BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.14739
www.bjog.org

Uterine Fibroids & Adenomyosis

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

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Accepted 13 June 2017.

Objective To assess the changes in antimüllerian hormone (AMH) levels after ablation for symptomatic uterine fibroids and adenomyosis using ultrasound-guided high-intensity focused ultrasound (USgHIFU).

Design A prospective study.

Setting Gynaecological department in multiple hospitals in South Korea.

Population Patients with uterus fibroids and adenomyosis.

Methods Seventy-nine women with symptomatic uterine fibroids and adenomyosis who met the inclusion criteria were enrolled in our study between January 2014 and December 2014. All patients underwent USgHIFU ablations. Each patient was examined before and after treatment, and at 6 and 12 months after treatment by T2-weighted MRI imaging (T2WI) and T1-weighted MRI imaging (T1WI) with gadolinium injection. Symptom severity scores (SSS), Uterine Fibroid Symptom Quality of Life (UFS-QOL) questionnaire subscales, and reductions of treated volume were assessed. AMH levels before and 6 months after HIFU ablation were compared to determine whether USgHIFU ablation affected ovarian reserve.

Main outcome measures HIFU treatment did not affect the ovarian function.

Results HIFU treatment time (mean ± standard deviation), HIFU ablation time, and treatment energy were 73.5 ± 25.6 minutes, 9994.7 ± 386.8 seconds, and 364 713.8 ± 156 350.7 Joules, respectively. AMH levels before and 6 months after HIFU ablation were 2.11 ± 2.66 and 1.84 ± 2.57 μg/l, respectively. There was no significant difference in AMH level between the two time points ($P > 0.05$).

Conclusions USgHIFU ablation for uterine fibroid and adenomyosis was effective without affecting ovarian reserve.

Keywords Adenomyosis, antimüllerian hormone, HIFU, ovarian reserve, uterine fibroid.

Tweetable abstract HIFU ablation is a safe and effective treatment for patients with uterine fibroids and adenomyosis that does not affect ovarian function.

Please cite this paper as: Lee J-S, Hong G-Y, Lee K-H, Kim T-E. 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 (S3): 18–22.

Introduction

Uterine fibroids are the most common benign genital tract tumours, and adenomyosis is the most frequently seen benign disorder of the uterus in women of reproductive age. Recently, reduced fertility and late parturition have been partially attributed to the increased incidence of uterine fibroid and adenomyosis. Various symptoms of the two disorders include dysmenorrhea, menorrhagia, vaginal haemorrhage, subfertility, and infertility. Currently, myomectomy and hysterectomy remains the treatment of choice for uterine fibroids and adenomyosis.

Radiofrequency (RF), uterine artery embolisation (UAE), and high intensity focused ultrasound (HIFU) have also been used in the treatment of uterine fibroids and adenomyosis.[1–4]

As a non-invasive technique, HIFU has the advantages of few adverse events and short hospital stay. However, no study has investigated whether HIFU treatment could affect ovarian function. Antimüllerian hormone (AMH) is an effective indicator to evaluate ovarian reserve in that the value is not affected by menstrual cycle of women. It reaches its highest level after puberty and gradually decreases over time in normo-ovulatory women.[5–9] The aim of this study is to evaluate the changes in AMH levels of patients with uterine fibroids or adenomyosis 6 months after HIFU treatment.

Materials and methods

The diagnosis of uterine fibroids and adenomyosis was made by medical history and physical examination, ultrasound (US), and magnetic resonance imaging (MRI). We included patients with symptomatic uterine fibroids and adenomyosis. The exclusion criteria were: (1) pedunculated uterine fibroids, asymptomatic uterine fibroids <5 cm in diameter; (2) asymptomatic focal adenomyosis; (3) an abdominal wall thickness of more than 5 cm; (4) suspected malignancy; (5) evidence of known or suspected extensive pelvic adhesions such as a history of acute pelvic inflammatory disease and severe pelvic endometriosis; (6) patients with body mass index (BMI) > 25, a history of smoking, alcohol, endocrine disease, polycystic ovarian disease, lower abdominal surgery including ovarian surgery, and chemotherapy prior to this treatment were also excluded.

HIFU ablation

HIFU treatment was performed using the Model JC Focused Ultrasound Tumor Therapeutic System (Chongqing Haifu Medical Technology, Chongqing, China).

Before the HIFU procedure, skin and bowel preparations and bladder volume controls with sterile saline were performed. During treatment, midazolam, propofol and fentanyl were intravenous injected for sedation and pain control in patients while 300–400 W levels of energy with HIFU were applied to a lesion. The condition of patients was monitored for 12 hours after treatment, and then oral prophylactic antibiotics and anti-inflammatory agents were prescribed before discharge. The decrease in lesion volume after HIFU treatment was measured in longitudinal (D1), anteroposterior (D2), and axial (D3) on MRI before and 6 months after treatment, and the measured data were evaluated using the equation below.

$$V = 0.5233 \times D1 \times D2 \times D3$$

Follow up

The effects and recurrences in all subjects of this study were examined by T2-weighted MRI imaging (T2WI) and T1-weighted MRI imaging (T1WI) with administration of gadolinium injection at pre-, post- and 6-month follow ups after treatment.

AMH test

Blood samples of 10 ml were taken before and 6 months after HIFU ablation and allowed to clot. Samples were centrifuged and the extracted serum was stored at −22°C within 3 hours until enzyme-immunometric assay (DSL, Webster, TX, USA). Inter- and intra-assay coefficients of variation were below 5% at 3 μg/l, and below 11% at 13 μg/l. The detection limit of the assay was 0.026 μg/l.

Statistical analysis

Statistical analyses were performed using R version 3.0.2.[10] Continuous variables with normal distribution were compared using paired *t*-test and grouped variables were compared using analysis of variance (ANOVA). If AMH level at each time point was not normally distributed, paired Wilcoxon's rank-sum test was used for comparing AMH levels. Statistical significance was defined as $P < 0.05$.

The improved symptoms and patient satisfaction were evaluated before and 6 months after treatment by the Symptom Severity Score (SSS) and Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire subscales.

Results

Demographic characteristics

The mean age of these patients was 40.5 years (range, 24–45 years). Of the 79 patients, 38 were nulliparous and 41 were multiparous. A total of 12 patients underwent caesarean section.

Treatment results

Therapeutic data of 45 patients with uterine fibroid and 34 patients with adenomyosis are summarised in Table 1

Table 1. Therapeutic data of the 79 patients participated in this study

	Mean ± SD
Treatment time (minutes)	73.5 ± 25.6
Ablation time (seconds)	994.7 ± 386.8
Treatment energy (Joules)	364 713.8 ± 156 350.7
AMH level before HIFU (μg/l)	2.11 ± 2.66
AMH level 6 months after HIFU (μg/l)	1.84 ± 2.57

SD, standard deviation.

HIFU treatment time (mean ± standard deviation), HIFU ablation time, and treatment energy were 73.5 ± 25.6 minutes, 994.7 ± 386.8 seconds, and 364 713.8 ± 156 350.7 Joules, respectively.

Pretreatment uterine fibroid volume, SSS, and UFS–QOL score were 174.02 ± 136.47 cm^3, 50.01 ± 7.81, and 61.27 ± 21.58, respectively. At 6 months after HIFU ablation, uterine fibroid volume, SSS, and UFS–QOL score had changed to 69.06 ± 56.93 cm^3, 22.06 ± 14.38, and 83.21 ± 20.53, respectively ($P < 0.01$, Table 2). Pretreatment uterine adenomyosis volume, SSS, and UFS–QOL score were 222.56 ± 112.64 cm^3, 61.57 ± 22.36, and 42.69 ± 23.19, respectively. At 6 months after HIFU ablation, uterine adenomyosis volume, SSS, and UFS–QOL score were 111.54 ± 75.49 cm^3, 27.64 ± 18.02, and 78.49 ± 20.98, respectively ($P < 0.01$, Table 3). All patients had regular cycles (28–35 days) before the treatment and at 6 months after HIFU ablation. AMH levels before and at 6 months after HIFU ablation were 2.11 ± 2.66 and 1.84 ± 2.57 μg/l, respectively. There was no significant difference in AMH level between the two time points ($P > 0.05$, shown in Figure 1).

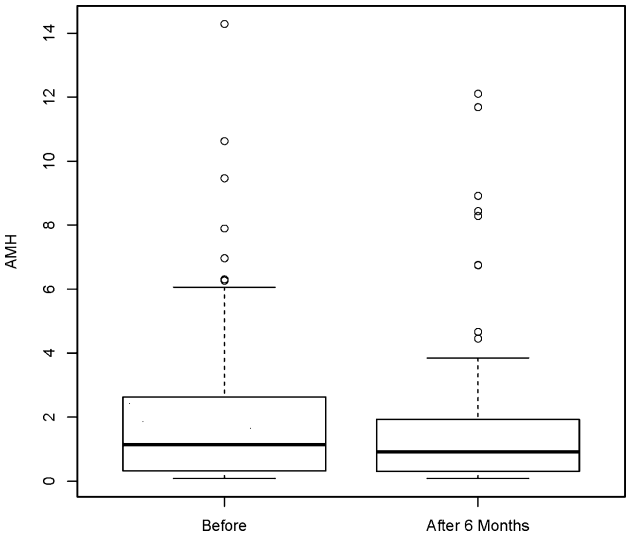

Figure 1. AMH levels after HIFU ablation for uterine fibroids and adenomyosis. AMH levels (μg/l) before and at 6 months after HIFU were not significantly different by Wilcoxon's rank sum test (*P*-value = 0.4709).

Discussion

HIFU is considered an alternative treatment for uterine fibroids and adenomyosis. Several studies have shown that HIFU is a safe non-invasive therapy with low rate of complication and speedy recovery of normal lifestyle in 1 day.[11–14] Ren et al. have reported that the reduction rates at 3, 6, and 12 months after USgHIFU ablation of fibroids were 27.2, 47.9, and 50.3%, respectively.[15] Wang et al.[16] have reported that the reduction rates at 3, 6, 12, and 24 months after USgHIFU ablation of fibroids were 46.7, 68.2, 78.9, and 90.1%, respectively. Our previous report showed that the uterine fibroid volume reduction rates compared to initial uterine fibroid volume at 3, 6, and 12 months after treatment were 58.08, 66.18, and 77.59%, respectively. Compared with the initial uterine fibroid SSS, the SSS reduction rates at 3, 6, and 12 months were 55.58, 52.76, and 50.39%, respectively. Compared with the initial uterine fibroid UFS-QOL score, the UFS-QOL rates at 3, 6, and 12 months after the treatment had increased to 42.66, 43.50, and 43.45%. The uterine volume reduction rates for adenomyosis compared to the initial uterine volume at 3, 6, and 12 months after the treatment were 43.99%, 47.01%, and 53.98%, respectively. Compared with the initial adenomyosis, SSS rates at 3, 6, and 12 months after the treatment had decreased to 55.61, 52.38, and 57.98%, respectively. Compared with the initial adenomyosis, the UFS-QOL scores had increased at 3, 6, and 12 months after the treatment to 80.06, 69.39, and 85.07%, respectively.[14]

AMH is a glycoprotein hormone belonging to transforming growth factor ß superfamily.[17] It is the only factor expressed exclusively in the gonads.[18] Serum concentrations of AMH are decreased over time in young normo-ovulatory women. However, there is no change in other markers associated with ovarian ageing such as FSH, inhibin B,

Table 2. Response of 45 uterine fibroids after HIFU ablation

	Mean ± SD		*P*-value
	Pre-treatment	6 months after treatment	
Uterine fibroid volume (cm^3)	174.02 ± 136.47	69.06 ± 56.93	<0.01*
SSS	50.01 ± 7.81	22.06 ± 14.38	<0.01*
UFS-QOL score	61.27 ±21.58	83.21 ± 20.53	<0.01*

SD, standard deviation; SSS, Symptom Severity Score. *Paired *t*-test.

Table 3. Response of 34 adenomyosis after HIFU ablation

	Mean ± SD		*P*-value
	Pretreatment	6 months after treatment	
Uterine adenomyosis volume (cm^3)	222.56 ± 112.64	111.54 ± 75.49	<0.01*
SSS	61.57 ± 22.36)	27.64 ± 18.02)	<0.01*
UFS-QOL score	42.69 ± 23.19)	78.49 ± 20.98)	<0.01*

SD, standard deviation; SSS, Symptom Severity Score. *Paired *t*-test.

estradiol, and the number of ovarian follicles on ultrasonography.[6,19,20] Others have reported that AMH is more strongly related to ovarian follicular status comapred with serum inhibin B, estradiol, FSH, or LH on cycle day 3.[21] Furthermore, serum AMH level has significantly greater reproducibility and cost-effectiveness compared with other markers of ovarian follicular status.[22]

Several studies have shown that serum AMH level was temporarily reduced after myomectomy, but it returned to its preoperative level in a short time. After hysterectomy, AMH level significantly decreased for 3 months. Hysterectomy appeared to affect reserve and function of ovaries significantly compared with myomectomy.[23] In another report regarding the effect of UAE and hysterectomy on ovaries, AMH levels were significantly decreased during the entire follow-up period in both treatment groups (UAE and hysterectomy) compared with expected AMH levels due to ageing, indicating that both UAE and hysterectomy could affect ovarian reserve.[24] In our study, despite a relatively small number of patients and a relatively short follow-up period, no significant difference in AMH level was found between pretreatment and 6 months after HIFU ablation. This could be explained by the fact that the ovary and its vessels are not involved in the treatment area. Therefore, HIFU ablation did not damage the ovarian blood flow. Our preliminary data suggest that HIFU ablation is effective for treatment of uterine fibroids and adenomyosis without affecting ovarian reserve.

Conclusion

In summary, this preliminary study has shown that AMH level did not change after HIFU treatment. Although further studies with large sample size are needed to explore the long-term outcome, the results of our study provide evidence that HIFU ablation is an effective treatment for uterine fibroids and adenomyosis without affecting ovarian reserve.

Disclosure of interests

The authors have no potential conflicts of interest to disclose.

Detail of ethics approval

The Ethics Committee on this study was approved by Incheon Christian Hospital.

Contribution to authorship

Jae-Seong Lee: data acquisition; analysis and interpretation; drafting the article and final approval of the version to be published. Gi-Youn Hong, Kye-Hwa Lee: data acquisition; analysis and interpretation; final approval of the version to be published. Tae-Eung Kim: responsible for the initial concept, data acquisition and final review of the manuscript.

Funding

This study was not funded.

Acknowledgements

We are grateful to the patients who participated in this study. Yong-Jae Yang contributed equally to this manuscript. ■

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