 (43.0)	NA	45 (56.9)	Good	Not blinded, measures of interest taken one time after intervention, lack of power calculation
Liu XF, 2017	Prospective	MRI	42.15 ± 5.08	302	302 (100)	NA	NA	Fair	Not blinded, eligibility criteria unclear, loss of follow-up >20%
Liu X, 2016	Retrospective	MRI	39.6 ± 5.1	208	208(100)	NA	NA	Good	Not blinded
Long L, 2015	Prospective	MRI	37.43 ± 5.08	47	47 (100)	NA	NA	Good	Not blinded, lack of power calculation
Park JL, 2016	Prospective	TVUS	37.1 ± 6.5	333	192 (57.6)	NA	141 (42.3)	Fair	Not blinded, eligibility criteria unclear, not all eligible patients were enrolled, measures of interest taken one time after intervention
Shui L, 2015	Retrospective	MRI	41.6 ± 4.6	224	224 (100)	NA	NA	Fair	Not blinded, eligibility criteria unclear, loss of follow up >20%
Zhang X, 2014	Prospective	MRI	41.0 ± 5.4	43	0	43 (100)	NA	Good	Not blinded, lack of power calculation, not all eligible patients were enrolled

MRI = magnetic resonance imaging; NA = not applicable; QUADAS = quality of included studies assessed; TVUS = transvaginal ultrasound.

Fig. 2

Quality assessment of the included studies in this systematic review.

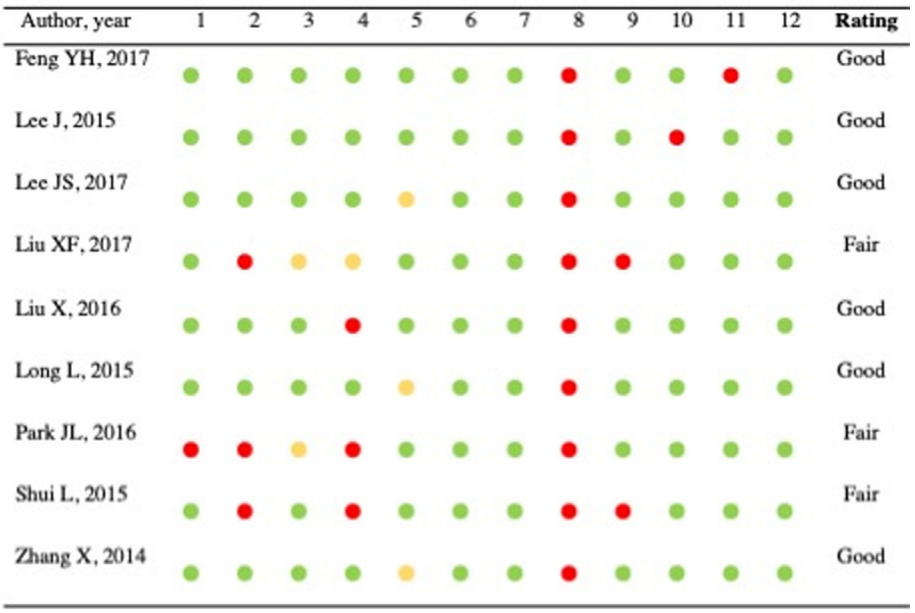


Table 2

Treatment Characteristics (Average Values) of High-intensity Focused Ultrasound Ablation

	n	Treatment Time (min)	Sonication/Ablation Time (s)	Nonperfused Volume (cm^3)	Nonperfused Volume Ratio (%)	Power (W)
Feng YH, 2017	417	85.2 ± 43.2	971.2 ± 623.45	59.65 ± 58.6	34.45	392.46 ± 20.94
Lee J, 2015	346	82.32	1049.4	NR	71.6	300–400
Lee JS, 2017	34	73.5 ± 25.6	994.7 ± 386.8	NR	NR	300–400
Liu XF, 2017	302	NR	1800	NR	NR	350–400
Liu X, 2016	208	67.50 ± 32.84	1156 ± 591.24	72.8 ± 57.3	57.39	485 ± 55
Long L, 2015	47	NR	NR	84.96 ± 72.19	61.36	300–400
Park JL, 2016	192	102	1211	NR	NR	300–400
Shui L, 2015	224	103.8 ± 59.4	1197.3 ± 744.2	49.4 ± 37.5	72.7	379.2 ± 30.8
Zhang X, 2014	43	90.7 ± 50.3	387.6 ± 20.7	NR	70.8	387.6 ± 20.7

NR = not reported.
Data expressed as mean ± standard deviation.

menstrual volume, and the Symptom Severity Score from the UFS-QOL questionnaire [12].

Four of 9 studies [5,8,20,25] with a total of 781 patients evaluated dysmenorrhea using the VAS score at 3, 6, 12, and 24 months after HIFU ablation for adenomyosis (Fig. 4). The pooled results showed a significant reduction in VAS after 3 months (SMD = 1.83; 95% CI, 1.67−1.98) and 12 months (SMD = 2.37; 95% CI, 2.19−2.55; Fig. 4). Only 1 study [8] with a total of 208 patients conducted a multivariate analysis on factors associated with clinical success of relieving dysmenorrhea (defined as greater than 20% VAS score reduction) at 3 and 6 months after HIFU ablation of adenomyosis. This study showed that greater clinical success was associated with the following factors: a higher NPVR ($p = .0001$), focal adenomyosis ($p < .01$), smaller uterine volume ($p < .001$), smaller adenomyotic lesion volume ($p < .001$), and age ≥40 years ($p = .016$).

Three of 9 studies [5,8,20] evaluated menstrual bleeding before and after HIFU ablation of adenomyosis. The results were not pooled because there were no uniform measures that could evaluate the menstrual volume between the studies. Although 1 study [8] with 302 patients showed no significant reduction in the quantitative menstrual volume after 12 months (64.3 mL to 43.7 mL, $p > .05$), the other 2

Table 3

Effect of High-intensity Focused Ultrasound on Uterine Volume and Adenomyotic Lesion

Author, Year	n	Follow-up (months)	Baseline		Posttreatment	
			Uterine Volume (cm^3)	AD Volume (cm3)	Uterine Volume (cm^3)	AD Volume (cm^3)
Feng YH, 2017	Diffuse (260) Focal (157)	3	319.0 ± 184.6 D 259.0 ± 119.7 F	238.9 ± 159.6 D 113.3 ± 78.8 F	NR	NR
Park JL, 2016	192	3, 6	NR	299.28 ± 165.12	NR	151.25 ± 79.73 (3 mo)† 134.45 ± 75.86 (6 mo)†
Lee J, 2015	346	3, 6, 12	264.14	NR	149.09 (3 mo) 131.32 (6 mo) 109.03 (12 mo)*	NR
Lee JS, 2017	34	12	222.56 ± 112.64	NR	114.57 ± 75.49*	NR
Liu XF, 2017	302	12	186.96 ± 18.16	NR	157.35 ± 8.04*	NR
Long L, 2015	47	12	331.309 ± 168.31	120.66 ± 90.52	262.07 ± 113.28*	84.75 ± 64.56*
Shui L, 2015	224	3, 12, 24	253.1 ± 109.3	62.2 ± 48.6	NR	NR
Liu X, 2016	208	40 (18−94)	274.4 ± 174.8	70.7 ± 33.0	NR	NR
Zhang X, 2014	43	6, 12	218.0 ± 73.1	49.2 ± 31.4	NR	NR

Data expressed as mean ± standard deviation.
AD, adenomyotic; D, diffuse; F, focal adenomyosis; HIFU, high-intensity focused ultrasound; NR, not reported.
* $p < .05$.
† $p < .001$.

studies found improvement in bleeding. One of these [25] showed a significant reduction in the qualitative assessment of menstrual volume in 224 patients using a 5-point scale after 3 months (2.9 ± 0.8 to 1.6 ± 0.9 points, p = .001), 12 months (1.5 ± 0.9 points, p = .001), and 24 months (1.6 ± 1.0 points, p = .001). Another study [20] also showed a significant reduction using a 5-point scale in abnormal uterine bleeding in 43 patients at 6 months (2.9 ± 1.0 to 1.4 ± 0.7, p <.05) and 12 months (1.2 ± 0.5, p <.01) after HIFU.

Three studies [5,6,22] evaluated the impact on symptoms after HIFU using the Symptom Severity Score of the UFS-QOL [12] questionnaire in a total of 427 patients with adenomyosis. The studies showed a cumulative improvement in symptom score at 3 (62.52 to 26.35, p <.05) [22], 6 (62.52 to 29.67; p <.05 [22] and 61.67 ± 22.36 to 27.6 ± 18.0; p <.05 [6]), and 12 months [62.52 to 26.37, p<0.05 [22]) after HIFU ablation.

HRQOL

Three studies [6,8,22] with a total of 682 patients evaluated for HRQOL using the UFS-QOL questionnaire [12] at 3, 6, and 12 months after HIFU treatment of adenomyosis (Table 4). The pooled results from the meta-analysis showed a significant improvement in the UFS-QOL score 6 months (SMD = 3.00; 95% CI, 2.84−3.16) and 12 months (SMD = 2.75; 95% CI, 2.59−2.90; Fig. 5).

Fertility Impact

One study [6] evaluated changes in anti-müllerian hormone (AMH) levels after HIFU ablation of 34 symptomatic patients with adenomyosis with a mean age of 40.5 ± 5.25 years (range, 24−45 years). AMH levels before and 6 months after HIFU ablation were compared to determine whether HIFU ablation affected the ovarian reserve. There was no significant difference in AMH levels before and 6 months after ablation with HIFU (2.11 ± 2.66 μg/L and 1.84 ± 2.57 μg/L, respectively; p >.05).

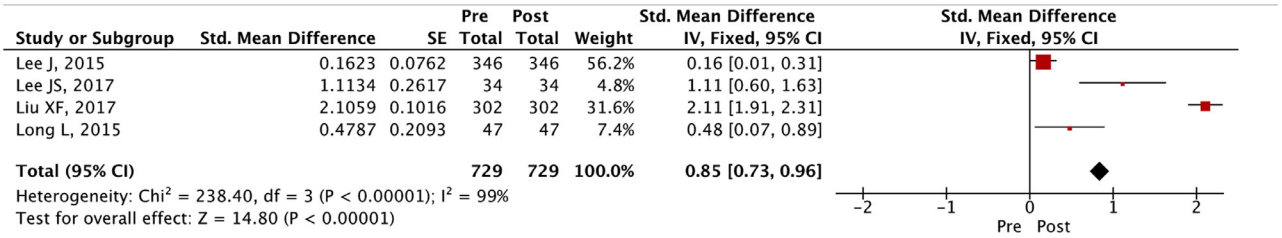
Pregnancy outcomes after HIFU were reported in only 1 series of 346 adenomyosis patients with adenomyosis with a mean age of 40.43 ± 5.0 years [22]. There were 6 pregnancies reported after intervention, of which 2 resulted in spontaneous abortion, 3 remained pregnant up to the end of the study, and 1 ended in a full-term delivery.

Adverse Reactions and Recurrence of Symptoms and Failures

Nine studies reported on adverse reactions after HIFU for adenomyosis [5,6,8,20,21,23−25,27] with a mean follow-up time of 18 months. Adverse reactions from the procedure are summarized in Table 5. According to the SIR classification system [13], of 1813 total patients, 1014 (55.9%) patients reported reactions categorized as grade A and 43 (2.4%) categorized as grade B. The most frequent adverse reactions were lower abdominal pain (n = 392, 21.6%) and pain/discomfort in the treated region (n = 233, 12.8%). The reported SIR grade B included only superficial 1° to 2° skin burns that were treated with local dressing only with complete resolution in 14 days [13]. There is little reporting on the recurrence of symptoms, the absence of efficacy or failure of HIFU, and worsening of symptoms. One study [23] reported that dysmenorrhea recurred in 45 of 173 cases (26%), and the median recurrence time was 12 months after treatment. Another study [25] reported that of the 109 patients with abnormal uterine bleeding treated by the HIFU technique, 20 (9.9%) did not respond to

Fig. 3

The meta-analysis of the effect of HIFU on the mean difference of uterine volume at baseline and at twelve months.



treatment, and 16 (7.9%) presented worsening of bleeding at the 2-year follow-up. Only 1 study had a long-term follow-up of 40 months, with 9.5% of patients lost to follow-up. None of the included studies evaluated for ovarian failure, impact on menopausal status, or abnormal uterine bleeding after HIFU.

Only 1 study [8] with 208 patients evaluated for the recurrence of symptoms after HIFU treatment of adenomyosis. After a mean follow up of 40 ± 12.6 months, recurrence of symptoms was noted in 45 of 208 (26%) patients. They reported that 72.9% of patients were symptom free after 36 months and that a greater body mass index (odds ratio = 1.222; 95% CI, 1.079−1.381; p = .001) and a lower mean acoustic intensity of HIFU (OR = 0.992; 95% CI, 0.986−0.998; p = .007) were associated with a higher recurrence rate at 3 years.

Discussion

HIFU has been used increasingly in recent years for the treatment of patients with adenomyosis. This systematic review identified 9 noncomparative studies from 2014 to 2017 and showed that there was a significant reduction in the adenomyotic lesion and uterine volume that was sustained up to 12 months after HIFU treatment. There was also a significant reduction in dysmenorrhea from pooled results in patients who were followed up to 24 months after treatment. In a few studies [3], the amount of menstrual bleeding was reduced up to 24 months in patients after HIFU. To date, there are no comparative and randomized clinical trials comparing the HIFU technique with other conservative treatments such as medical therapy, uterine artery embolization, or surgical resection. Thus far, there is limited evidence regarding the impact of HIFU on ovarian reserve, and there are insufficient data regarding pregnancy outcomes.

Previous studies have shown that the extent or severity of adenomyosis infiltrating the uterus has been found to correlate with the patient's pain [28]. These studies with histologic confirmation have shown that the severity of pelvic pain varies according to the infiltration of disease (i.e., 4.3% in grade I infiltration of the uterus, 42.4% in grade II,

Fig. 4

The meta-analysis of the effect of HIFU on the mean difference of dysmenorrhea (VAS, 0−10) at baseline and three and twelve months.

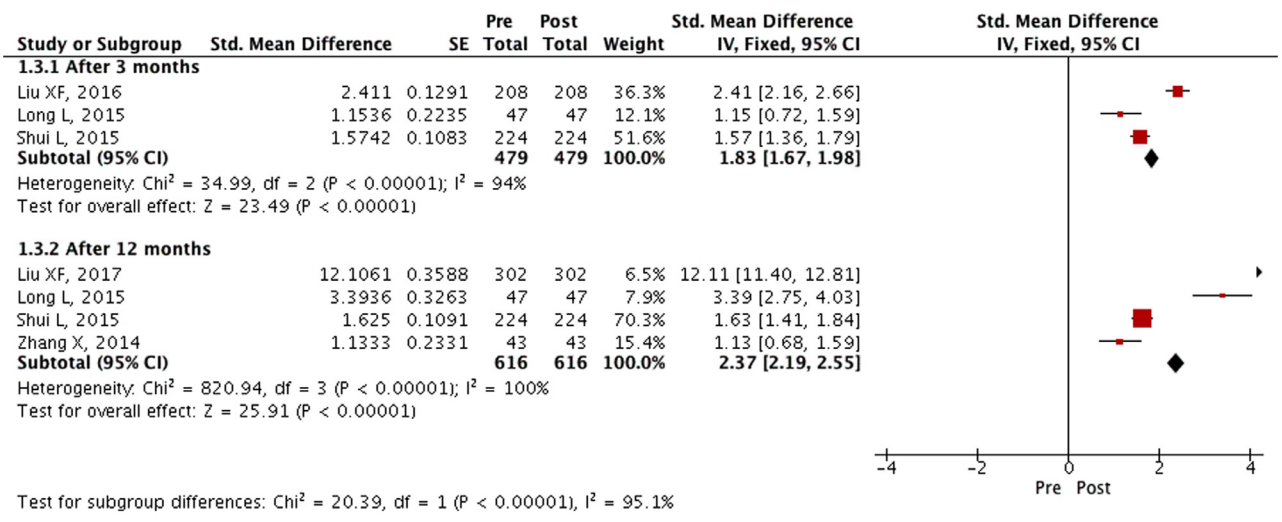


Table 4

Effect of High-intensity Focused Ultrasound on Symptoms and Quality of Life for Patients with Adenomyosis

Author, Year	n	Follow-up (months)	HRQOL			Symptom Severity Score		Symptoms Relieved (%)	Recurrence/Insufficient Effect
			Type	Pre	Post	Pre	Post		
Feng YH, 2017	417	3	NR	NR	NR	NR	NR	95.5	NR
Park JL, 2016	192	3, 6	NR	NR	NR	NR	NR	69.8	NR
Lee J, 2015	346	3, 6, 12	UFS	43.6	77.61 ± 16.6 (3 mo)* 72.99 ± 16.6 (6 mo)* 79.76 ± 16.6 (12 mo)*	62.52	26.35 (3 mo)* 29.67 (6 mo)* 26.37 (12 mo)*	95.9	7 new HIFU, 5 hysterectomies, 2 new lesions, 14 symptom recurrence
Lee JS, 2017	34	12	UFS	42.7 ± 23.2	78.49 ± 20.98 (6 mo)	61.67 ± 22.36	27.6 ± 18.0 (6 mo)*	100	NR
Liu XF, 2017	302	12	UFS	24.5 ± 8.2	66.24 ± 9.85*	NR	NR	91.0	NR
Long L, 2015	47	12	FSFI	20.8 ± 1.3	23.93 ± 2.19 (3 mo)* 27.41 ± 2.65 (6 mo)* 30.33 ± 2.89 (12 mo)*	36.6 ± 19.44	12.9 ± 10.3 (12 mo)*	100	2 patients lost follow-up, 2 became pregnant
Shui L, 2015	224	3, 12, 24	NR	NR	NR	NR	NR	82	Aggravation of AUB: 4.6%; lost follow-up: 18% (1 year) and 36% (2 years), aggravation dysmenorrhea: 7.95%
Liu X, 2016	208	40 (18−94)	NR	NR	83.2	NR	NR	93.0	22 lost to follow-up Dysmenorrhea recurrence: 42 (20.0%)

AUB = abnormal uterine bleeding; FSFI = Female Sexual Function Index; HIFU = high-intensity focused ultrasound; NR = not reported; QOL = quality of life; UFS = Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire.

* $p < .05$.

Fig. 5

The meta-analysis of the HIFU effect on the mean difference in the quality of life (QOL) score using the Uterine Fibroid Symptom questionnaire at baseline and twelve months.

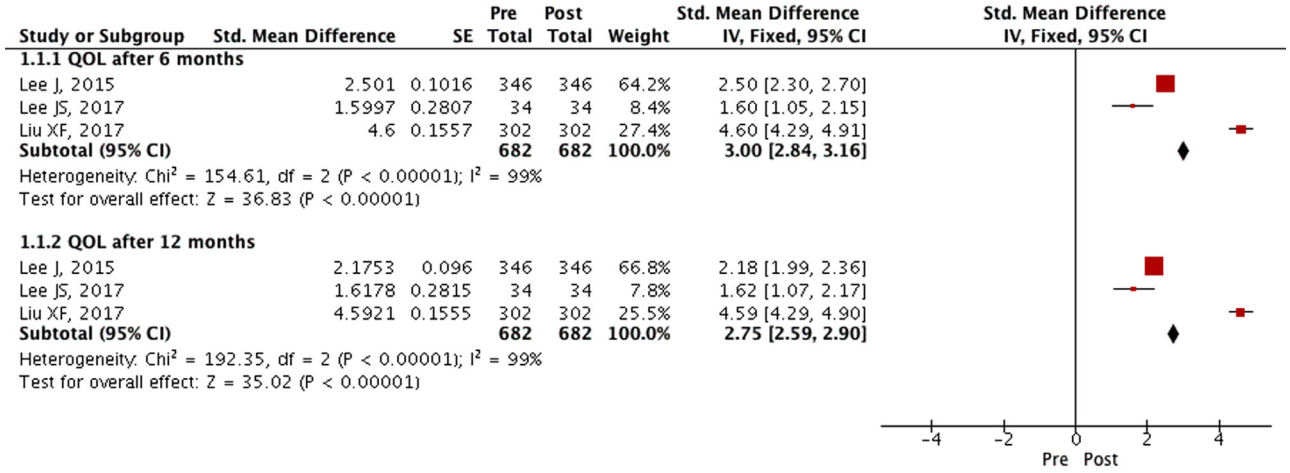


Table 5

Adverse Effects Reported of High-intensity Focused Ultrasound Ablation for Adenomyosis

Complication	SIR Grade	Total (% of Patients)
Lower abdominal pain	A	392 (21.6)
Pain or discomfort in treated region	A	233 (12.8)
Vaginal discharge	A	170 (9.4)
Sacral tail or hip pain	A	132 (7.3)
Superficial skin burn	B	43 (2.4)
Leg pain or sciatic nerve pain	A	47 (2.5)
Lower limb paresthesia	A	13 (0.7)
Transient hematuria	A	10 (0.6)
Nausea or vomiting	A	6 (0.3)
Dysuria	A	6 (0.3)
Stinging feeling in anus	A	5 (0.2)

SIR = Society of Interventional Radiology clinical practice guidelines.
Data expressed as n (%).

and 83.3% in grade III penetration) [28]. Similarly, an increasing number of ultrasound signs for adenomyosis showed a significant association with dysmenorrhea score [29]. Therefore, it appears relevant that ablation with HIFU that results in a reduction of uterine and adenomyosis volume would correlate with a reduction in pain. This systematic review and meta-analysis suggest that the HIFU ablative technique for adenomyosis resulted in a progressive reduction in uterine volume (by 43% in 3 months [21,22,24,25] and 69% in 12 months [5,6,8,22,25,26]) and size of the adenomyotic lesion (by 49.4% in 3 months [21,24,25] and 67% in 12 months [5,20,25]) over time. An improvement in HRQOL (SMD = 2.75) was also noted up to 12 months after HIFU treatment. Studies included in this review suggested an improvement of symptoms including dysmenorrhea (58%), dyspareunia (45%), and abnormal uterine bleeding (45%). However, these symptoms were not systematically assessed in all studies, and many of the studies did not have long-term follow-up. Also, studies reported a large variation in sonication time, likely related to the extent of the disease, although not specified by the authors of the studies. The length of sonification time could affect the long-term treatment outcome and impact on patient symptoms.

Adenomyosis has been suggested to be a contributing factor for infertility [30]. Moreover, patients with adenomyosis are less likely to achieve successful pregnancy after artificial reproductive therapy, with a pregnancy rate of only 28% compared with 40% in patients without adenomyosis [4]. Even with conservative surgical treatment for adenomyosis, the spontaneous pregnancy rate is low at 18% and can reach up to 40% when followed by artificial

reproductive therapy. In a study that evaluated the use of gonadotropin-releasing hormone agonist analogs for 24 weeks after surgery, the pooled spontaneous pregnancy rate was higher compared with no adjuvant therapy (40.7% vs 15.0%, p = .002) [4]. Adenomyosis has also been associated with poor pregnancy outcomes and increases the risk by 2.2 times for early miscarriages [31].

Other treatment options such as uterine-sparing surgeries for adenomyosis can be challenging. This is primarily because of the difficulty in defining the endometrial-myometrial limits in patients with diffuse adenomyosis [21,32]. By definition, resection of focal adenomyosis often results in the removal of healthy myometrium, if not, in leaving disease behind. Surgeries for adenomyosis resection have been associated with subsequent uterine rupture in pregnancy, in addition to surgical complications such as unplanned hysterectomy and ovarian failure [21,33]. In this context, the consideration of alternative adenomyosis-reduction techniques becomes relevant for symptomatic patients who desire uterine-sparing treatment.

For patients desiring fertility, HIFU may result in less uterine scarring when compared with surgery [30] although pregnancy outcomes after HIFU for adenomyosis are as yet limited with only 1 study [30] that showed 6 pregnancies and, thus far, 1 successful delivery. Therefore, recommendation of this procedure for patients desiring fertility should be approached with caution because HIFU may induce uterine necrosis and scarring and may make it susceptible to uterine rupture in a subsequent pregnancy [33].

This systematic review revealed that the overall rates of severe adverse effects and complications after HIFU for the treatment of adenomyosis were low at 2.8%. The most common bothersome symptoms were lower abdominal pain, pain or discomfort in the treated region, vaginal discharge, and superficial skin burns [23,25].

The strengths of this systematic review include an extensive literature search and methodology following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Critical assessment of each of the studies was performed by multiple evaluators following the QUADAS system, and, when appropriate, a meta-analysis was also conducted. By nature of a systematic review, the limitations in the ability to make conclusive statements are defined by the methodologies implemented by the included studies. At this time, the evidence on the efficacy of HIFU is from noncomparative studies that evaluated only symptomatic premenopausal women with no pelvic adhesions, no history of previous lower abdominal surgery, a body weight <100 kg, and abdominal wall thickness <5 cm. Generalization of the results from this review would be limited to this patient population. Also, in all selected studies, patients with severe pelvic endometriosis and/or pelvic adhesions were excluded, despite the fact that adenomyosis and endometriosis have many common presenting features and can be associated in about 35% of the time [34]. Multicenter studies involving a large and diverse group of patients that compare the short- and long-term efficacy of HIFU with other uterine-sparing modalities are still needed to contribute to the current gap in the literature.

Conclusions

This review suggests a potential benefit for HIFU in the treatment of adenomyosis-related symptoms; however, findings of the meta-analysis were based on fewer, nonuniform studies, which did not equally account for each specific symptom/parameter across the board. To date, there are no comparative and randomized clinical trials and studies comparing the HIFU technique with other conservative treatment options. Further studies are highly needed to ensure that this therapy is a safe mode for women who desire future fertility or uterine preservation.

References

1. Abbott JA. Adenomyosis and abnormal uterine bleeding (AUB-A)-pathogenesis, diagnosis, and management. *Best Pract Res Clin Obstet Gynaecol*. 2017;40:68–81.
2. Vannuccini S, Petraglia F. Recent advances in understanding and managing adenomyosis. *F1000 Res*. 2019;8:283.
3. Ozdegirmenci O, Kayikcioglu F, Akgul MA, et al. Comparison of levonorgestrel intrauterine system versus hysterectomy on efficacy and quality of life in patients with adenomyosis. *Fertil Steril*. 2011;95:497–502.
4. Rocha TP, Andres MP, Borrelli GM, Abrão MS. Fertility-sparing treatment of adenomyosis in patients with infertility: a systematic review of current options. *Reprod Sci*. 2018;25:480–486.
5. Long L, Chen J, Xiong Y, et al. Efficacy of high-intensity focused ultrasound ablation for adenomyosis therapy and sexual life quality. *Int J Clin Exp Med*. 2015;8:11701–11707.
6. Lee JS, Hong GY, Lee KH, Kim TE. Changes in anti-müllerian hormone levels as a biomarker for ovarian reserve after ultrasound-guided high-intensity focused ultrasound treatment of adenomyosis and uterine fibroid. *BJOG*. 2017;124:18–22.
7. Cheung VYT. High-intensity focused ultrasound therapy. *Best Pract Res Clin Obstet Gynaecol*. 2018;46:74–83.
8. Liu XF, Huang LH, Zhang C, Huang GH, Yan LM, He J. A comparison of the cost−utility of ultrasound-guided high-intensity focused ultrasound and hysterectomy for adenomyosis: a retrospective study. *BJOG*. 2017;124:40–45.
9. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.
10. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol*. 2003;3:25.
11. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain*. 1983;17:45–56.
12. Coyne KS, Soliman AM, Margolis MK, Thompson CL, Chwalisz K. Validation of the 4 week recall version of the Uterine Fibroid Symptom and Health-related Quality of Life (UFS-QOL) Questionnaire. *Curr Med Res Opin*. 2017;33:193–200.
13. Sacks D, McClenny TE, Cardella JF, Lewis CA. Society of Interventional Radiology clinical practice guidelines. *J Vasc Interv Radiol*. 2003;14:S199–S202.

14. Wang W, Wang Y, Tang J. Safety and efficacy of high intensity focused ultrasound ablation therapy for adenomyosis. *Acad Radiol*. 2009;16:1416–1423.
15. Zhou M, Chen J-Y, Tang L-D, Chen W-Z, Wang Z-B. Ultrasound-guided high-intensity focused ultrasound ablation for adenomyosis: the clinical experience of a single center. *Fertil Steril*. 2011;95:900–905.
16. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27:1785–1805.
17. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
18. Rohatgi A. WebPlotDigitizer. 2011. Available at: https://automeris.io/WebPlotDigitizer. Accessed April 15, 2019.
19. Faraone SV. Interpreting estimates of treatment effects: implications for managed care. *P T*. 2008;33:700–711.
20. Zhang X, Li K, Xie B, He M, He J, Zhang L. Effective ablation therapy of adenomyosis with ultrasound-guided high-intensity focused ultrasound. *Int J Gynaecol Obstet*. 2014;124:207–211.
21. Feng Y, Hu L, Chen W, Zhang R, Wang X, Chen J. Safety of ultrasound-guided high-intensity focused ultrasound ablation for diffuse adenomyosis: a retrospective cohort study. *Ultrason Sonochem*. 2017;36:139–145.
22. Lee J, Hong G, Park B, Kim T. Ultrasound-guided high-intensity focused ultrasound treatment for uterine fibroid & adenomyosis: a single center experience from the Republic of Korea. *Ultrason Sonochem*. 2015;27:682–687.
23. Liu X, Wang W, Wang Y, Wang Y, Li Q, Tang J. Clinical predictors of long-term success in ultrasoundguided high-intensity focused ultrasound ablation treatment for adenomyosis a retrospective study. *Medicine (Baltimore)*. 2016;95:e2443.
24. Park J, Lee JS, Cho JH, Kim S. Effects of high-intensity-focused ultrasound treatment on benign uterine tumor. *J Korean Med Sci*. 2016;31:1279–1283.
25. Shui L, Mao S, Wu Q, et al. High-intensity focused ultrasound (HIFU) for adenomyosis: two-year follow-up results. *Ultrason Sonochem*. 2015;27:677–681.
26. Zhang X, Zou M, Zhang C, et al. Effects of oxytocin on high intensity focused ultrasound (HIFU) ablation of adenomysis: a prospective study. *Eur J Radiol*. 2014;83:1607–1611.
27. 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;27:682–687.
28. Gordts S, Grimbizis G, Campo R. Symptoms and classification of uterine adenomyosis, including the place of hysteroscopy in diagnosis. *Fertil Steril*. 2018;109. 380−388.e1.
29. Naftalin J, Hoo W, Pateman K, Mavrelos D, Foo X, Jurkovic D. Is adenomyosis associated with menorrhagia. *Hum Reprod*. 2014;29:473–479.
30. Dueholm M. Minimally invasive treatment of adenomyosis. *Best Pract Res Clin Obstet Gynaecol*. 2018;51:119–137.
31. Dueholm M. Uterine adenomyosis and infertility, review of reproductive outcome after in vitro fertilization and surgery. *Acta Obstet Gynecol Scand*. 2017;96:715–726.
32. Farquhar C, Brosens I. Medical and surgical management of adenomyosis. *Best Pract Res Clin Obstet Gynaecol*. 2006;20:603–616.
33. Bohlmann MK, Hoellen F, Hunold P, David M. High-intensity focused ultrasound ablation of uterine fibroids - potential impact on fertility and pregnancy outcome. *Geburtshilfe Frauenheilkd*. 2014;74:139–145.
34. Di Donato N, Montanari G, Benfenati A, et al. Prevalence of adenomyosis in women undergoing surgery for endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2014;181:289–293.