

Ovarian Reserve After Ultrasound-Guided High-Intensity Focused Ultrasound for Uterine Fibroids: Preliminary Experience

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Abstract

Objective: To determine the effect on ovarian reserve of ultrasound-guided high-intensity focused ultrasound (HIFU) in the treatment of uterine fibroids.

Methods: We performed a mid-study analysis of markers of ovarian reserve using data from a prospective cohort study evaluating the safety of ultrasound-guided HIFU for uterine fibroids. Blood samples obtained from 12 women with uterine fibroids less than one week before treatment were used for measurement of serum anti-Müllerian hormone (AMH), and this testing was repeated in the first, third, sixth, and 12th month after ultrasound-guided HIFU treatment.

Results: Fourteen fibroids from 12 patients were treated using ultrasound-guided HIFU. The median baseline fibroid volume was 101.2 cm³ (range 18.5 to 349.2 cm³). The median treatment time was 140.5 minutes (46 to 192 minutes), and median sonication time was 1449 seconds (range 541 to 2445 seconds). The median energy delivered was 575 521.5 joules (range 216 400 to 898 273 joules). The median AMH levels (ng/mL) before treatment and at one, three, six, and 12 months after treatment were 0.3 (range 0.01 to 1.94), 0.47 (0.01 to 1.43), 0.205 (0.01 to 1.81), 0.26 (0 to 2.37), and 0.06 (0.02 to 1.04), respectively. There was no significant difference between the AMH levels before and at any time after treatment. No patient became amenorrheic or reported symptoms suggestive of menopause after treatment.

Conclusion: Our preliminary experience suggests that ovarian reserve does not seem to be affected by ultrasound-guided HIFU in the treatment of uterine fibroids.

Résumé

Objectif : Déterminer l'effet des ultrasons focalisés de haute intensité (UFHI) guidés par échographie sur la réserve ovarienne, dans le traitement des fibromes utérins.

Méthodes : Nous avons réalisé une analyse mi-étude des marqueurs de la réserve ovarienne en nous appuyant sur les données d'une étude de cohorte prospective ayant permis d'évaluer l'innocuité des UFHI guidés par échographie dans le traitement des fibromes utérins. Des échantillons sanguins prélevés auprès de 12 femmes présentant des fibromes utérins, moins d'une semaine avant le traitement, ont servi à mesurer les concentrations sériques de l'hormone antimüllérienne (HAM). Nous avons répété cette analyse aux premier, troisième, sixième et douzième mois ayant suivi le traitement fondé sur les UFHI guidés par échographie.

Résultats : Quatorze fibromes présents chez 12 patientes ont fait l'objet d'un traitement fondé sur les UFHI guidés par échographie. Le volume médian de base des fibromes était de 101,2 cm³ (intervalle de 18,5 à 349,2 cm³). La durée médiane du traitement a été de 140,5 minutes (intervalle de 46 à 192 minutes) et la durée médiane de sonication a été de 1 449 secondes (intervalle de 541 à 2 445 secondes). Le niveau médian d'énergie libérée lors des traitements a été de 575 521,5 joules (intervalle de 216 400 à 898 273 joules). Les concentrations médianes de l'HAM (ng/ml) avant le traitement, puis aux premier, troisième, sixième et douzième mois après le traitement, ont été de 0,3 (intervalle de 0,01 à 1,94), de 0,47 (0,01 à 1,43), de 0,205 (0,01 à 1,81), de 0,26 (0 à 2,37) et de 0,06 (0,02 à 1,04), respectivement. Nous n'avons constaté aucun écart significatif entre les concentrations d'HAM mesurées avant le traitement, puis à tout autre moment à la suite de cette intervention. Aucune patiente n'a connu d'aménorrhée ni n'a fait mention de symptômes laissant présumer la survenue de la ménopause à la suite du traitement.

Conclusion : Notre expérience préliminaire laisse entendre que les UFHI guidés par échographie ne semblent pas nuire à la réserve ovarienne, dans le cadre du traitement des fibromes utérins.

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Key Words: Anti-Müllerian hormone, fibroids, high-intensity focused ultrasound

Competing interests: None declared.

Received on November 18, 2015

Accepted on January 21, 2016

<http://dx.doi.org/10.1016/j.jogc.2016.02.006>

INTRODUCTION

Uterine fibroids, a common gynaecologic disorder among reproductive-aged women, can be asymptomatic but also can give rise to significant symptoms, most commonly abnormal uterine bleeding and pelvic discomfort.^{1,2} Many minimally invasive treatment options are available for the management of uterine fibroids, including uterine artery embolization or occlusion and radiofrequency ablation.¹ UAE has a long track record and has been shown to be effective in properly selected patients.¹ However, radiofrequency ablation lacks long-term data¹ and still is considered investigational in our institution.

Recently, high-intensity focused ultrasound therapy has received increasing interest in the management of uterine fibroids.¹ This form of treatment induces focal thermocoagulation of the fibroids. Although it has been shown in some studies to be safe, effective, and acceptable to patients,^{2–5} its overall clinical efficacy and safety have not been well-established. MRI and, more recently, ultrasound have been used to target and monitor the ablation process.^{2,6} In 2012, the use of ultrasound-guided HIFU as a treatment option for uterine fibroids was introduced in our centre, to be used as a research tool and potentially a clinical service in the future.²

When contemplating the best course of treatment for uterine fibroids in reproductive-aged women, it is important to consider the potential impact of the procedures on ovarian reserve because ovarian dysfunction can lead to accelerated onset of menopause and diminished fertility. To concentrate ultrasound waves in the fibroid, HIFU uses an external ultrasound energy source to induce thermal ablation of the fibroid deep under the intact skin.² Although this treatment specifically targets the centre of fibroids, 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.

Ovarian reserve can be estimated using various methods, including sonographic identification of stromal blood flow and antral follicle count and measurement of serum FSH, estradiol, and anti-Müllerian hormone levels.⁷ Serum AMH measurement is considered to be more useful and reliable

than other tests because its measurement is not influenced by menstrual cycle changes and the use of hormones, and a decrease in AMH levels can occur before detection of increased levels of FSH.^{7–9}

The objective of this study was to examine the possible impact of ultrasound-guided HIFU on ovarian reserve. The study was performed in a cohort of women who were being recruited for a prospective study evaluating the therapeutic efficacy of HIFU in the treatment of uterine fibroids. To our knowledge, no previous study has addressed this issue, and we believe that if HIFU treatments are to continue, evidence that HIFU does not have a significant effect on ovarian function is needed.

METHODS

This study was conducted as part of an ongoing prospective study on the therapeutic efficacy of HIFU in the treatment of uterine fibroids and was focused on the possible effects of this treatment on ovarian function. Women who were premenopausal, over 40 years with their family completed, and with fibroid symptoms not controlled by standard medical therapies were eligible for the study. Women with a uterus larger than a 20 weeks' gestation uterus, fibroid(s) more than 10 cm in diameter, pedunculated fibroids, or features suggestive of malignancy were excluded. We also excluded women with a thick abdominal wall (more than 5 cm as measured using MRI), a history suggestive of possible extensive pelvic adhesions (such as a history of pelvic inflammatory disease, major abdominal surgery, or pelvic endometriosis), and a history of hormone therapy including oral contraceptives within the preceding six months. More than 50 women were screened for eligibility, but only 12 were considered eligible and agreed to participate in the study. Signed informed consent was obtained from all patients.

A detailed medical history was obtained from each woman, followed by a gynaecological examination, transabdominal and transvaginal ultrasound assessment, and MRI. Although signal intensity of T2-weighted MRI and vascularity on ultrasound imaging were assessed as possible indicators of subsequent therapeutic effect,¹⁰ these findings were not used as criteria for eligibility in our study. In addition, post-treatment non-perfused volume^{2,10} was not measured because we did not have access to MRI shortly after treatment, and we believed that the degree of reduction in fibroid volume and improvement in symptoms were more relevant indicators of successful treatment. Fibroid volume was measured in longitudinal, anteroposterior, and transverse dimensions and was calculated using the following formula: $V = 0.5233 \times$

ABBREVIATIONS

AMH	anti-Müllerian hormone
HIFU	high-intensity focused ultrasound
UAE	uterine artery embolization

$D1 \times D2 \times D3$, where V indicates fibroid volume; $D1$, longitudinal dimension; $D2$, anteroposterior dimension; and $D3$, transverse dimension.

Over the past 10 years, ultrasound-guided HIFU has been used in our centre to treat solid tumours.¹¹ The procedure is performed using the JC HIFU system (Chongqing Haifu Technology, Chongqing, China; [Figure 1](#)). A therapeutic ultrasound transducer with a frequency of 0.8 MHz and a diameter of 12 cm ([Figure 2](#)), which focuses ultrasound energy at a focal length of 15 cm, is used for the treatment. A diagnostic probe of frequency 3.5 MHz ([Figure 2](#)), situated in the centre of the therapeutic transducer, allows for real-time ultrasound monitoring during HIFU treatment. Both transducers are submerged in a water reservoir filled with degassed water. During treatment, the location of the transducers, water flow, and the acoustic output power (which can be up to 400 W) are controlled through a master computer unit.²

Before HIFU treatment, all patients undergo mechanical bowel preparation. The lower anterior abdominal wall is shaved and the urinary bladder is catheterized to control bladder volume. With patients in the prone position and under the influence of intravenous conscious sedation, the lower abdominal skin is put in contact with degassed water, with minimal displacement of the focused area. Using an acoustic power output of 350 to 400 W in slices of 5 mm, and with the guidance of real-time ultrasound monitoring, the majority of the fibroid is ablated.² The adequacy of ablation also is determined by the degree of greyscale changes noted in the real-time ultrasound monitor.¹²

Blood samples were obtained for measurement of serum AMH one week or less before treatment and at one, three,

Figure 2. Real-time diagnostic ultrasound scanner integrated in the centre of the therapeutic ultrasound transducer



six, and 12 months after treatment. All AMH levels reported in this study were measured in a single run via enzyme-linked immune analysis with an AMH Gen II enzyme-linked immunosorbent assay kit (Beckman Coulter Inc., Brea, CA).

Statistical analysis using the Mann-Whitney test was used to compare AMH levels before and after treatment. A P -value of <0.05 was considered statistically significant.

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

RESULTS

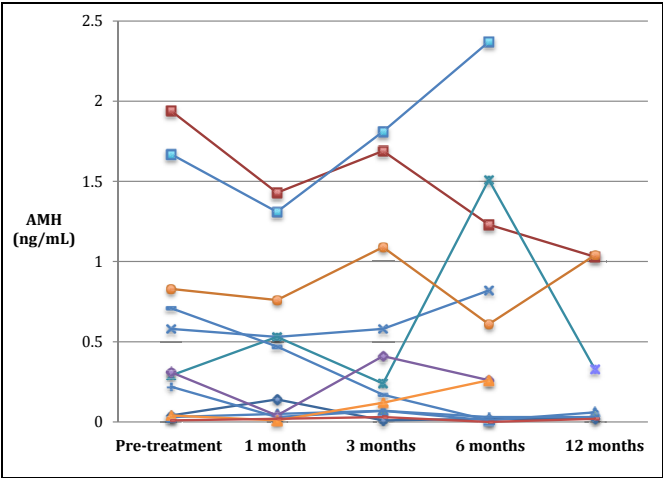
The study involved 12 patients with a mean age ($\pm$ SD) at the time of treatment of 46.3 ± 3.3 years (range 41 to 51 years). Ten of the 12 patients (83.3%) were multiparous. Fourteen fibroids were treated with HIFU; the median baseline fibroid volume was 101.2 cm^3 (range 18.5 to 349.2 cm^3). The median treatment time and median sonication time were 140.5 minutes (range 46 to 192 minutes) and 1449 seconds (range 541 to 2445 seconds), respectively. The median energy delivered was 575 521.5 joules (range 216 400 to 898 273 joules).

Of the 12 treated patients, all completed six months of follow-up, but only seven patients completed 12 months of follow-up. The AMH levels of each patient and the median AMH levels before treatment and at one, three, six, and 12 months after treatment are shown in [Figure 3](#) and the [Table](#), respectively. There was no statistically significant

Figure 1. JC high-intensity focused ultrasound system



Figure 3. AMH levels of each patient



difference between the AMH levels before or at any time after treatment. No patient became amenorrheic or reported symptoms suggestive of menopause.

One patient had a minor skin burn with blister formation; this resolved without sequelae. The most common adverse event after treatment was pelvic and back pain of mild degree, occurring in four patients. In two patients, the pain lasted less than one week, and in the other two patients the pain resolved within three months. There was no other adverse event in the post-treatment period.

DISCUSSION

In this study, we found that there was no change in AMH levels in premenopausal women who underwent ultrasound-guided HIFU for uterine fibroids within a period of six to 12 months, suggesting that ovarian reserve was unlikely to be affected by this treatment modality. Despite the small number of patients, this preliminary analysis was informative because the findings are reassuring with regard to the effect of HIFU treatment on ovarian reserve.

The effect on ovarian reserve of certain modalities for treating uterine fibroids, notably hysterectomy and UAE,

has been a matter for concern, as shown in measurements of FSH and AMH levels at baseline and after treatment.^{13–16} Hysterectomy interrupts the utero-ovarian ligament and anastomosing vessels and has been shown to advance the age of menopause by four years compared with women who do not undergo hysterectomy.¹³ UAE potentially affects the collateral blood supply to the ovaries.¹⁷ Immediately after UAE, complete loss of ovarian perfusion in some women has been demonstrated on ultrasound.¹⁸ Moreover, histopathological assessment has demonstrated the presence of embolization particles in ovarian tissue.^{19,20} HIFU, on the other hand, does not cause anatomical distortion or occlusion of the ovarian blood supply and thus does not affect ovarian perfusion. This may be an advantage of HIFU over hysterectomy or UAE in the treatment of fibroids, but this observation will need to be confirmed by further studies.

AMH differs from other markers of ovarian reserve in that it is independent of menstrual cycle fluctuations and is able to demonstrate early ovarian reserve changes, whereas FSH and estradiol levels can only be used to determine the long-term consequences of ovarian insult.^{7–9} Some women in our study cohort had low baseline AMH levels (Figure 3), which could be explained by the fact that all our patients were over 40 and potentially perimenopausal. Whether our findings apply to younger women of reproductive age undergoing HIFU requires further evaluation.

The primary limitation of this study is the small sample size, which precluded drawing firm conclusions from the data. Other markers of ovarian reserve, including serum FSH, serum estradiol, ovarian volume, and antral follicle count, were not assessed. Furthermore, the duration of follow-up was only 12 months. However, to our knowledge, this is the first study to evaluate the effects of HIFU on ovarian reserve in premenopausal women. Despite these limitations, until further evidence is available, our findings provide important safety information on the effect of HIFU on ovarian reserve for women who are considering HIFU as a treatment modality for fibroids.

CONCLUSION

Using AMH as a marker, our findings suggest that ovarian reserve is not affected by ultrasound-guided HIFU in the treatment of uterine fibroids in premenopausal women over age 40.

ACKNOWLEDGEMENTS

The authors thank Dr. Raymond Li for his advice on AMH measurement and Dr. S.F. Ngu for her assistance in

Table. Serum AMH levels before and after treatment		
	AMH level (ng/mL)	
	Median	Range
Pre-treatment	0.3	0.01 to 1.94
Post-treatment		
1 month	0.47	0.01 to 1.43
3 months	0.205	0.01 to 1.81
6 months	0.26	0 to 2.37
12 months (n = 7)	0.06	0.02 to 1.04

the initial planning of this study. Both are members of the Department of Obstetrics and Gynaecology, Queen Mary Hospital, Hong Kong.

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