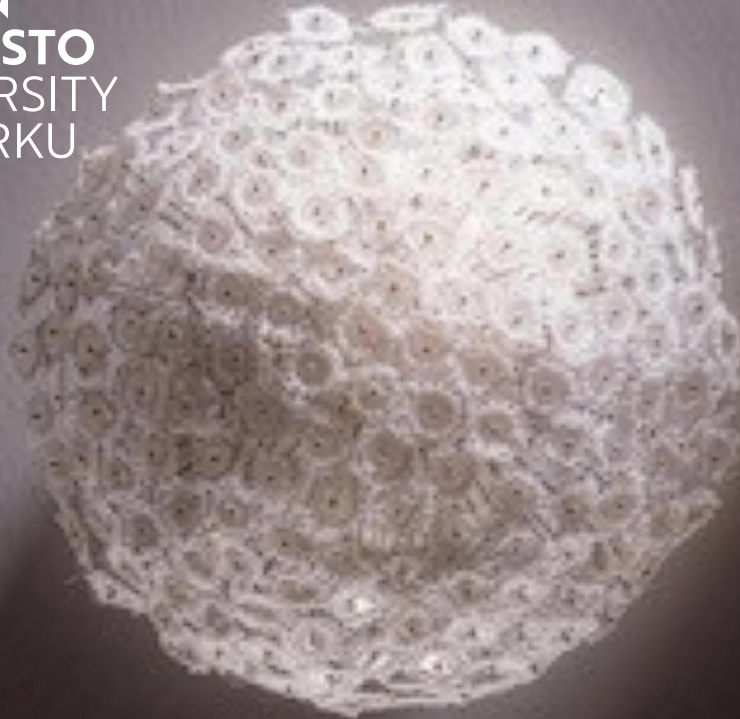




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Magnetic resonance- guided high-intensity focused ultrasound for the treatment of uterine fibroids

Saara Otonkoski



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MAGNETIC RESONANCE- GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND FOR THE TREATMENT OF UTERINE FIBROIDS

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ISBN 978-952-02-0520-1 (PRINT)
ISBN 978-952-02-0521-8 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2026

To all my loved ones

UNIVERSITY OF TURKU

Faculty of Medicine

Institute of Clinical Medicine, Department of Obstetrics and Gynecology

SAARA OTONKOSKI: Magnetic resonance-guided high-intensity focused ultrasound for the treatment of uterine fibroids

Doctoral Dissertation, 130 pp.

Doctoral Program in Clinical Research

February 2026

ABSTRACT

Uterine fibroids are common benign tumors of the uterus. Treatment options include various medical, surgical, and radiological approaches. Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) is a relatively novel, noninvasive, uterus-sparing technique for treating fibroids. However, not all fibroids can be successfully ablated with MR-HIFU; fibroid perfusion is one of the most important prognostic factors for treatment success. This study investigated the safety and efficacy of MR-HIFU in the treatment of fibroids. The effect of administration of oxytocin on fibroid blood flow was assessed by comparing dynamic contrast enhanced MR images obtained without and with administration of oxytocin to 17 women with uterine fibroids and 11 controls. In addition, the effect of MR-HIFU on ovarian reserve was evaluated by measuring the anti-Müllerian hormone (AMH) levels of 74 women before treatment and three months afterward. The efficacy of MR-HIFU in reducing fibroid-related symptoms and improving the patients' quality of life (QoL) was assessed using the fibroid-specific Uterine Fibroid Symptom and Quality of Life (UFS-QoL) questionnaire up to 12 months post-treatment in 174 women. The effect of the treatment on the two primary fibroid-related symptoms, bleeding and bulk symptoms, was further analyzed in 163 women presenting with an isolated symptom. Major part of these participants overlapped with those included in the earlier study. The findings showed that oxytocin significantly reduced uterine fibroid blood flow, from a median of 39.9 (IQR 21.9–134.5) ml/100 g/min to 3.5 (IQR 2.1–12.1) ml/100 g/min ($p < 0.0001$, power = 0.87). MR-HIFU did not affect the ovarian reserve significantly: the median AMH was 1.20 (IQR 0.72–2.21) $\mu\text{g/l}$ before treatment and 1.23 (IQR 0.66–2.37) $\mu\text{g/l}$ three months afterward ($p = 0.90$). MR-HIFU effectively alleviated fibroid-related symptoms, bleeding as well as bulk symptoms. At 12 months, compared with baseline, QoL scores had improved and symptom severity had decreased significantly ($p < 0.01$). These improvements were observed across all symptomatic patients and in the subgroup with isolated bleeding or bulk symptoms. In conclusion, MR-HIFU was a safe and effective treatment for relieving fibroid symptoms and for improving quality of life over a 12-month follow-up period. Oxytocin reduced fibroid blood flow effectively and may serve as a potential adjunct for enhancing treatment efficacy.

KEYWORDS: fibroid, high-intensity focused ultrasound, oxytocin, ovarian reserve, symptoms, quality of life

TURUN YLIOPISTO

Lääketieteellinen tiedekunta

Kliininen laitos, Synnytys- ja naistentautioppi

SAARA OTONKOSKI: Magneettiohjattu korkeaintensiteettinen kohdennettu ultraäänihoito myoomien hoidossa

Väitöskirja, 130 s.

Turun kliininen tohtoriohjelma

Helmikuu 2026

TIIVISTELMÄ

Myoomat ovat yleisiä, hyvänlaatuisia kohdun lihaskasvaimia. Myoomien hoitovaihtoehtoja ovat lääkkeelliset, kirurgiset sekä radiologiset hoidot. Magneettiohjattu korkeaintensiteettinen kohdennettu ultraäänihoito (Magnetic resonance-guided high-intensity focused ultrasound, MR-HIFU) on uudenlainen kajoamaton, kohdun säästävä hoitomenetelmä, jota voidaan käyttää myoomien hoidossa. Kaikki myoomat eivät sovellu MR-HIFU-hoitoon ja myoomien verenvirtaus on yksi keskeinen hoidon onnistumistulokseen vaikuttava tekijä. Tässä tutkimuksessa selvitettiin MR-HIFU-hoidon tehoa ja turvallisuutta myoomien hoidossa. Tutkimuksessa arvioitiin oksitosiinin vaikutusta myooman verenkiertoon tekemällä dynaaminen varjoainetehosteinen magneettikuvaus 17 myoomapotilaalle ja 11 verrokkihenkilölle ilman oksitosiinia ja oksitosiinin kanssa. MR-HIFU-hoidon vaikutusta potilaiden munasarjareserviin tutkittiin mittaamalla 74 naiselta anti-Müllerian-hormonin (AMH) pitoisuudet ennen hoitoa ja kolme kuukautta hoidon jälkeen. Tutkimuksessa selvitettiin myös MR-HIFU-hoidon tehoa myoomaoireisiin myoomaspesifisen oire- ja elämänlaatukselyn avulla 12 kuukauden seurannan ajan 174 potilaalta. Lisäksi tutkittiin MR-HIFU-hoidon tehoa kahteen erilliseen myoomaoireeseen (vuoto- ja paineoireeseen) 163 potilaalle; näistä potilaista merkittävä osa oli samoja kuin edellisessä tutkimuksessa. Tutkimuksen tulokset osoittivat, että oksitosiini vähentää myoomien verenvirtausta merkittävästi. Verenvirtauksen mediaani ilman oksitosiinia oli 39,9 (IQR 21,9–134,5) ml/100g/min ja oksitosiinin kanssa 3,5 (IQR 2,1–12,1) ml/100g/min, ($p < 0.0001$, power=0.87). MR-HIFU-hoito ei aiheuttanut merkittävää muutosta potilaiden munasarjareserviin, sillä AMH-arvojen mediaani ennen hoitoa oli 1,20 (IQR 0,72-2,21) $\mu\text{g/l}$ ja hoidon jälkeen 1,23 (IQR 0,66-2,37) $\mu\text{g/l}$ ($p=0,90$). Tutkimuksessa todettiin, että MR-HIFU-hoito on tehokas myoomaoireiden hoitomenetelmä: potilaiden elämänlaatu parani ja oireet lievenivät merkittävästi 12 kuukauden seurannassa ($p<0.01$) sekä kaikilla myoomaoireisilla että niillä potilailla, joilla on erillinen vuoto-oire tai paineoire. Yhteenvetona todetaan, että MR-HIFU on tehokas ja turvallinen myoomaoireiden lievittämisen ja elämänlaadun parantamisen menetelmä. Oksitosiini vähentää tehokkaasti myoomien verenkiertoa, ja tätä ominaisuutta voidaan käyttää MR-HIFU-hoidon tehostamiseksi.

AVAINSANAT: myooma, korkeaintensiteettinen kohdennettu ultraääni, oksitosiini, munasarjareservi, oireet, elämänlaatu

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Abbreviations

AFC	Antral follicle count
ADC	Apparent diffusion coefficient
AMH	Anti-Müllerian hormone
BPA	Bisphenol A
DCE	Dynamic contrast enhanced
DES	Diethylstilbestrol
DWI	Diffusion weighted imaging
EDC	Endocrine disrupting chemicals
FDA	Food and drug administration
FH	Fumarase hydrate
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone
HIFU	High intensity focused ultrasound
HRQL	Health-related quality of life
HSD	Honestly significant difference
IQR	Interquartile range
LNG-IUD	Levonorgestrel-intrauterine-device
LH	Luteinizing hormone
MWA	Microwave ablation
MRI	Magnetic resonance imaging
MR-HIFU	Magnetic resonance-guided high-intensity focused ultrasound
NPV	Non-perfused volume
NPV%	Non-perfused volume ratio
NPV/TFL	Non-perfused volume/total fibroid load
NSAID	Non-steroidal anti-inflammatory drug
QoL	Quality of life
QALY	Quality adjusted life year
ROI	Region of interest
SIR	Society of interventional radiology
SHBG	Sex hormone binding globulin
SSS	Symptom severity score

SUI	Stress urinary incontinence
TVUS	Transvaginal ultrasound
T1W	T1-weighted
T2W	T2-weighted
UFS-QoL	Uterine fibroid symptom and quality of life
UAE	Uterine artery embolization
USGS	Ultrasound guided sclerotherapy

List of original publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals I–IV.

- I Otonkoski S, Sainio T, Komar G, Suomi V, Saunavaara J, Blanco Sequeiros R, Perheentupa A, Joronen K. Oxytocin selectively reduces blood flow in uterine fibroids without an effect on myometrial blood flow: a dynamic contrast enhanced MRI evaluation. *Int J Hyperthermia* 2020;37(1):1293–1300.
- II Otonkoski S, Sainio T, Mattila S, Blanco Sequeiros R, Perheentupa A, Komar G, Joronen K. Magnetic resonance-guided high-intensity focused ultrasound for uterine fibroids and adenomyosis has no effect on ovarian reserve. *Int J Hyperthermia* 2023; 40(1): 2154575. doi: 10.1080/02656736.2022.2154575.
- III Otonkoski S, Viitala A , Komar G, Sainio T, Yanovskiy A, Blanco Sequeiros R, Perheentupa A, Joronen K. Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) effectively reduces fibroid-related symptoms and improves quality of life -a prospective single-centre 12-month follow-up study. *Acta Obstetricia et Gynecologica Scandinavica*, 2025 Jun; 104(6):1172–1180.
- IV Otonkoski S, Viitala A, Komar G, Sainio T, Yanovskiy A, Lehtonen I, Perheentupa A, Blanco Sequeiros R, Joronen K. Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) therapy of uterine fibroids effectively reduces both bleeding and bulk symptoms-a prospective single-centre 12-month follow-up study, Manuscript.

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1 Introduction

Uterine fibroids are the most common benign tumors in women, affecting more than two-thirds of women of reproductive age. Although fibroids are usually asymptomatic, approximately one-third of women experience fibroid-related symptoms that markedly impair the patients' Quality of life (QoL) (Stewart et al. 2017). The most frequent manifestations include heavy or irregular menstrual bleeding, pelvic pressure, increased urinary frequency, and lower abdominal pain. In addition, fibroids may impair fertility and complicate pregnancy (Vannuccini et al. 2024).

Health-related QoL is a patient-reported measure encompassing the physical, social and emotional consequences of a medical condition. Several validated instruments have been developed to assess health-related QoL. The Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QoL) is a disease-specific tool designed to evaluate the impact of fibroid symptoms and treatment outcomes (Spies et al. 2002). Given the benign nature of fibroids, symptom relief and improvement in QoL should remain the primary goals of therapy, which should be as safe and non-invasive as possible (Jacoby et al. 2016).

Uterine-preserving therapies are particularly important for women desiring future fertility, and the impact of these therapies on ovarian reserve must be taken into consideration when choosing appropriate treatment. Anti-Müllerian hormone (AMH) is regarded as a reliable biomarker for assessing ovarian reserve (Moolhuijsen et al. 2020).

Medical, surgical, and radiological therapies are available to alleviate fibroid-related symptoms. Medical management serves as a convenient first-line approach, particularly for bleeding symptoms. While hormonal treatments may reduce fibroid volume and associated symptoms, their benefits typically wane after discontinuation. Radiological treatments are based on ablation of the fibroids and are effective in treating fibroid symptoms (Morris et al. 2023). Radiological interventions require specialized equipment and expertise, which limits accessibility. Surgical removal, although effective, carries the risks of complications associated with surgery. Optimal treatment selection should consider several factors, including patient age,

symptom profile, fertility intentions, and characteristics of the fibroids (size, location, number, and structure).

Tumor ablation is an effective and safe treatment for various conditions and carries a lower risk of complications than surgery (Liang et al. 2021). Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) uses focused ultrasound energy to induce thermal ablation and tissue necrosis within the target area (Bachu et al. 2021). Magnetic resonance imaging (MRI) provides precise anatomical visualization and real-time thermometry, ensuring superior treatment accuracy compared with other imaging modalities. MR-HIFU is a noninvasive, radiation-free, and outpatient-compatible therapy, and constitutes a promising therapeutic alternative for patients with symptomatic fibroids. Patient selection is based on clinical assessment, symptom evaluation, and MRI characteristics (Knorren et al. 2024; Palumbo et al. 2021; Verpalen et al. 2019; Keserci et al. 2018; Funaki et al. 2007).

Although MRI is not routinely required for diagnosis, it provides valuable information about fibroid structure and vascularity, factors critical for determining the suitability of radiological therapies. Signal intensity on T2-weighted (T2W) images is a well-established predictor of MR-HIFU success (Funaki et al. 2007). Fibroid vascularity serves as an important prognostic indicator: highly vascular fibroids are less responsive to MR-HIFU due to increased heat dissipation and a lower temperature rise in the target tissue (Andrews et al. 2019). These findings have prompted interest in pharmacological modulation of fibroid blood flow to enhance treatment efficacy (Łoziński et al. 2021).

The introduction of new therapeutic modalities into clinical practice requires evaluation of safety, efficacy, and integration into public healthcare systems. Scientific and technical innovation should be driven by patient-centered objectives. The aim of this research was to assess the effect of oxytocin on the blood flow of fibroids and its potential to enhance treatment efficacy, to evaluate the impact of MR-HIFU on ovarian reserve, and to examine the effects of MR-HIFU on fibroid-related symptoms and QoL.

2 Review of the literature

2.1 Uterine fibroids

Uterine fibroids, also known as leiomyomas, are the most common tumors in women. They are hormonally dependent benign tumors. Macroscopically fibroids are usually round-shaped, and their structure ranges from solid to soft. Histologically, they consist of smooth muscle and fibroblasts, with an excessive amount of extracellular matrix. The size, location, imaging appearance, histological structure and also the behavior of fibroids vary (Banerjee et al. 2022). Fibroids are typically surrounded by a pseudocapsule, which separates the fibroid tissue from the surrounding myometrium (Yang et al. 2022). Figure 1 shows fibroids removed surgically from the uterus.



Figure 1. Uterine fibroids removed from the uterus by myomectomy.

2.1.1 Prevalence of uterine fibroids

The prevalence of uterine fibroids is estimated to be as high as 70% in women by age 50, but the figure varies by study design, diagnostic methods, and population. Although most women are asymptomatic, it is estimated that 30% of women with fibroids have various fibroid-related symptoms (Giuliani et al. 2020; Stewart et al. 2017).

The prevalence rates of uterine fibroids in the U.S. are based largely on data from hospital discharge summaries and large prospective cohort studies. Rates range from 12.8 per 1000 person-years (all diagnoses: ultrasound, pelvic examination, or hysterectomy) to two per 1000 person-years for hysterectomy-confirmed cases (Wise et al. 2016, Okolo et al. 2008). Women of African descent have the highest prevalence of uterine fibroids. Their risk of having a fibroid is two to three times higher than that of other populations (Anchan et al. 2023). In a large U.S. cohort of nearly two million women, 4.4% received a fibroid diagnosis during the follow-up time of 13 years. Women of African descent had a more than three times greater age-standardized incidence of fibroid diagnoses compared to white women (incidence rate range 3.11; 95% CI, 3.05-3.17) (Mitro et al. 2025). In an older, large international internet-based survey that included nearly 22,000 women, the women's self-reported prevalence of uterine fibroids ranged from 4.5% in the UK to 9.8% in Italy (Zimmermann et al. 2012)

2.1.2 Pathogenesis of uterine fibroids

The current understanding of the pathogenesis of uterine fibroid covers a broad range of mechanisms, including genetic and epigenetic alterations, hormonal regulation, autocrine and paracrine growth factors, and environmental and metabolic influences. Fibroids arise from a single smooth muscle cell in the myometrium, i.e., fibroids are monoclonal in nature. Increasing evidence supports that they originate from stem cells (Yang et al. 2022; Ciarmela et al. 2022; Giuliani et al. 2020). The factors identified as risk or protective factors in fibroid development are presented in more detail in Table 1.

Table 1. Factors associated with the risk of developing uterine fibroids.

Increased risk for fibroids	Decreased risk for fibroids
+ Increasing age ^{1,2}	- High parity ^{2,3}
+ Ethnicity of African descent ^{1,2}	- Breastfeeding ¹⁴
+ Family history ¹	- Use of oral contraceptives (some evidence) ^{1,5}
+ Genetic disorders (HLRCC, translocation between chromosomes 12 and 14) ^{5,6}	- Diet rich in green vegetables and flavonoids ^{15, 16, 17}
+ Obesity ^{7,8,9}	- Physical exercise, ¹⁸
+ Hypertension ⁹	
+ Early menarche, late menopause ^{1,5,10}	
+ Nulliparity ^{2,3}	
+ Vitamin D deficiency ^{11, 12}	
+ Stress ^{2,10}	
+ Alcohol consumption, smoking (unclear) ³	
+ Endocrine disrupting chemicals ¹³	
+ Alterations in the microbiome ³	

1 (Stewart et al. 2017) , 2 (Pavone et al. 2018), 3 (Yang et al. 2022), 4 (Ooi, 2020), 5 (Dolmans et al. 2024), 6 (He et al. 2022), 7 (Ciavattini et al. 2017), 8 (Sommer et al. 2015), 9 (Boynton-Jarrett et al. 2005), 10(Salehi et al. 2023), 11(Vahdat et al. 2022), 12 (Combs et al. 2023), 13 (Bariani et al. 2020), 14 (Delli Carpini et al. 2019), 15 (Tinelli et al. 2021), 16 (Takala et al. 2019), 17 (Wise et al. 2011), 18 (Baird et al. 2007)

2.1.2.1 Genetic predisposition and risk factors for fibroid development

Many gene alterations have been associated with the etiology of uterine fibroids. *MED12* is the most frequently mutated gene in fibroids (He et al. 2022). The *MED12* is a so-called transcriptional regulator and its inactivation results in the upregulation of growth factor-beta (TGF- β). This affects genes encoding excessive extracellular matrix and collagen formation. *MED12* mutations occur more frequently in women of African than non-African descent (He et al. 2022). Other genes related to uterine fibroids are *HMGA*, *COL4A5* and *COL4A* (Yang et al. 2022; Pavone et al. 2018).

Some genetic disorders such as the Hereditary Leiomyomatosis and Renal Cell Cancer syndrome (HLRCC) increase the risk of uterine fibroids substantially. HLRCC is an autosomal dominant hereditary cancer syndrome. In the fibroids of these patients, loss of the fumarate hydratase (FH) enzymatic function is always detected histochemically in the tumor tissue (Ooi, 2020). A translocation between

chromosomes 12 and 14 is also a known risk factor for uterine fibroids in adolescent patients (Yang et al. 2022).

Besides genetic predisposition, numerous other acquired factors affect the risk of uterine fibroid development. Research in this area is challenging because most fibroids are asymptomatic, which, again, introduces bias into epidemiological data. (Yang et al. 2022; Giuliani et al. 2020; Stewart et al. 2017).

2.1.2.2 Role of steroid hormones in uterine fibroids

Uterine fibroids are known to be dependent on estrogens and progesterone (Banerjee et al. 2022), the key steroid hormones acting in the female reproductive system. Fibroblasts in the uterine fibroid tissue contain both estrogen and progesterone receptors. Estrogen stimulation leads to proliferation of fibroblast cells. Fibroblasts are apparently also more sensitive to estrogen stimulation than normal myometrial cells (Luo et al. 2014). Furthermore, estrogens increase the expression of progesterone receptors in fibroids which amplifies the tissue response to progesterone (Dolmans et al. 2024; Yang et al. 2022; Maclean et al. 2022; Bulun et al. 2015).

Progesterone stimulates cellular proliferation and the accumulation of extracellular matrix. It affects also cellular apoptosis. The proliferation of fibroid cells is most active during the secretory phase of the menstrual cycle where progesterone levels are high (Maclean et al. 2022).

2.1.3 Classification of uterine fibroids

Uterine fibroids are a heterogeneous group of tumors. Conventional or typical fibroids account for up to 90% of the uterine fibroids. The remaining fibroids can be categorized into various subtypes, which include cellular leiomyomas (characterized by increased cellularity), lipoleiomyomas (containing mature fat cells), apoplectic leiomyomas (involving hemorrhagic changes), and hydropic leiomyomas (with significant fluid accumulation) (Tu et al. 2023).

Uterine fibroids can occur in any part of the uterus and rarely also outside the uterus. Conventionally, their location is described as submucosal, intramural, or subserosal. To improve accuracy and consistency, the widely used FIGO classification offers a more detailed system by dividing fibroids into eight groups (Group 0 – Group 7) based on their relation to the endometrium (Tu et al. 2023; Munro et al. 2011). The FIGO classification is shown in Figure 2.

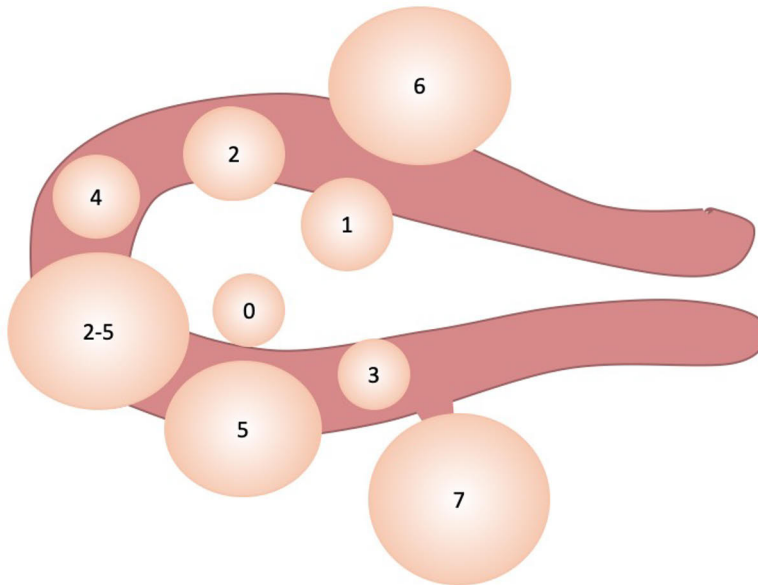


Figure 2. FIGO classification of uterine fibroids into types 0 to 7; 0= intracavitary pedunculated fibroid, 1= submucosal fibroid with less than 50 % located intramurally, 2= submucosal with 50 % or more located intramurally, 3= intramural, in contact to the endometrium, 4= 100 % intramural, 5= subserosal with 50 % or more intramural, 6= subserosal with less than 50% intramural and Group 7= subserosal and pedunculated, 2-5= submucous and subserous with <50% in the endometrial and peritoneal cavities. Figure created by author.

2.1.4 Diagnostics of uterine fibroids

The diagnosis of uterine fibroids is usually based on clinical examination and ultrasound imaging. Transvaginal ultrasound (TVUS) is the imaging method of choice due to its safety, availability, and low cost. TVUS detects fibroids with a sensitivity of 99% and a specificity of 91% (Mension et al. 2024). On ultrasound, fibroids appear as round, homogenic, usually hypoechoic masses, but they may also be isoechoic or hyperechoic. Vascularity is often circumferential, and posterior acoustic shadowing is common. Calcifications may appear, especially in older women. Saline-infused sonography is useful when submucosal fibroids are suspected (Farkas et al. 2023).

MRI is used for fibroid imaging when ultrasound is insufficient for diagnosis or before planned treatment. MRI is an imaging modality based on the nuclear magnetic resonance of the hydrogen atom, whose nucleus consists of a proton. The external magnetic field created by the MRI scanner aligns the spins of the hydrogen protons. The protons are then excited with a radiofrequency pulse. When the protons return to their normal state “relax”, they release the energy they absorbed. This release occurs through two relaxation processes called T1 and T2. The scanner measures the

signals produced by these relaxation processes. Tissues with fast T1 relaxation appear bright on T1-weighted images, for example fat. Tissues with slow T2 relaxation appear bright on T2-weighted images, for example urine (Plewes et al. 2012). MRI provides the highest accuracy for characterizing uterine masses before interventions (Awiwi et al. 2022). Its features include a large field of view, excellent soft tissue contrast, diffusion, and multiplanar sequences. On MRI, typical fibroids appear as well-circumscribed round masses with low signal intensity on both T1W and T2W images (Hindman et al. 2023).

In a double-blind study comparing the accuracy of TVUS and MRI in fibroid detection, measuring, and mapping, TVUS was as effective as MRI in detecting fibroids. However, TVUS was less effective than MRI for precise mapping of the location and extent of fibroids, particularly when the fibroids were large or when multiple fibroids were present (Dueholm et al. 2002).

Besides signal intensity, various other parameters related to uterine fibroids can be assessed from MR images to provide quantitative information about tissue structures. Diffusion weighted imaging (DWI) is a widely used MRI technique. From diffusion weighted images, apparent diffusion coefficient (ADC) values can be calculated, and ADC maps obtained. ADC values reflect the motion of water molecules in different compartments: intracellular, extracellular, and intravascular spaces and thus tissue cellularity and microcirculation can be evaluated by examining ADC maps (Sainio et al. 2021).

2.1.4.1 Differential diagnosis of uterine fibroids

In the differential diagnosis of uterine fibroids adenomyosis, leiomyosarcoma, metastatic diseases, endometrial lesions such as polyps (which are usually smaller), and endometrial malignancies must be considered.

Uterine leiomyosarcoma is a rare disease (3–7/100,000 in the US), but unfortunately, it is sometimes difficult to distinguish from a benign fibroid. Compared to uterine fibroids, leiomyosarcomas tend to be larger (over 8 cm), contain areas of necrosis and cysts, and have irregular borders and increased vascularity. In a recent systematic review, ultrasound had a pooled sensitivity of 0.76 (95% CI 0.70–0.81) and specificity of 0.89 (95% CI 0.87–0.92) for differentiating between benign fibroids and malignant leiomyosarcoma (Hindman et al. 2023). Risk factors for uterine sarcoma include advancing age, African decent, and postmenopausal status (Hindman et al. 2023). The prevalence of malignancy in a fibroid uterus increases if the patient is symptomatic. Notably, however, a uterine sarcoma can also be asymptomatic, albeit in only about 1–2% of patients. Previously, rapid growth of a uterine mass was thought to be a suspicious feature, distinguishing fibroids from sarcomas, but studies have shown that this is not always the case, since also benign

fibroids, particularly those under 5 cm, can grow quickly. Nevertheless, a rapidly growing uterine mass in a postmenopausal woman, especially if she experiences symptoms, should raise a suspicion of uterine leiomyosarcoma. In such cases, hysterectomy and proper histological evaluation is required (Hindman et al. 2023).

2.1.5 Symptoms related to uterine fibroids

Uterine fibroids can cause a wide range of symptoms, the most common of which are heavy menstrual bleeding, bulk symptoms (pressure symptoms), and lower pelvic pain (Donnez et al. 2016). In addition, fibroids can cause irregular bleeding, frequent urinating, and interfere with fertility (Vannuccini et al. 2024). Different fibroid symptoms often co-exist and that is why many patients with fibroids have more than one symptom at a time.

2.1.5.1 Bleeding symptoms

The most common symptoms of uterine fibroids are abnormal uterine bleedings. In a cohort of 1,384 symptomatic patients, 75% experienced heavy menstrual bleeding, and 55% had anemia (Anchan et al. 2023). A recent review reported that 46% of women with abnormal uterine bleeding had an associated uterine fibroid (Mension et al. 2024).

There are several theories explaining the mechanisms behind heavy bleedings in patients with uterine fibroids. The presence of fibroids alters endometrial vascular function and architecture and leads to increased production of angiogenic factors. Distortions of the uterine cavity, an increase in the endometrial surface area, and dilated blood vessels on the surfaces of the fibroids contribute to heavier bleeding. Impaired myometrial contractility and venous ectasia, which occurs when the uterus is compressed by fibroids, augment blood loss further (Vannuccini et al. 2024).

Most commonly bleeding symptoms are associated with FIGO 0–2 fibroids and even very small submucosal fibroids can cause difficult bleeding symptoms. Since fibroids interfere with endometrial and uterine homeostasis in many ways, as described above, fibroids that are not directly in contact with uterine cavity can still present with bleeding symptoms (Puri et al. 2014).

2.1.5.2 Bulk symptoms and urinary tract symptoms

There is no clear association between the size or the number of fibroids and the presence of bulk symptoms (Dancz et al. 2014). Bulk symptoms and urinary tract symptoms are frequently reported together, probably due to the pressure exerted by fibroids on pelvic structures, including the urinary bladder. Both bulk symptoms and

urinary tract symptoms appear to decrease significantly within six weeks after surgical fibroid treatment, regardless of the surgical approach (myomectomy, hysterectomy) or the location, number, or size of fibroids based on two prospective cohort studies with 55 and 61 women (Berujon et al. 2022; Houlihan et al. 2018)

The most reported urinary symptoms are urgency, dysuria, and stress urinary incontinence (SUI) (Mourgues et al. 2019). Two prospective cohort studies (55 and 61 women), reported that most (64–97%, respectively) of the women with uterine fibroids experience urinary tract symptoms (Berujon et al. 2022; Houlihan et al., 2018). However, the relationship between fibroid size or location and urinary tract symptoms is still controversial. While some studies suggest that anteriorly located fibroids sized ≥ 5 cm are more likely to cause urinary symptoms than others, this finding has not been consistently observed across all studies. (Mourgues et al. 2019).

2.1.5.3 Pain

Pain is a significant fibroid-related symptom. It can present as painful menstruation (dysmenorrhea), lower abdominal pain, pelvic pain, lower back pain, and painful intercourse (Donnez et al. 2016; Zimmermann et al. 2012). The reported prevalence of these pain symptoms among women with uterine fibroids ranges from 17% to 60%, depending on the type of pain assessed (Zimmermann et al. 2012).

2.1.5.4 Subfertility

The effects of fibroids on natural fertility are controversial. According to a systematic review and meta-analysis, women with multiple uterine fibroids had significantly lower spontaneous pregnancy rates than women without fibroids (OR 0.60, 95% CI 0.44–0.86) (Pritts et al. 2024). On the other hand, no significant difference in clinical pregnancy rates has been documented between women with a single fibroid and those without fibroids (Somigliana et al. 2021).

There are several mechanisms by which fibroids may interfere with fertility such as the anatomical distortion of the endometrial cavity, disruption of myometrial contractility and endometrial receptivity, and alteration of endometrial microbiome (Munro et al. 2025).

Submucosal fibroids (FIGO types 0–3) are, in particular, associated with impaired fertility. They may disrupt myometrial contractility, which can negatively affect sperm and embryo transport. In addition to their potential anatomical effects on the uterine cavity and fallopian tubes, fibroids are thought to alter endometrial receptivity of the embryo through the effects of various cytokines and growth factors (Munro et al. 2025).

An important signaling molecule associated with endometrial receptivity is the cytokine TGF β 3, which is overexpressed in the presence of fibroids. This overexpression leads to a reduction in BMP2, a growth factor essential for endometrial receptivity. Fibroids may also induce inflammatory responses in the endometrium and alter the uterine microbiome (Munro 2019).

Also, the vascular architecture of the endometrium is altered in the presence of fibroids, and this is known to affect endometrial hemostasis (Munro et al. 2025).

2.1.6 Treatment modalities of uterine fibroids

There are various methods for treating uterine fibroids. The modern choice for treating uterine fibroids is based on the patient's symptoms, age, menopausal state, and the patient's preference regarding uterine and fertility preservation. Risk factors related to the different treatments, including the risk of fibroid and symptom recurrence, are reviewed together with the patient (de Smit et al. 2025; Vannuccini et al. 2024).

2.1.6.1 Pharmacological treatments

Pharmacological treatments can be categorized into non-hormonal and hormonal therapies. A key limitation of pharmacological interventions is that their effects are mostly reversible and thus the benefits are lost if the medication is discontinued.

2.1.6.1.1 Non-hormonal treatments

Nonsteroidal anti-inflammatory drugs (NSAID) reduce prostaglandin synthesis in the endometrium. In general, this reduces menstrual pain and bleeding. However, there is less data on their effect on fibroid-related menorrhagia. NSAIDs do not affect fibroid size or structure. NSAIDs can be combined with other fibroid treatments (Vannuccini et al. 2024). Tranexamic acid, a synthetic analog of lysine, reduces bleeding by inhibiting fibrinolysis (Vannuccini et al. 2024).

2.1.6.1.2 Hormonal treatments

Oral progestins and combined oral contraceptives are common treatments for heavy menstrual bleeding. Besides providing contraception, they inhibit endometrial proliferation and keep the endometrium thin. The modern low-dose estrogen contraceptive pills do not apparently increase the size of fibroids and they may even have some protective effect against fibroids (Kwas et al. 2021).

The 52-mg levonorgestrel intrauterine device (LNG-IUD) is effective in treating heavy menstrual bleeding. It releases levonorgestrel into the uterine cavity and acts directly on the endometrium, causing endometrial atrophy and inactivity without suppressing ovulation. The LNG-IUD decreases the duration and amount of fibroid-related bleeding but does not alter fibroid size (Socolov et al. 2011; Murat Naki et al. 2010; Zapata et al. 2010). LNG-IUD expulsion can occur in women with fibroids. A long-term follow-up study involving 116 women reported a 15.4% expulsion rate within one year in women with fibroids and 9.5% in women without fibroids ($p=0.176$). The average LNG-IUD usage time was significantly higher in women without fibroids ($p=0.03$) (Balica et al. 2021).

Gonadotropin-releasing hormone (GnRH) agonists (leuproreline acetate, triptorelin, goserelin acetate) are synthetic peptides that mimic natural GnRH. They down-regulate GnRH receptors, lower the levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and reduce gonadal steroid levels including estrogen. Hypoestrogenism inhibits fibroid growth and can shrink fibroids. Fibroid volume may decrease up to 65% in six months, but this effect is partly reversible as fibroids regrow in 20% of women (Vannuccini et al. 2024). GnRH agonists cause strong hypoestrogenic adverse effects, such as hot flashes, vaginal dryness, sleep problems, mood swings, and joint pain. Long-term use lowers bone density (Ciebiera et al. 2023). For these reasons, GnRH agonists are usually used only for a short time to shrink fibroids and decrease bleeding before other permanent treatments. To prevent adverse effects, add-back estrogen therapy can be used.

Oral GnRH antagonists (relugolix, elagolix, linzagolix) bind GnRH receptors and quickly suppress FSH and LH, causing a reversible menopause-like hypoestrogenic state. They are efficient in controlling fibroid-related bleeding. Estrogen and progestin add-back therapy is used, as with GnRH agonists. These combined drugs are often well tolerated and have few adverse effects, making them an option for long-term use in women with fibroid-related bleeding symptoms (Vannuccini et al. 2024; Al-Hendy et al. 2021).

Selective progesterone receptor modulators can act as agonists or antagonists depending on the type of progesterone receptors in each target tissue. Ulipristal acetate can significantly shrink fibroids and reduce bleeding symptoms in fibroid patients (Donnez et al. 2014). Since May 2018, continuous use has been limited because there have been rare cases where ulipristal acetate is associated to drug-induced liver injury (Semmler et al. 2025). Ulipristal acetate is not currently available in Finland. The currently available drugs in Finland to treat uterine fibroids are summarized in Table 2 (Diaz et al. 2025; Vannuccini et al. 2024).

Table 2. Drugs available currently in Finland for treatment of uterine fibroids.

Drug	Mode of action	Reduction in bleeding	Reduction in fibroid size	Other important considerations
NSAID	Reduction of prostaglandin synthesis in the endometrium	-62% in 6 months ¹	No ¹	Risk of GI bleeding in long-term use ¹
Tranexamic acid	Inhibition of fibrinolysis	Yes ¹	No ¹	
Oral progestins	Prevention of estrogen dependent stimulation of the endometrium	Yes ³	No ³	
Oral combined contraceptives	Inhibition of endometrium proliferation and maintenance of thin endometrium	Yes (limited data on fibroid patients) ^{1,5}	Not significantly ¹	Risk of thromboembolism ¹
LNG-IUD	Atrophy and inactivation of the endometrium	40% had amenorrhea at 1 year ⁴	No ⁴	Risk of IUD expulsion ²
GnRH agonists	Hypoestrogenic state induced by reduction of FSH and LH and reduction of gonadal steroid levels	Yes ⁵	Yes ⁵	Menopausal symptoms and loss of bone density. Add-back therapy recommended if used over 6 months ⁵
GnRH antagonist + add-back therapy	Suppression of FSH and LH and reduction of gonadal steroid levels	-50% blood loss by the first menstruation after treatment and remaining reduced by 90% after 52 weeks of use ^{1,5}	No ¹	

(NSAID= Non-Steroidal Anti-Inflammatory, LNG-IUD= Levonorgestrel Intra Uterine Device, GnRH= Gonadotropin releasing hormone) 1= Vannucini et al. 2024, 2= Balica et al. 2021, 3= Kwas et al. 2021, 4= Socolov et al. 2011, 5= ACOG practice bulletin 2021

2.1.6.2 Surgical treatments

Myomectomy is a surgical procedure where one or multiple fibroids are removed from the uterus via hysteroscopy, laparoscopy, or laparotomy. The hysteroscopic approach is possible when treating FIGO types 0, 1, and, in some cases, type 2 fibroids. Especially, small fibroids (<2 cm) can be removed in an outpatient setting. The risks related to this treatment are blood loss, damage to the surrounding

myometrium, intrauterine adhesion formation, uterine perforation, and fluid extravasation. Laparoscopic and open (laparotomy) myomectomy can be performed to treat fibroids located in the myometrium or subserosal area (FIGO types 3-7). In myomectomy, a vertical or transverse incision is made in the uterine wall, and the fibroid is then exposed and excised by separating the outer wall of the fibroid from the myometrium. Adequate closure of the myometrial defect is crucial to decrease the future risk of rupture of the uterus (Vannuccini et al. 2024; Donnez et al. 2016). Laparoscopic myomectomy is associated with less postoperative pain and shorter hospital stay compared to open myomectomy (Bhave Chittawar et al. 2014). Myomectomy via laparotomy can be chosen for some patients if the fibroids are very large (>12 cm) or multiple fibroids are to be removed during the same operation (Donnez et al. 2016). Based on a Cochrane review, there is no difference in the risk of fibroid recurrence between open or laparoscopic myomectomy and more studies are needed to assess the rates of uterine rupture later in life (Bhave Chittawar et al. 2014). A systematic review and meta-analysis with 32 studies and nearly 6500 patients compared the perioperative and postoperative outcomes of laparoscopic and robot-assisted myomectomy. The operating time was significantly longer for the robotic assisted procedure (mean difference 43.58 min, 95% CI: 25.22–61.93, $p < 0.001$). There were no significant differences regarding blood loss, conversion to laparotomy, complications, hospital stay, and pregnancy rate (Chen et al. 2024).

Hysterectomy has been standard treatment for symptomatic uterine fibroids for decades, especially for women not wishing to preserve their fertility. It is a definitive treatment with no risk of symptom recurrence or uterine fibroid recurrence later in life. The annual number of hysterectomies in Finland has shown a decreasing trend. In 2024, a total of 4,081 hysterectomies were performed. Based on a study examining hysterectomy indications in Finland during 2017–2018, in which 21% of hysterectomies were performed due to uterine fibroids, it can be estimated that approximately 900 hysterectomies are carried out for this indication annually in Finland (Vikstedt et al. 2021).

Vaginal hysterectomy should be the primary approach if the size of the uterus is < 12 weeks of gestation (Matteson et al. 2017). For larger uteri, laparoscopic hysterectomy is preferred to abdominal hysterectomy because of less postoperative morbidity and mortality. The complications related to hysterectomy are blood loss, infection, and damage to surrounding tissues (Vannuccini et al. 2024). Hysterectomy offers symptom relief and improvement in QoL also long-term (Rahkola-Soisalo et al. 2020). Importantly, however, recent research has also identified negative effects of hysterectomy, *e.g.*, on long-term cardiovascular and mental health (Thao et al. 2025).

A multicenter study with 2,482 patients compared the complications related to myomectomy and hysterectomy and found that myomectomy took longer (mean

154±74.5 vs. 146 ±70.5 min, $p < 0.001$), required amounts of intraoperative hemostatics (25% vs. 9.1% $p < 0.001$), and caused a higher intraoperative blood loss (mean 222.7±313 vs. 87.4±145.9 ml, $p < 0.0001$). On the other hand, myomectomy was associated with fewer infections (3.1 vs. 5.8 $p < 0.0001$) and readmissions (2% vs. 5.6%, $p < 0.0001$) (Carlson et al. 2024).

2.1.6.3 Interventional radiological treatments

There are various radiological treatment options for uterine fibroids. Radiological treatments require special equipment as well as radiological expertise, and thus many of them are not widely available. Treatment modalities not currently available in Finland are only shortly presented in this section.

Uterine artery embolization (UAE) is based on introducing embolic particles into the uterine arteries. This treatment modality was first reported in 1995 and has been shown to be effective and safe for the treatment of symptomatic uterine fibroids (de Bruijn et al. 2016). The aim of this procedure is to occlude the arteries supplying blood flow to the fibroid. The five-year follow-up results of the REST trial with 157 women involved, which compared UAE with surgical treatments, showed that there was no difference in symptom severity, patient satisfaction, or adverse events between the groups. The cumulative need for re-intervention after these treatments was 32% for UAE and 4% for surgery (Moss et al., 2011). The EMMY trial, a randomized controlled trial with 177 women, comparing UAE and hysterectomy, showed equal and stable QoL in both groups in the 10-year follow-up. The re-intervention rate in the UAE group was 31% (de Bruijn et al., 2016). A disadvantage of UAE is that the desire for future pregnancies is currently a relative contraindication to UAE, but larger studies are being pursued (Kröncke 2023; J Zhang et al. 2022).

In radiofrequency ablation an electrode array is placed in the fibroid and thermal ablation is achieved by dispersing radiofrequency energy through the fibroid tissue. Ultrasound guided sclerotherapy (USGS) and percutaneous or transvaginal ultrasound-guided microwave ablation (MWA) are minimally invasive treatments that can be used for symptomatic uterine fibroids (Jonsdottir et al. 2025; J. Zhang et al., 2022). All of these techniques have shown promising results of symptom reduction. However, studies to compare these treatments with more conventional treatment options are still lacking, as is data on long-term efficacy and fertility impacts. Figure 3 summarizes the fibroid treatment options.

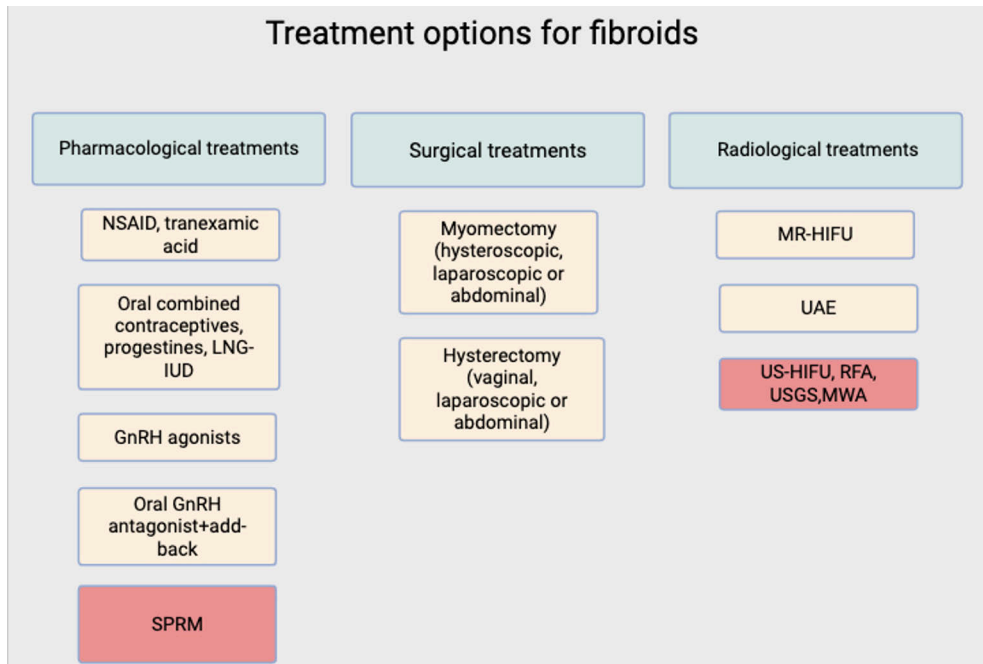


Figure 3. Treatment options for symptomatic uterine fibroids. Red boxes are modalities that are not available in Finland at the time. (SPRM=Selective Progesterone Receptor Modulator, MR-HIFU=Magnetic Resonance-guided High-Intensity Focused Ultrasound, UAE=Uterine Artery Embolization, US-HIFU=Ultrasound-guided High-Intensity Focused Ultrasound, RFA=Radiofrequency Ablation, USGS=Ultrasound-guided Sclerotherapy, MWA=Microwave Ablation)

2.2 High Intensity Focused Ultrasound (HIFU)

High Intensity Focused Ultrasound (HIFU) uses high-intensity ultrasound waves to heat and ablate target tissue. HIFU has a wide range of medical indications, including benign gynecological tumors, prostate cancer, bone metastases, and some neurological conditions (Bachu et al. 2021) In gynecology, the main use is for uterine fibroids, but HIFU can also be used to treat adenomyosis and abdominal wall endometriosis in selected cases. Rarely, HIFU is used for deep infiltrating endometriosis, cesarean scar pregnancies, and palliative treatment of gynecological malignancies. These indications are primarily topics of ongoing research (Knorren et al. 2024; Bachu et al.2021).

HIFU treatment can be performed either under ultrasound (US-HIFU) or magnetic resonance (MR-HIFU) guidance. US-HIFU is more affordable, does not require patient enclosure in the MR machine and is also quieter. Sonographic greyscale changes during treatment indicate a tissue response (Orsi et al. 2010). In comparison, MR-HIFU offers superior soft tissue contrast and real-time temperature monitoring (Dohmen et al. 2024; Orsi et al. 2010).

2.2.1 HIFU technology

The absorption of ultrasound causes accumulation of energy and raises the tissue temperature. In 1932 Freundlich et al. first suggested the therapeutic potential of high-intensity ultrasound. Targeting ultrasound beams to a point produced an intense effect at target, while tissues along the path remained unharmed. Until 1990, HIFU was performed under ultrasound guidance (Napoli et al. 2021). The first combined MR and HIFU device was introduced in 2003. There is a strong interest in HIFU technology in many fields and it continues to evolve (Bachu et al. 2021).

In the procedure, a HIFU-transducer delivers several beams at a constant, high frequency (1–7 MHz). The sound waves travel through the tissues and converge at the intended focal point. As the waves convert to thermal energy in the tissues, they cause coagulative necrosis at the point of convergence, which results in thermal ablation. Tissue necrosis begins when the temperature reaches 60°C, the threshold of protein denaturation. Temperatures over 96°C should be avoided because the consequent boiling and bubble formation make the effects less predictable and could be harmful to surrounding tissues. Figure 4 illustrates the HIFU procedure.

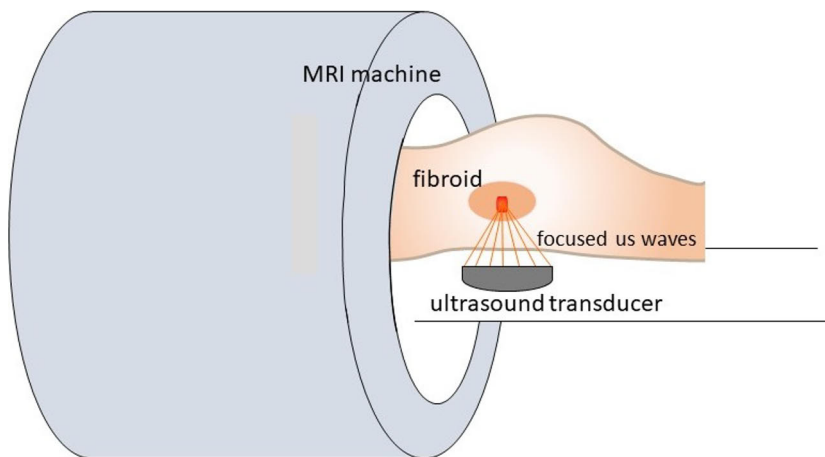


Figure 4. An illustration of the MRI and the ultrasound transducer generating focused ultrasound waves targeted at the fibroid tissue. Illustration provided by K. Joronen.

2.3 MR-HIFU in the treatment of uterine fibroids

In 2004, the FDA approved MR- HIFU for treating symptomatic uterine fibroids. Until 2009, regulations allowed only a restricted treatment protocol: a three-hour maximum treatment time, no sensitive structures near the beam path, a 30 mm safety margin to the spine, and a 10 mm safety margin from the treatment cell to the uterine serosa. The targeted volume of the ablated tissue was limited to 30–40% of the total

fibroid volume. In 2009, these criteria were modified, and an unrestricted protocol aiming at complete ablation was allowed (Verpalen et al. 2019). In 2015, the FDA approved MR-HIFU with the next-generation ExAblate system, which allows treatment for women who also consider future pregnancies (Napoli et al. 2021).

2.3.1 Suitability criteria and patient selection for MR-HIFU

The selection criteria for MR-HIFU therapy vary depending on the practices of individual centers. In general, this treatment is suitable for premenopausal women with symptomatic fibroids. However, pedunculated fibroids, suspected malignancy, extensive pelvic adhesions, and claustrophobia are generally considered contraindications to MR-HIFU. Large scars or tattoos in the skin area of the lower abdomen may increase the risk of skin burns during treatment. The patient's eligibility for MR-HIFU is assessed not only clinically but also with a contrast-enhanced pelvic MRI. Several MR parameters, such as signal intensity, ADC values, and fibroid perfusion, predict treatment outcomes (Sainio et al. 2021; Mindjuk et al. 2015). Figure 5 summarizes the specific criteria based on the latest evidence that determine a patient's suitability for MR-HIFU treatment (Knorren et al. 2024; Palumbo et al. 2021; Keserci et al. 2018; Sridhar et al. 2018).

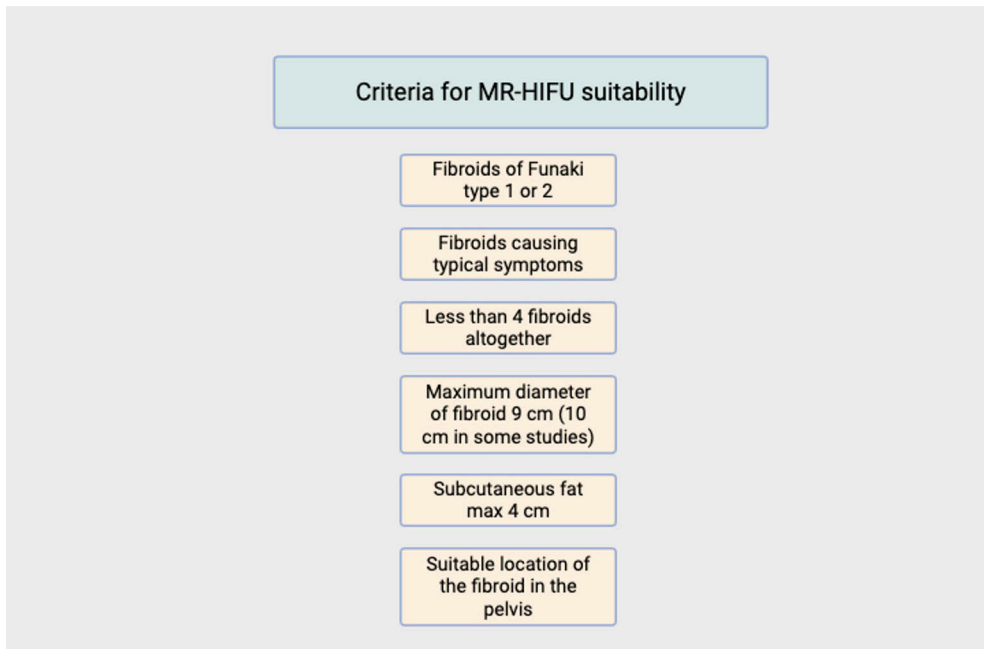


Figure 5. Suitability criteria for MR-HIFU based on the most recent evidence (Knorren et al. 2024, Palumbo et al. 2021, Kereci et al. 2018, Sridhar et al. 2018)

2.3.1.1 Funaki classification of uterine fibroids

The Funaki classification is widely used for selecting patients for MR-HIFU therapy. The classification is based on T2-weighted MR images, where the signal intensity of the fibroids is compared to that of the myometrium and skeletal muscle. According to this assessment, fibroids are categorized into three types: Type 1 (hypointense), Type 2 (intermediate), and Type 3 (hyperintense). Funaki Types 1 and 2 are generally considered suitable for MR-HIFU treatment, since they are more responsive to thermal ablation. In contrast, achieving adequate heating and necrosis in Funaki Type 3 fibroids is more challenging. This limitation may be due to the increased water content, higher vascularity, and increased blood flow, which facilitate heat dissipation and reduce the achievable tissue temperature rise (Verpalen et al. 2020; Funaki et al. 2007). The Funaki classification is illustrated in Figure 6.

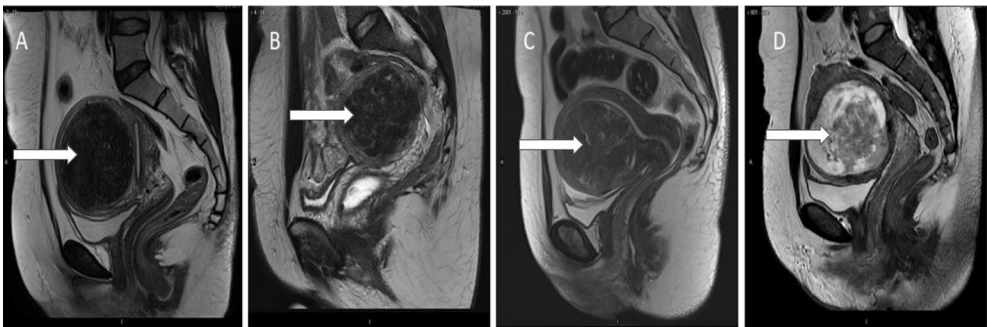


Figure 6. Funaki classification of uterine fibroids (white arrows) in a T2 weighted (T2W) magnetic resonance image (MRI). A= Funaki type 1 fibroid (hypointense), B= Funaki type 2 fibroid (intermediate), C= Funaki type 2 fibroid (also intermediate), D= Funaki type 3 fibroid (hyperintense). Image from the author's own files.

2.3.2 MR-HIFU treatment in practice

During treatment, the patient lies prone on the table with the pelvis positioned over the transducer and within the MRI scanner. Because the procedure lasts several hours, a urine catheter is inserted, and compression stockings are recommended to prevent deep venous thrombosis. Bladder and rectal filling may be used when it's appropriate to adjust the uterus and its proximity to bowel loops. Once optimally positioned, T2W multiplanar MR images are obtained for treatment planning. The ellipsoid treatment cells are placed individually to cover the entire area. Test sonications determine the treatment energy needed for maximal temperature increase at the target site, and each sonication is followed by a cooling period. Real-time thermometry regulates tissue heating and protects surrounding areas (Sridhar et al. 2018). Magnetic resonance allows both planning and monitoring of the thermal

ablation and provides a temperature map needed to maintain the optimal temperature range at 60–65 °C within the treatment cells and to prevent overheating (Filipowska et al. 2014).

After the procedure, the technical outcome and efficacy of the treatment are objectively assessed by quantifying the non-perfused volume (NPV). For this, a control T1-weighted MR (T1W) image is obtained immediately post-procedure. The non-perfused volume ratio (NPV%) is determined by dividing the NPV by the total fibroid volume. An NPV% of 80% or greater is now established as the benchmark for procedural planning. Evidence indicates that achieving this threshold is associated with superior clinical outcomes (Sridhar et al. 2018; Mindjuk et al. 2015).



Figure 7. The MR-HIFU machine in the Turku University Hospital. The transducer is embedded in the MR-table.

2.3.3 Results of MR-HIFU treatments

There are several parameters that can be used to evaluate the efficacy of MR-HIFU. The impact of the treatment on patient symptoms and QoL can be assessed through standardized questionnaires or structured interviews. Changes in fibroid size may be determined by measuring its diameter or volume. The technical indicators of

treatment success are the NPV% and the incidence of adverse events (AE). Finally, the rate of re-interventions needed later serves as an important measure of long-term treatment effectiveness.

2.3.3.1 Efficacy of MR-HIFU in treating fibroid symptoms, improving quality of life, and reducing fibroid size

Alleviating fibroid-related symptoms is a primary goal for the management of uterine fibroids. Another key outcome measure is the reduction in fibroid volume following treatment. Several instruments have been developed to assess fibroid-related symptoms, and among these the UFS-QoL questionnaire is most widely used and validated (Spies et al. 2002).

In published studies on the effects of MR-HIFU treatments, there is considerable heterogeneity in study designs, sample sizes and follow-up durations. Table 3 provides a summary of the original studies that have examined the effects of MR-HIFU on patient symptoms, QoL, fibroid volume, re-intervention rates, and adverse events.

Table 3. Summary of original studies (randomized controlled, prospective, retrospective) on the effect of MR-HIFU on fibroid symptoms, quality of life, fibroid volume decrease, re-intervention rates, and adverse events

Author, year	Study design	Number of patients	Follow-up (months)	Parameters	Mean NPV% in treatments	Symptoms and QoL	Fibroid volume decrease	Re-intervention rates	Adverse events (serious)
Jacoby et al. 2016	Randomized placebo-controlled trial	20	3 and 24	UFS-QoL, MRI	43%	1 month SSS and QoL decreases ($p < 0.05$) with MR-HIFU and placebo ($p = .97$ for difference). At 3 months the SSS score decreased with MR-HIFU 31 points vs. placebo 13 points, $p = .20$. At 12 months, significant improvement in SSS and QoL in MR-HIFU group compared to baseline ($p < 0.05$)	-18% (3 months) with MR-HIFU	30% (24 months)	0% (0%)
Peregrino et al. 2025	Prospective follow-up study	52	12	UFS-QoL, MRI	NR	QoL increased 81%	-42% (12 months)	6% (12 months)	8% (0%)
Bifton et al. 2023	Prospective multicenter trial	99	36	UFS-QoL, MRI	NR	SSS decrease at all time points ($p < 0.001$)	NR	15% (36 months)	0.2% (0.01%)
Lozinski et al. 2021	Prospective follow-up study	356	6	MRI, non-standardized questionnaire	71%	76% of the patients had improvement in QoL	-39% (6 months)	NR	4% (0%)
Xu et al. 2015	Prospective follow-up study	43	6	UFS-QoL, MRI	84%	Decrease in SSS ($p < 0.05$)	-40% to -60% (6 months)	NR	4.7% (0%)
Kim et al. 2011	Prospective follow-up study	40	36	UFS-QoL, MRI	32%	Decrease in SSS and increase in QoL ($p < 0.001$)	-32% (36 months)	NR	0%
Funaki et al. 2009	Prospective follow-up study	91	24	UFS-QoL, MRI	36-55%	Decrease in SSS of Funaki type 1 and 2 ($p < 0.001$)	-40% (24 months)	14-22% (24 months)	NR

Stewart et al. 2006	Prospective multicenter study	109	12	UFS-QoL	10%	Decrease in SSS and increase in Qo (p < 0.0001 for both)	NR	NR	NR	NR (0%)
Mindjuk et al. 2015	Retrospective study	252	19	UFS-QoL, MRI	89%	93% received significant improvement in symptoms	NR	13 % (19 months)	NR	1.8% (0%)
Gorny et al. 2011	Retrospective study	150	12	Non standardized questionnaire	45%	88% of patients had relief in symptoms. No correlation between symptom relief and NPV%	NR	7% (12 months)	NR	12% (0.8%)
Kociuba et al. 2023	Retrospective case-control study	372	6	Non standardized questionnaire on AE	71–73%	NR	NR	NR	NR	9% (0%)
Verpalen et al. 2020	Retrospective cohort study	123	64	MRI, non-standardized questionnaire	48%	NR	NR	33% (64 months)	NR	14% (1.6%)
Quinn et al. 2014	Retrospective cohort study	280	60	MRI, patient records	44%	NR	NR	59% (60 months)	NR	3.9% (1.1%)
Okada et al. 2009	Retrospective analysis	287	12	MRI, patient records on AE	47%	NR	NR	8% (12 months)	NR	NR (0%)
Inbar et al. 2025	Retrospective cohort study	99	84	MRI, Patient records	76%	NR	NR	33% (84 months)	NR	NR
LeBlang et al. 2011	Retrospective cohort study	80	6	MRI	55%	NR	-31% (6 months) (p < 0.0001). Correlation between NPV% and fibroid shrinkage (p < 0.0001)	NR	NR	4% (0%)

NR= Not reported, MRI=Magnetic Resonance Imaging, UFS-QoL= Uterine Fibroid Symptom and Quality of Life, SSS=Symptom Severity Score, QoL= Quality of Life, NPV%= Non-Perfused Volume ratio. Adverse events=mild adverse events not requiring treatment. Serious adverse events= events requiring treatment and hospitalization , AE=Adverse event

Follow-up studies have consistently reported a reduction in symptom severity within three to 36 months after MR-HIFU treatment, although the magnitude of improvement, the follow-up times, and the assessment methods vary across studies. Similarly, a reduction in fibroid volume has been observed in all studies assessing this (Peregrino et al. 2025; Bitton et al. 2023; Mindjuk et al. 2015; Jacoby et al. 2016; Kim et al. 2011; Funaki et al. 2009; E. A. Stewart et al. 2006).

Funaki type 1 and 2 fibroids are more suitable for MR-HIFU than type 3 in the light of SSS and fibroid volume reduction (Funaki et al. 2009).

The correlation between NPV% and self-reported symptom relief has been somewhat controversial in earlier studies. In a retrospective study with 130 patients, there was no consistent correlation between the NPV% and self-reported symptom relief (Gorny et al. 2011). In another retrospective study with 252 patients, NPV% was identified as the only parameter significantly correlated with symptom improvement (Mindjuk et al. 2015). In a prospective multicenter trial with 99 women, a new metric was introduced: the ratio of non-perfused volume to total fibroid load (NPV/TFL). Higher NPV/TFL values were significantly correlated with sustained reductions in bleeding and bulk symptoms (UFS-QoL scores) (Bitton et al. 2023).

Reviews and meta-analyses have found that higher NPV% values are associated with greater improvements in patients' QoL. When NPV% exceeds 50%, the mean reduction in symptom severity at 36 months was 74% (Verpalen et al. 2019). When an unrestrictive treatment protocol is used, the mean symptom reduction at 12 months was 60% and the mean fibroid shrinkage is 40% (VerpGizzo et al. 2014).

The PROMISE trial (Jacoby et al. 2016) is thus far the only sham-controlled randomized study evaluating MR-HIFU for fibroid treatment. 13 women received MR-HIFU and seven received sham treatment; both groups underwent identical preparation and positioning on the MR-HIFU system. In the sham control group, the procedure was conducted without releasing thermal energy from the transducer. Four weeks post-procedure, both groups reported symptom improvement, *i.e.*, there was a notable placebo response. At 12 weeks, the fibroid volume decreased significantly more in the MR-HIFU group (18%) than in the sham control group (3%) ($p = 0.04$). At 12 and 24 months, 90% of women in the MR-HIFU group experienced significant symptom reduction and improved QoL compared to baseline ($p < 0.05$). From the sham control group 5/7 women crossed over to MR-HIFU before the 24-month time point.

In conclusion, recent evidence indicates that higher NPV% are associated with greater symptom relief. While some studies have reported a correlation between NPV% and fibroid shrinkage, this finding has not been consistently demonstrated across all investigations (Leblang et al. 2010).

2.3.3.2 Reintervention rates and adverse events related to MR-HIFU

The factors associated with a need for re-intervention after MR-HIFU are patient age at the time of MR-HIFU, achieved NPV%, operators' experience, and duration of follow-up (Peregrino et al. 2025; Mindjuk et al. 2015; Gorny et al. 2011; Kim et al. 2011; Okada et al. 2009).

Women under 43 years had a significantly higher risk of re-intervention than older women and the patients' age was identified as the sole significant predictor of future re-intervention in a retrospective cohort study with 99 women (Inbar et al. 2025). In another retrospective study with 252 women and a follow-up time of 19 months (Mindjuk et al. 2015), NPV% was the only statistically significant variable predicting re-intervention risk. A higher NPV% was associated with a lower likelihood of re-intervention (OR 0.67 per 10% NPV% increase, 95% CI 0.53–0.83). In the randomized, sham-procedure controlled, clinical PROMISE trial with 20 women, 30% of women treated with MR-HIFU (mean NPV% 43%) underwent reintervention for uterine fibroids within 24 months, compared to 71% of women in the sham-control group (Jacoby et al. 2016).

A Japanese study investigated the impact of the learning curve on treatment outcomes among 287 women treated with MR-HIFU, who were divided chronologically into two equal groups. Over time, a significant improvement in mean NPV% was observed, increasing from 39% to 54% ($p < 0.001$). Correspondingly, the 12-month re-intervention rate decreased significantly from 12% in the former group to 5% in the latter group ($p = 0.04$) (Okada et al. 2009).

Adverse events (AEs) are commonly classified according to the Society of Interventional Radiology (SIR) criteria, which categorize complications from Class A (no therapy required) to Class F (death) (Baerlocher et al. 2023). The reported AEs related to MR-HIFU are pain, skin burns, urinary tract infections, sciatic neuropraxia, deep vein thrombosis, and skin ulceration (Kociuba, et al. 2023).

The incidence of serious AEs related to MR-HIFU is low. Minor complications (SIR Class A–B) occur in approximately 0–14% of cases, while serious complications (SIR Class C–F), such as deep vein thrombosis, skin burns, or neuropathy, occur among 0% to 1.6% of the patients (Ali et al. 2024; Kociuba, et al. 2023; Verpalen et al. 2020; Mindjuk et al. 2015; Quinn et al. 2014; Gorny et al. 2011).

In a retrospective case-control study involving 372 women treated with MR-HIFU, 8.9% of the patients experienced AEs during or after treatment (Kociuba et al. 2023). Patients who experienced AEs were compared with patients who did not, and there was no association between AEs and technical treatment parameters, such as fibroid location, fibroid volume, NPV%, or uterine position. Of the patients who experienced AEs, 27% had one single event, while 73% had multiple AEs (Kociuba

et al. 2023). The experience of the operators has been shown to influence the incidence of AE's (Okada et al. 2009).

The risk of needing a re-intervention due to symptom recurrence is inherent to all uterus-preserving treatments. Re-intervention rates following MR-HIFU vary widely across studies, which can be attributed to differences in follow-up duration, the proportion of successful treatments, and variations in study populations.

2.3.3.3 Predicting the treatment outcome

Several studies have investigated factors that may help predict MR-HIFU treatment outcomes and guide patient selection. In a retrospective study with 66 women (Keserciet al. 2018) the following factors were identified as predictors of treatment success (NPV% of $\leq 90\%$): subcutaneous fat thickness of the abdominal wall, fibroid peak enhancement, time to peak enhancement, and fibroid-to-myometrium enhancement ratio. Dynamic contrast-enhanced (DCE) MRI curve types correlated with therapeutic efficacy, suggesting that DCE imaging might identify lesions that would respond poorly despite favorable baseline characteristics (Łoziński et al. 2021).

In a retrospective cohort study with 255 patients and a mean NPV% of 89%, the following factors were positively associated with higher NPV% values: fibroids without septations, absence of subserosal components, and low signal intensity on T2-weighted MRI. Fibroids located near the spine had lower NPV% values (Mindjuk et al. 2015).

More recently, an interpretable MRI radiomics model was developed to predict residual fibroid regrowth after MR-HIFU. Using radiomic features and logistic regression models, the study showed that MRI-based radiomic parameters (218 features from T2W imaging and contrast-enhanced T1W imaging), may serve as potential biomarkers for the preoperative evaluation of which fibroids are suitable for MR-HIFU treatment (Y. Liu et al. 2025).

2.3.3.4 Cost-effectiveness of MR-HIFU

The high prevalence of uterine fibroids affects global health care expenditures. In 2022, the annual economic burden associated with uterine fibroid-related health care costs in the United States was estimated to reach 41.4 billion dollars (Hazimeh et al. 2024). Similarly, in Finland, this condition causes strain on the national health care system; for example, the lifetime risk for needing a hysterectomy for uterine fibroids is estimated to be nearly 5% and other treatment modalities will have already been attempted before this definitive intervention (Pynnä et al. 2021; Hakkarainen et al.2021).

There is only limited evidence on the cost-effectiveness of MR-HIFU for fibroid treatment. An original cost-effectiveness analysis in Canada on the long-term costs and effects of MR-HIFU compared to hysterectomy, myomectomy and UAE found that MR-HIFU might be a cost-effective strategy. Potential one-year savings were calculated in different scenarios with two to six centers providing MR-HIFU to replace either all types of procedures or only uterine preserving treatments. The one-year savings rose to 3.4 million dollars when MR-HIFU replaced all uterine preserving treatments (Babashov et al. 2015). Another cost-effectiveness analysis which incorporated treatment-specific short-term and long-term utilities and quality-adjusted life years (QALY) resulted in a finding that MR-HIFU was a cost-effective noninvasive strategy for eligible women first-line (Kong et al. 2014). Still another cost-effectiveness analysis found that MR-HIFU, myomectomy and UAE were all similarly effective in terms of QALY gained and all these treatments were judged to be cost-effective in a five-year time frame (Cain-Nielsen et al. 2014).

2.3.4 Oxytocin and other uterotonic drugs in increasing the efficacy of MR-HIFU

Several approaches have been explored to improve the efficacy of MR-HIFU treatment. Oxytocin is a nonapeptide hormone synthesized in the hypothalamus. It has many physiological functions, the best known of which are its role in generating contractions during pregnancy and labor. It is widely used in obstetric care, especially during the second stage of labor and after labor to decrease postpartum hemorrhage. Oxytocin has also a role in the physiology of the nonpregnant uterus, especially when fibroids are present (Jeong et al. 2016; Busnelli et al. 2010).

Oxytocin has been used in connection with various fibroid treatment modalities to enhance therapeutic efficacy. Thus, oxytocin has been used in MR-HIFU and US-HIFU and in surgery to reduce intraoperative blood loss during myomectomy (Fu et al. 2019; Lozinski et al. 2018; Atashkhoei et al. 2017; K. H. Lee et al. 1998).

Misoprostol is a synthetic analog of natural prostaglandin E1. Misoprostol reduces blood loss during myomectomies and the proposed mechanisms of action behind this are uterine vasoconstriction and reduced uterine arterial blood flow (Wetherell et al. 2022; Wali et al. 2021).

In a prospective cohort study with 247 women with fibroids and treated with MR-HIFU, preprocedural misoprostol and periprocedural oxytocin significantly increased the NPV% compared to controls without these medications (62% vs. 77–85%, $p < 0.001$). The sonication time was also reduced, but there was no long-term difference in fibroid volume (Łoziński et al. 2021).

A retrospective study with 283 women evaluated the role of DCE-MRI in selecting patients for MR-HIFU and assessed the effect of uterotonic drugs on

NPV%. The study subjects received either vaginal misoprostol/diclofenac, intravenous oxytocin, or no uterotonic treatment. Patients exhibiting a “washout” perfusion curve on DCE-MRI (the contrast agent demonstrated rapid washout from the tissue, suggesting high blood flow in the lesion) benefited most from administration of uterotonics (Łoziński et al. 2021).

Based on the most recent evidence, oxytocin is currently used in MR-HIFU treatments in Finland to increase treatment efficacy.

2.4 Comparison of MR-HIFU with other uterus-preserving fibroid treatments

Current fibroid management aims to relieve symptoms and enhance QoL by using the most effective, safe, and minimally invasive approaches. Several comparative studies and meta-analyses have evaluated the efficacy and safety of MR-HIFU in relation to other uterine-sparing treatments, such as UAE, myomectomy, and US-HIFU. Table 4 presents studies comparing MR-HIFU with other uterus-preserving therapies.

Table 4. Summary of studies comparing MR-HIFU with other uterus-preserving fibroid treatments.

Study	Study design	Number of Patients	Follow-up (months)	Comparison	Parameters	Main outcome	Re-intervention rates
Original studies							
Laughlin Tommaso et al. 2019	Randomized controlled study	83	36	UAE vs. MR-HIFU	Patient records on need for additional treatments, AMH values, UFS-QoL	Risk of secondary fibroid treatment higher with MR-HIFU than UAE (HR 2.81;95%CI 1.01-7.79, p=0.47)	UAE 13%, MR-HIFU 30% (p=0.047)
Mohr-Sasson et al. 2018	Follow-up cohort study	154	31–36	MR-HIFU vs. myomectomy	UFS-QoL	No difference in UFS-QoL between treatments (p=0.43)	Myomectomy 8 %, MR-HIFU 13 % (p=0.312).
Barnard et al. 2017	Comprehensive cohort	83	1.5	UAE vs. MR-HIFU	Patient records	Shorter recovery time and minor need for opioid analgesics after MR-HIFU (p < .001 for each).	NR
Ikink et al. 2014	Comparative study	119	3	UAE vs. MR-HIFU	UFS-QoL	SSS and HRQL improved with both modalities (P < 0.001).	MR-HIFU 35%, UAE 4.5%, (p=0.002)
Froeling et al. 2013	Retrospective analysis	77	61	UAE vs. MR-HIFU	UFS-QoL	SSS and HRQoL scores better after UAE than MR-HIFU (p= 0.019 and 0.049 respectively)	MR-HIFU 67%, UAE 12%, (p <0.001)
Reviews and meta-analyses							
Dou et al. 2024	Systematic review and meta-analysis	5216 (18 studies)	60	MR-HIFU vs. US-HIFU	Patient records	Re-intervention rate at 12, 24 and 60 months lower with US-HIFU compared to MR-HIFU treated (p < 0.001 each)	Re-intervention rates lower with NPV% over 50% with both modalities.

Study	Study design	Number of Patients	Follow-up (months)	Comparison	Parameters	Main outcome	Re-intervention rates
Morris et al. 2023	Systematic review and meta-analysis	NR (37 studies)	6	MR-HIFU, US-HIFU, UAE, and RFA.	Overall health and fibroid-specific questionnaires	Minimally invasive approaches significantly improved overall QoL at 3 months and decreased symptom severity at 6 months.	NR
Yerezhhepbayeva et al. 2022	Systematic review and meta-analysis	2218 (29 studies)	24	UAE vs. MR-HIFU	MRI	Fibroids shrinkage larger with UAE (68%) than MR-HIFU (35%) (p=0.0001). More complications after UAE (p < 0.001)	NR
Liang et al. 2021	Systematic review and meta-analysis	4205 (13 studies)	NR	Focused radiofrequency and HIFU vs. myomectomy and hysterectomy	Patient records, UFS-QoL	The major complication rate was lower for the ablative methods compared to myomectomy (RR 0.111, 95%CI 0.070-0.175, p= .0)	No difference was found between the thermal ablative group and myomectomy group (p=0.16)
Liu et al. 2021	Systematic review and meta-analysis	4592 (5 studies)	6–62	UAE vs. MR-HIFU	UFS-QoL, patient records	SSS and QoL increased significantly in both groups, but the increase was greater in UAE (p < 0.001).	MR-HIFU 30-67%, UAE 7-17%, (p < 0.001)
Yu et al. 2021	Systematic review and meta-analysis	6247 (48 studies)	12	US-HIFU vs. MR-HIFU	Patient records	Fibroid volume decreased by US-HIFU 66% vs. 36% by MR-HIFU. For US-HIFU the NPV% was 81% and for MR-HIFU 59%.	US-HIFU 5.2%, MR HIFU 13%

MR-HIFU= Magnetic Resonance-Guided High-Intensity Focused Ultrasound, UAE= Uterine Artery Embolization, UFS-QoL= Uterine Fibroid Symptom and Quality of Life, AMH= Anti-Müllerian Hormone, NR= Not reported

2.4.1 Comparison between MR-HIFU and UAE

Several studies have compared MR-HIFU and UAE for fibroid treatment (Table 4). Both treatments have been found to reduce symptom severity and increase the patients' QoL (Morris et al. 2023; L. Liu et al. 2021; Mohr-Sasson et al. 2018; Froeling et al. 2013). Some studies have found that UAE is more effective in reducing symptoms and increasing QoL (Liu et al. 2021; Froeling et al. 2013) than MR-HIFU. Studies have had variable follow-up times and NPV%-values in the MR-HIFU treatment groups.

Reduction in fibroid volume has been recorded with both treatment modalities, but evidence shows larger shrinkage with UAE than MR-HIFU (Yerezhepbayeva et al. 2022; L. Liu et al. 2021).

The re-intervention rate seems to be higher after MR-HIFU but results are heterogeneous, probably due to large variations in follow-up times, treatment success and study settings (12-month re-intervention after MR-HIFU 35% vs. UAE 4.5 %, $p=0.002$ ((Ikink et al. 2014)), and 36 months re-intervention after MR-HIFU 30% vs. UAE 13%, , HR 2.81;95%CI 1.01-7.79, $p=0.047$ ((Laughlin-Tommaso et al. 2019)). Recovery was faster after MR-HIFU than UAE in a randomized trial with 83 patients and a follow up time of six weeks (Barnard et al. 2017).

Both treatment modalities, MR-HIFU and UAE, are effective in treating fibroid symptoms and QoL. Fibroid shrinkage seems to be greater after UAE and re-intervention rates higher after MR-HIFU, but studies are very heterogeneous.

2.4.2 Comparison between MR-HIFU and US-HIFU

A review and meta-analysis of 48 studies compared MR-HIFU and US-HIFU. US-HIFU achieved larger NPV% (81% vs. 59%), greater fibroid shrinkage (66% vs. 36%), and lower re-intervention rates (5.2% vs. 13.4%) (Yu et al. 2021). Another meta-analysis on the same subject confirmed significantly lower re-intervention rates after US-HIFU (0.9% vs. 12% at 12 months $p=0.08$; 15% vs. 53% at 60 months, $p<0.001$), particularly when NPV% was over 50% (Dou et al. 2024). Since US-HIFU is not available in Finland and in the other Nordic countries, the generalizability of these findings is uncertain.

2.4.3 Comparison between MR-HIFU and myomectomy

Long-term outcomes of MR-HIFU compared to myomectomy were reported in a prospective follow-up study with 154 women and a follow-up time of 31 months. The difference in re-intervention rates at 31 months (13% vs. 8%) was non-significant ($p=0.3$). The QoL scores at the end of the follow-up were comparable ($p=0.4$) (Mohr-Sasson et al. 2018). In a systematic review and meta-analysis with

4,205 patients, ablative methods (HIFU, RFA) were compared to myomectomy. The ablative treatments were associated with fewer complications, shorter hospital stays, and better recovery than myomectomy (Liang et al. 2021).

The MYCHOICE study (Anneveldt et al. 2021) is an ongoing national, multicenter, open label randomized controlled trial, with data collection projected to be completed by 2026. The trial compares MR-HIFU with standard fibroid treatments, including hysterectomy, myomectomy, and UAE. The study aims to evaluate the long-term effectiveness and cost-effectiveness of MR-HIFU compared with conventional fibroid treatment. A randomized controlled trial of this scale may provide important new evidence and provide guidance on the management of uterine fibroids.

2.5 Ovarian reserve and uterine fibroid treatments

When evaluating different fibroid treatments, patients' reproductive intentions should be carefully considered. The potential impact of treatment on ovarian reserve is particularly relevant for younger patients who may wish to conceive in the future, as well as for those already experiencing infertility. In the latter group, distinguishing whether infertility results directly from fibroids or something else is sometimes difficult, since other factors contributing to infertility are often present.

AMH is a dimeric glycoprotein secreted by granulosa cells in females. In the ovary, AMH inhibits recruitment of primordial follicles into the growing follicle pool. The term *ovarian reserve* refers to the remaining pool of primordial follicles within the ovaries. AMH is produced by preantral and small antral follicles and is currently considered to be the most reliable biomarker for assessing ovarian reserve (Gowkielewicz et al. 2024). Serum AMH levels correlate strongly with the number of growing follicles, although the rate of age-related decline in AMH varies among women (Moolhuijsen et al. 2020). Another method of estimating the ovarian reserve is the antral follicle count (AFC). AMH has less intercycle and intracycle variation than AFC (Biniash et al. 2022; Van Disseldorp et al. 2010). AMH typically becomes undetectable approximately five years before menopause; however, there is substantial interindividual variability in AMH levels among women of the same chronological age (Iwase et al. 2018; Broer et al. 2014). The use of combined oral contraceptives is known to reduce AMH levels, especially after over six months of use but this effect is reversible (Amer et al. 2020).

Studies on the effects of UAE on ovarian reserve have yielded controversial results. A retrospective cohort study with 32 patients treated with UAE demonstrated significantly lower serum AMH levels 12 months after treatment (Arthur et al. 2014). Similarly, a significant and sustained reduction in AMH levels following UAE was found in a follow-up study with 177 women and with a follow-up time of

24 months (Hehenkamp et al. 2007). In contrast, a more recent meta-analysis with six studies and 353 women, did not find any significant effect of UAE on AMH levels; the follow up time was three to 12 months (weighted mean difference -0.58 ng/ml; 95% CI -1.5–0.36) (El Shamy et al. 2020). The possible causative mechanisms the adverse effect of UAE on ovarian reserve are vascular occlusion and hypoxic ovarian damage (Kim et al. 2016).

Evidence suggests that HIFU treatment does not affect the ovarian reserve adversely to any significant extent. However, most available studies focus on ultrasound-guided US-HIFU, not MR-HIFU. Several investigations have reported that serum AMH levels remain stable at three, six, and 12 months post-treatment compared with baseline values (Gu et al. 2024; Qu et al. 2020; J. S. Lee et al. 2017).

2.6 Fibroid treatments and future pregnancies

For women hoping to conceive, the treatment options for fibroid symptoms are myomectomy and radiological treatments. All available hormonal therapies also act as contraceptives and are thus unsuitable.

A systematic review evaluated pregnancy outcomes after myomectomy, HIFU, and UAE and found that live birth rates were highest following myomectomy (76%) and HIFU (71%), and lowest after UAE (61%). This difference is statistically significant ($p < 0.001$). The miscarriage rates were 19%, 12%, and 27%, respectively (difference between myomectomy and HIFU vs. UAE $p < 0.001$). The authors concluded that myomectomy and HIFU are preferable for women who desire pregnancy and have symptomatic fibroids, whereas UAE may be associated with poorer outcomes (Khaw et al. 2020).

Similarly, a review covering 21 studies included 124 pregnancies after MR-HIFU. The reported live birth rate was 73% and there were no uterine ruptures. Two cases of placenta previa occurred, but data heterogeneity and lack of age-related analysis limited conclusions (Anneveldt et al. 2021).

In a meta-analysis, comparable live birth rates were found after US-HIFU (74%), MR-HIFU (70%), and UAE (71%). Miscarriage was more frequent following UAE (19%) than MR-HIFU (16%) and US-HIFU (11%). Despite potential confounding factors such as age and comorbidities, all three uterus-preserving modalities were considered feasible options for women desiring pregnancy (Akhatova et al. 2023).

Cohort data further support these findings. In the retrospective FUMOS study with 132 women, (Verpalen et al. 2020), four of 11 women seeking pregnancy after MR-HIFU conceived (36%), resulting in seven live births. In another cohort study, 99 MR-HIFU-treated women were followed for seven years. 38% attempted conception, and 65% of these achieved pregnancies. The miscarriage rate was 22% and live birth rate of 72% (Inbar et al. 2025).

Collectively, current evidence supports the use of MR-HIFU for women who are planning future pregnancies and who have fibroids needing treatment. No interval between MR-HIFU and conception is considered necessary as the first successful pregnancies have been reported one to two months after the therapy. It must be emphasized that there is no data stating that MR-HIFU improves fibroid-related infertility. The golden treatment standard for these patients is still myomectomy (Khaw et al. 2020).

3 Aims of the study

The objective of this doctoral thesis was to assess the effectiveness and safety of MR-HIFU in treating uterine fibroids. The specific aims were:

To assess the effect of oxytocin infusion on the blood flow of different types of uterine fibroids and surrounding tissues using contrast-enhanced MRI.

To evaluate the impact of MR-HIFU on ovarian reserve of women treated for fibroids or adenomyosis by comparing serum AMH levels before and three months after treatment.

To examine the effects of MR-HIFU treatment on fibroid-related symptoms and QoL in patients with symptomatic uterine fibroids over a 12-month follow-up period.

To examine the effects of MR-HIFU treatment on specific fibroid-related symptoms and QoL in patients with isolated bleeding or bulk symptoms over a 12-month follow up.

4 Patients, materials and methods

4.1 Ethical considerations

4.1.1 Study I

Study I followed the ethical regulations of the Ethics Committee of the Hospital District of Southwest Finland and the National Committee of Medical Research Ethics (T366/2017 25.1.2018). Written informed consent for the MRI study and oxytocin administration was obtained from all patients and healthy volunteers in study I. The study was reported to the EudraCT database (EudraCT:2017-0005022-38) and registered at ClinicalTrials.gov NCT03937401.

4.1.2 Studies II-IV

For studies II-IV, approval of the Ethics Committee of the Hospital District of Southwest Finland (ETMK: 95/1801/2015 16.6.2015) was obtained. The studies are registered at ClinicalTrials.gov NCT02914704. Written informed consent was obtained from all patients recruited in the studies.

4.2 Study population

For Study I, 17 premenopausal women with one or more uterine fibroids were enrolled. The inclusion criteria were sufficient physical and mental health for undergoing MRI, the presence of fibroid-related symptoms, and premenopausal status. All participants did not subsequently receive MR-HIFU treatment, since the imaging procedure was part of the assessment to determine eligibility for MR-HIFU. Eleven premenopausal women without uterine fibroids or other uterine pathology were recruited as a control group.

The study population in studies II, III and IV was recruited from the patient population treated with MR-HIFU at the Turku University Hospital. The recruitment time interval for the MR-HIFU research project started in May 2016 and is ongoing. The patient populations in studies II-IV overlap to some extent, as shown in the recruitment schedule presented in detail in Figure 8.

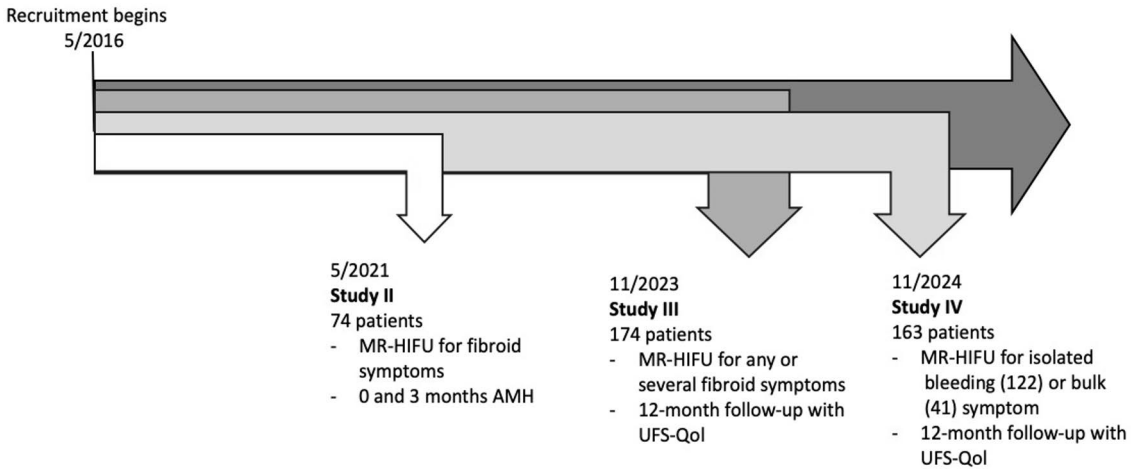


Figure 8. Timeline showing the recruitment of patients in Turku University Hospital to a prospective study from the beginning of the MR-HIFU treatments in May 2016. After study III, 20 new patients were enrolled in study IV. Otherwise the study population consists of the same patients as in study III but only those with an isolated bleeding- or bulk symptom were enrolled. The recruitment to a prospective study continues.

In study II, 74 premenopausal women treated with MR-HIFU for fibroid symptoms or adenomyosis, with a baseline AMH level of 0.1 $\mu\text{g/l}$ or above, were enrolled.

In study III, a total of 175 women presenting with any or several uterine fibroid symptoms and treated with MR-HIFU were included.

In study IV, a total of 163 women with isolated bleeding or bulk symptoms related to uterine fibroids and treated with MR-HIFU, were enrolled. 122 of these patients had a bleeding symptom and 41 had a bulk symptom. The patient characteristics in studies I-IV are shown in Table 5.

Table 5. Patient characteristics in studies I-IV.

Variable	Study I		Study II	Study III	Study IV	
Number of patients	28		74	174	163 ¹	
	Fibroid patients 17	Controls 11			Patients with bleeding symptom 122	Patients with bulk symptom 41
Age, mean (range) or median (range)	Mean 38 (26–49)	Mean 26 (24–33)	Mean 38 (24–49)	Median 39 (24–57)	Median 40 (24–55)	Median 38 (24–57)
BMI, Mean (range) or median (range)	Mean 23 (19–34)	Mean 21 (20–22)	NR	Median 24 (18–39)	Median 24 (19–39)	Median 24 (18–37)
Leading symptom						
Bleeding symptom N (%)	NR		NR	127 (73%)	122 (75%)	0 (0%)
Bulk symptom N (%)	NR		NR	50 (29%)	0 (0%)	41 (25%)
Pain N (%)	NR		NR	33 (19%)	0 (0%)	0 (0%)
Infertility N (%)	NR		NR	8 (5%)	0 (0%)	0 (0%)
More than one leading symptom N (%)	NR		NR	42 (25%)	0 (0%)	0 (0%)
FIGO types of fibroids						
FIGO 0 N (%)	0 (0%)		NR	7 (4%)	7 (6%)	1 (2%)
FIGO 1 N (%)	2 (11%)		NR	24 (12%)	26 (21%)	8 (20%)
FIGO 2 N (%)	3 (18%)		NR	52 (26%)	37 (31%)	4 (10%)
FIGO 3 N (%)	1 (6%)		NR	64 (32%)	43 (35%)	6 (15%)
FIGO 4 N (%)	1 (6%)		NR	20 (10%)	4 (3%)	8 (20%)
FIGO 5 N (%)	0 (0%)		NR	17 (9%)	3 (3%)	11 (27%)
FIGO 6 N (%)	1 (6%)		NR	15 (8%)	0 (0%)	0 (0%)
FIGO 7 N (%)	1 (6%)		NR	0 (0%)	0 (0%)	0 (0%)
FIGO 2-5 N (%)	8 (47%)		NR	NR	NR	NR
Funaki type						
Funaki 1 N (%)	0 (0%)		6 (8.3%)	22 (11%)	11 (9%)	6 (15%)
Funaki 2 N (%)	12 (71%)		60 (83%)	159 (80%)	101 (83%)	32 (78%)
Funaki 3 N (%)	5 (29%)		6 (8.3%)	17 (9%)	9 (8%)	1 (2%)
Mean fibroid diameter (cm)	6.2		5.8	4.9	4.9	7.1
Mean NPV%	NR		NR	69%	72%	59%

1= There were 20 new patients in study IV recruited after study III. From the whole data only those with isolated bleeding or bulk symptoms were enrolled in study IV. NR= Not Reported

4.3 Equipment and imaging protocols

All MRI images were acquired with the same MR scanner (Ingenia 3.0T, Philips, Best, The Netherlands). Women were positioned prone during the MRI scan of the pelvis. A 32-channel torso coil was used. The imaging protocol included dynamic contrast enhanced (DCE) imaging for quantitative perfusion analysis.

In study I, an additional MRI scan was performed later with the same imaging protocol under continuous intravenous infusion of oxytocin.

In studies II, III, and IV MR-HIFU was performed using an extracorporeal clinical tabletop system (Sonalleve V2, Profound medical Inc., Mississauga Canada). The radiologist planned the treatment by positioning the ellipsoid treatment cells into the targeted fibroid one by one to cover the whole fibroid. Treatment power was selected based on test sonication to achieve the best possible temperature rise in the target tissue. During sonication, heating of the targeted area and any undesired heating of surrounding tissue were monitored with real-time MR thermometry.

4.3.1 Objective outcome measures

In study I the arterial input function was determined from the iliac artery by placing a circular region of interest (ROI) onto the artery lumen. Averaged blood flow values were obtained for the fibroids, myometrium, and muscle. The fibroid ROIs were drawn within three middle slices of the fibroid to include most of the fibroid. The myometrium ROIs were drawn on the negative side of the fibroid in three of the most representative slices of myometrium and the muscle ROIs were drawn on the abdominal muscle within the three middle slices.

In studies II-IV, to evaluate the NPV and to calculate the NPV%, a contrast-enhanced T1W MR image was acquired after the treatment. The total treatment energy was calculated from the treatment data by multiplying used power and sonication time for each sonication and summing up the energies for all sonications.

In study II, the AMH levels were measured before the MR-HIFU treatment and three months after treatment. For the assessment of the AMH levels, 5 ml of serum was collected and stored in ≤ -20 °. The Elecsys AMH Plus assay was used; it has an analytical imprecision less than 5 % and the lower level of quantification 0.03 $\mu\text{g/l}$ (Roche Diagnostics).

4.3.2 Subjective outcome measures

In Studies III and IV the primary indication for MR-HIFU treatment (type of fibroid symptom) was recorded for all patients. The reported symptoms were categorized as bleeding (heavy or irregular bleeding), bulk (feeling of heaviness or urinary symptoms), and pain (dysmenorrhea or lower abdominal pain).

The clinical efficacy of MR-HIFU in alleviating fibroid-related symptoms was assessed using the UFS-QoL questionnaire, originally developed in 2002 (Spies et al. 2002). The questionnaire was designed to measure both symptom severity and health-related quality of life (HRQL) in women with uterine fibroids. Its validation included 110 patients with confirmed fibroids and 29 women without fibroids,

assessed using three established questionnaires as well as physician and patient measures of symptom severity (Spies et al. 2002).

The UFS-QoL is a self-report questionnaire consisting of two main sections, the SSS and the QoL. The QoL section is further divided into six subscales: Concern (five items), Activities (seven items), Energy/Mood (seven items), Control (five items), Self-Consciousness (three items), and Sexual Function (two items). Responses are rated on a five-point Likert scale ranging from “none of the time” or “not at all” to “all of the time” or “a very great deal.”

Scores for symptom severity and QoL are calculated according to standardized formulas, yielding a total SSS and QoL score. The SSS ranges from 0 to 100, with higher scores indicating more severe symptoms, whereas in the QoL score, which also ranges from 0 to 100, higher scores indicate better QoL. A decrease of 10 points in SSS is considered a clinically relevant result (Spies et al. 2002). An official Finnish translation of the UFS-QoL, provided by SIR, was used in these studies, although it has not been formally validated in Finland. The Finnish version of the questionnaire is presented in Figure 9.

**MYOOMIEN OIREET:
TERVEYTTÄ JA ELÄMÄNLAATUA KOSKEVA KYSELY (UFS-QOL)**

Potilaan nimi: _____

Potilastunnus: _____

Päivämäärä: _____

Alla on lueteltu oireita, joita esiintyy myoomista (kohdun lihaskasvaimista) kärsivillä naisilla. Miettikää, miten kukin oire liittyy teidän myoomiinne tai kuukautiskiertoonne. Kysymykset koskevat sitä, miten paljon vaivaa teillä on kolmen viime kuukauden aikana ollut kustakin oireesta.

Oikeita tai väriä vastauksia ei ole. Vastatkaa jokaiseen kysymykseen rastittamalla sopivin ruutu. Jollei kysymys sovi tilanteeseenne, merkitkää vastaukseksi "ei lainkaan".

Kuinka paljon vaivaa seuraavat asiat ovat aiheuttaneet teille kolmen viime kuukauden aikana?	Ei lainkaan	Vähän	Jonkin verran	Paljon	Erittäin paljon
1. Runsas vuoto kuukautisten aikana	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
2. Verihyytymät kuukautisvuodossa	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
3. Kuukautisten keston vaihtelu verrattuna aikaisempaan	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
4. Kuukautiskierron pituuden vaihtelu verrattuna aikaisempaan	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
5. Kireyden tai paineen tunne alavatsan alueella	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
6. Tihentynyttä virtsaamista päiväsaikaan	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
7. Tihentynyttä virtsaamista yöaikaan	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
8. Uupumuksen tunne	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Seuraavat kysymykset koskevat tuntemuksianne ja kokemuksianne siitä, miten myoomien oireet ovat vaikuttaneet elämääne. Miettikää, miten kukin kysymys liittyy kokemuksiinne myoomista kolmen viime kuukauden aikana.

Oikeita tai väriä vastauksia ei ole. Vastatkaa jokaiseen kysymykseen rastittamalla sopivin ruutu. Jollei kysymys sovi tilanteeseenne, merkitkää vastaukseksi "ei lainkaan".

Kuinka usein myoomiin liittyvät oireet ovat kolmen viime kuukauden aikana...	Ei lainkaan	Harvoin	Toisinaan	Usein	Koko ajan
9. hermostuttaneet, koska kuukautisten alkamista tai kestoa ei ole voinut ennustaa?	<input type="checkbox"/> 1	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
10. saaneet teidät jännittämään matkustamista?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
11. häirinneet liikkumistanne?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
12. saaneet olonne väsyneeksi?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
13. saaneet teidät vähentämään urheiluun tai muuhun liikkumiseen käyttämääne aikaa?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
14. saaneet teidät tuntemaan, ettette hallitse elämääne?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

15. aiheuttaneet huolta alusvaatteiden tahriintumisesta?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
16. saaneet teidät tuntemaan itsenne vähemmän aikaansaavaksi?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
17. saaneet olonne uneliaaksi tai veltoksi päiväsaikaan?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
18. saaneet teidät vaivautuneeksi painonnousun takia?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
19. saaneet teidät tuntemaan, että teidän on vaikea suoriutua tavanomaisista toimistanne?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
20. häirinneet sosiaalista elämääne?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
21. saaneet teidät tietoiseksi vatsanne koosta ja ulkonäöstä?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
22. aiheuttaneet huolta vuodevaatteiden tahriintumisesta?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5

Kuinka usein myömyihin liittyvät oireet ovat kolmen viime kuukauden aikana...	Harvoin				
	Ei lainkaan	Toisinaan	Usein	Koko ajan	
23. saaneet olonne surulliseksi, lannistuneeksi tai toivottomaksi?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
24. saaneet olonne apeaksi ja alakuloiseksi?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
25. saaneet olonne lopen uupuneeksi?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
26. aiheuttaneet huolta ja hätää terveydestänne?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
27. saaneet teidät suunnittelemaan toimenne huolellisemmin?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
28. aiheuttaneet teille vaivan tunnetta, koska joudutte aina pitämään mukanaan ylimääräisiä siteitä, tamponeja ja vaatteita vahinkojen välttämiseksi?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
29. saaneet teidät kiusaantumaan?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
30. saaneet teidät tuntemaan epävarmuutta tulevaisuudesta?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
31. saaneet olonne ärtyisäksi?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
32. aiheuttaneet huolta päällysvaatteiden tahriintumisesta?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
33. vaikuttaneet siihen, minkä kokoisia vaatteita käytätte kuukautisten aikana?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
34. saaneet teidät tuntemaan, ettette pysty hallitsemaan terveyttänne?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
35. saaneet teidät tuntemaan olonne heikoksi, ikään kuin voimat valuisivat teistä pois?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
36. vähentäneet sukupuolista halukkuuttanne?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5
37. saaneet teidät välttämään seksiä?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5

Figure 9. The Uterine Fibroid-related Symptom Severity and Quality of Life Questionnaire (UFS-QoL) in Finnish (officially translated and provided by SIR).

The patients filled in the UFS-QoL questionnaire before treatment, and this was set as the baseline in the studies. All patients were evaluated with the UFS-QoL questionnaire three months and 12 months after the treatment.

4.4 Statistical analysis

In studies I and II the statistical analyses were performed by using the JMP Pro statistical software (Study I version 13.1.0 and Study II version 16.2.0 (SAS Institute Inc.)). A p-value of less than 0.05 was considered statistically significant.

In study I each dataset was analyzed for normal distribution with the Shapiro-Wilk test. Normally distributed numerical data were presented as mean \pm standard deviation and data with a skewed distribution were presented as median and interquartile range (IQR). Normally distributed data were compared with the Tukey-Kramer test for all pairs and data with skewed distribution were compared with a nonparametric Steel-Dwass method for all pairs. A retrospective power analysis was performed using standard least squares to ensure enough patients in the fibroid group.

In study II the normal distribution of each dataset was analyzed with the Shapiro-Wilk W test. The correlation between normally distributed parameters was analyzed by the Pearson product-moment correlation and non-normally distributed parameters were analyzed by Spearman's rank correlation analysis. Group means of normally distributed datasets were compared using the Tukey-Kramer honestly significant difference (HSD) test for all pairs and non-normally distributed datasets were compared using the Steel-Dwass method for all pairs.

In study III and IV for all the outcome parameters, the Shapiro-Wilk test and visual density distribution evaluation were used to assess whether the data was normally distributed. Since most of the parameters were found not to be normally distributed, a paired Wilcoxon signed-rank test was used to calculate the statistical significance of parameter changes between time points.

5 Results

5.1 Effect of oxytocin on blood flow of uterine fibroids, myometrium and skeletal muscle (study I)

The study I showed that oxytocin infusion decreased significantly the blood flow of every fibroid analyzed. The median blood flow of all fibroids without oxytocin was 39.9 (IQR 21.9–134.5) ml/100g/min and with oxytocin 3.5 (2.1–12.1) ml/100g/min, ($p < 0.0001$, power=0.87). Oxytocin had no marked effect on blood pressure and no adverse effects were recorded. Oxytocin infusion did not affect the size of the fibroids nor the uterus. Figure 10 shows a fibroid without oxytocin and with oxytocin.

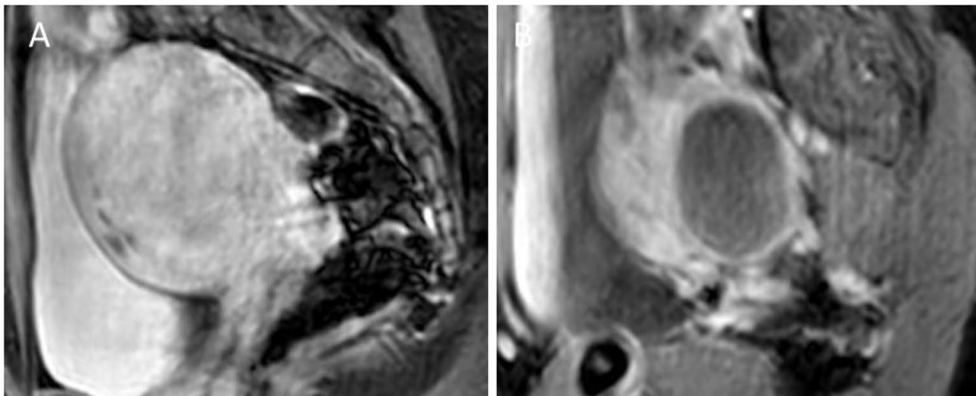


Figure 10. Contrast-enhanced T1-weighted (T1W) MR image of a fibroid A) without oxytocin and B) with oxytocin. Image from the author's own files.

Figure 11 demonstrates the effect of oxytocin on the blood flow of all fibroids investigated.

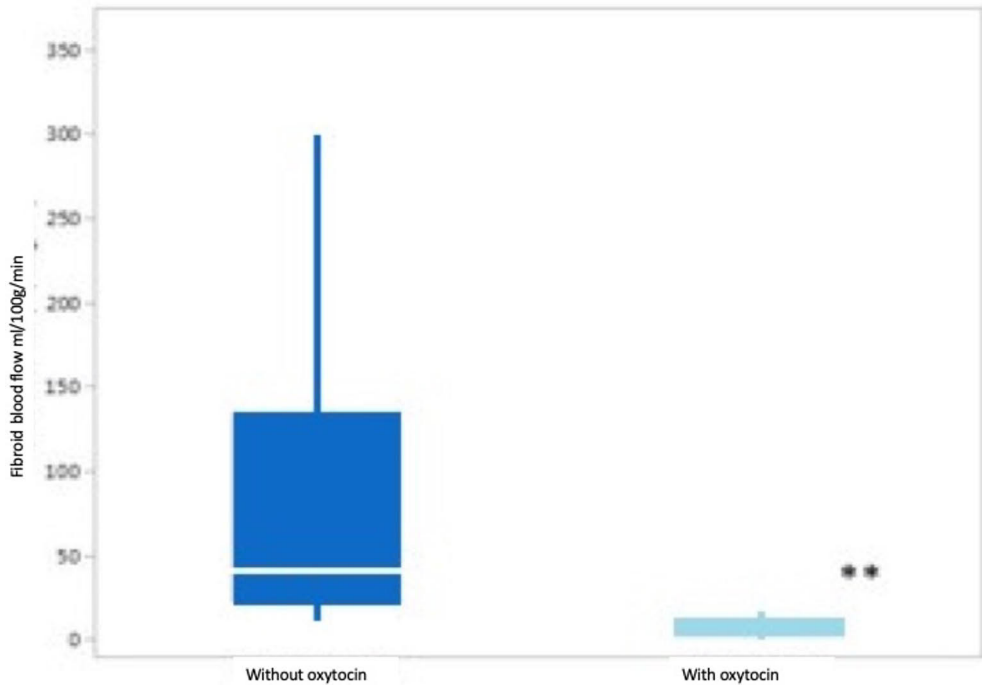


Figure 11. Median blood flow of all fibroids without oxytocin and with oxytocin, ** P-value < 0.0001. Modified from original publication I

Oxytocin had no significant effect on the blood flow of the myometrium in fibroid patients or in controls. In the fibroid group, the median myometrial blood flow without oxytocin was 61.1 (IQR 26.4–165.2) ml/100g/min and during oxytocin infusion 69.4 (IQR 21.5–134.6) ml/100g/min ($p= 0.81$). In the control group, the corresponding blood flow values were 59.4 (IQR 43.6–109.2) and 68.6 (IQR 30.8–101.4) ml/100g/min ($p= 0.74$), Figure 12.

Oxytocin increased slightly but statistically significantly the blood flow in skeletal muscle. In the fibroid patients the median blood flow in the skeletal muscle was 2.1 (IQR 1.6–2.8) ml/100g/min at baseline and 3.7 (IQR 2.7–5.3) ml/100g/min during oxytocin infusion ($p = 0.04$). In the control group, the skeletal muscle blood flow was 2.0 (IQR 1.6–4.4) ml/100 g/min without oxytocin and 4.9 (IQR 3.2–6.3) ml/100 g/min with oxytocin, ($p = 0.04$), Figure 13.

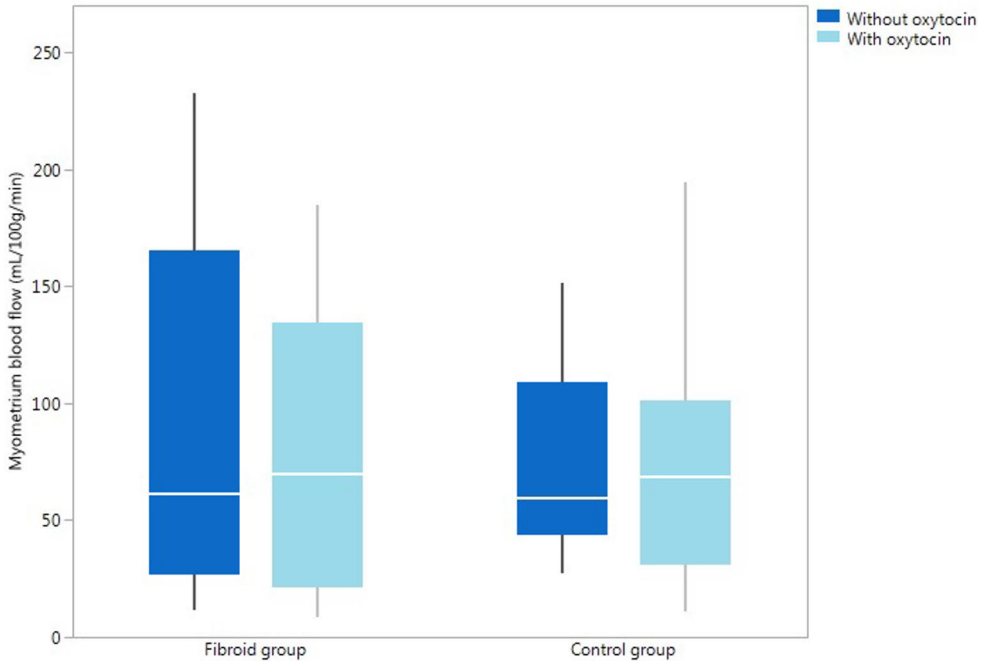


Figure 12. Median blood flow of the myometrium without oxytocin and with oxytocin in patients with fibroids and controls. Changes were not significant. Modified from original publication I.

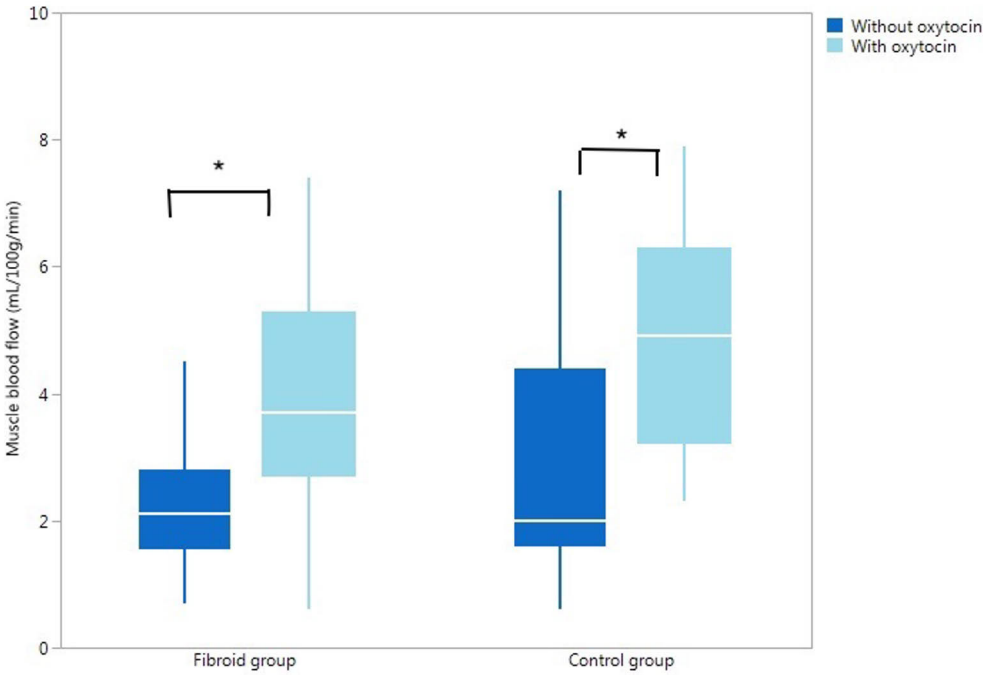


Figure 13. Median blood flow of the skeletal muscle with oxytocin and without oxytocin in patients with fibroids and controls. * p-value <0.05. Modified from original publication I

5.2 Effect of MR-HIFU treatment on ovarian reserve (study II)

The study II showed that MR-HIFU treatment of uterine fibroids or adenomyosis did not affect AMH levels. To analyze the safety of MR-HIFU with regard to the ovarian reserve of women with different initial reserves, the patients were divided into three subgroups by baseline AMH levels. The median AMH levels of all the groups studied are shown in Table 6.

Table 3. Changes in serum anti-Müllerian hormone (AMH) values at baseline and 3 months after magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU).

Patients	AMH ug/l at baseline, Median (IQR)	AMH ug/l 3 months after MR-HIFU, median (IQR)	p-value
All patients together (N=74)	1.20 (0.72-2.21)	1.23 (0.66-2.37)	p=0.90
Group 1 (N=28)	0.58 (0.25-0.81)	0.52 (0.33-0.98)	p=0.3
Group 2 (N=31)	1.62 (1.18-1.88)	1.68 (0.96-2.26)	p=1.0
Group 3 (N=15)	3.65 (3.22-4.50)	3.78 (3.28-4.42)	p=1.0

AMH= anti-Müllerian hormone, IQR= Interquartile range, Group 1= AMH 0.1–1.0 µg/l (low baseline AMH), Group 2 = AMH 1.0–2.5 µg/l (intermediate baseline AMH), Group 3= AMH over 2.5 µg/l (high baseline AMH).

The changes in median AMH levels from baseline to three months after treatment were not statistically significant in any of the groups. Nor were there any statistically significant differences in AMH levels by fibroid location (anterior wall, posterior wall, fundus or lateral wall).

The overall mean NPV% in this study was 59%. The total delivered treatment energies and the total delivered acoustic energies at the focus were recorded. The delivered energies and the changes in AMH levels did not correlate significantly.

5.3 Effect of MR-HIFU on fibroid-related symptoms and QoL (study III)

The effect of MR-HIFU on fibroid-related symptoms and QoL was assessed by investigating 174 premenopausal women with symptomatic uterine fibroids treated with MR-HIFU. The clinical follow-up demonstrated a significant reduction in fibroid-related symptoms as well as improvement in QoL. The median NPV% in these treatments was 69% (IQR 47–89).

The median SSS decreased from 56 (IQR 44–69) at the baseline to 28 (IQR 16–44) at three months and to 25 (IQR 16–38) at 12 months after treatment. The change was significant from baseline to three months and to 12 months ($p < 0.01$ and $p < 0.01$, respectively) but not from three months to 12 months ($p = 0.3$). The QoL increased from a median of 48 (IQR 33–66) at baseline to 73 (IQR 59–93) at three months ($p < 0.01$) and to 78 (IQR 66–90) at 12 months after treatment ($p < 0.01$). The change in QoL was also statistically significant between three and 12 months ($p = 0.02$). The SSS and the HRQL at baseline, three, and 12 months are shown in Figure 14.

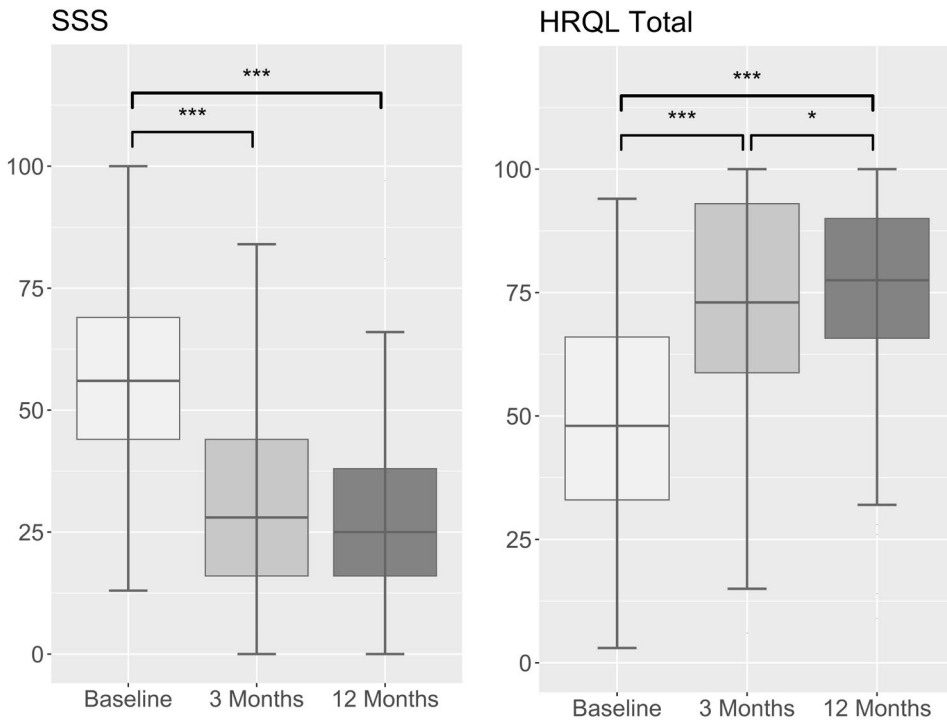


Figure 14. Median Symptom severity score (SSS) and median Quality of Life (HRQL) score at baseline, 3 months, and 12 months after MR-HIFU treatment. * $p < 0.05$, *** $p < 0.001$ (Modified from original publication III)

The results in the QoL subgroups were similar. Across all QoL subgroups (Concern, Activities, Energy/Mood, Control, Self-Consciousness, Sexual), the scores improved significantly at three and at 12 months compared with baseline ($p < 0.01$ for all comparisons). In the subgroups Concern, Control and Energy/Mood, the change was also significant between three months and 12 months ($p < 0.05$ each). The subgroup results are shown in Table 7.

Table 4. Changes in the Quality of Life subgroups (Concern, Activities, Energy, Control, Self-conscious, Sexual).

QoL Subgroups	Baseline QoL, Median (IQR)	3 months QoL, Median (IQR)	12 months, QoL, Median (IQR)	Significance of Δ in score change
Concern	35 (20–65)	65 (45–90)	70 (55–90)	0–3 months $p < 0.001$ 3–12 months $p < 0.05$ 0–12 months $p < 0.001$
Activities	46 (29–71)	75 (57–96)	82 (64–93)	0–3 months $p < 0.001$ 3–12 months NS 0–12 months $p < 0.001$
Energy/mood	46 (31–68)	77 (61–95)	82 (64–100)	0–3 months $p < 0.001$ 3–12 months $p < 0.05$ 0–12 months $p < 0.001$
Control	50 (30–70)	80 (56–95)	85 (65–100)	0–3 months $p < 0.001$ 3–12 months $p < 0.01$ 0–12 months $p < 0.001$
Self-conscious	58 (25–75)	75 (54–100)	75 (58–92)	0–3 months $p < 0.001$ 3–12 months NS 0–12 months $p < 0.001$
Sexual	50 (25–75)	75 (50–100)	75 (50–100)	0–3 months $p < 0.001$ 3–12 months NS 0–12 months $p < 0.001$

QoL=Quality of Life, IQR= Interquartile range, NS= Non-significant

The re-intervention rate during the 12-month follow-up was 2% (one myomectomy, two hysterectomies). The complication rate was low. Out of the 174 treated women, two in SIR criteria group B had first-degree skin burns which were treated with a topical agent and anti-inflammatory medication. Three patients in SIR criteria group C had the following complications: two patients had nonspecific inflammatory reactions requiring short hospitalization and one patient had pulmonary embolization two weeks after the MR-HIFU.

5.4 Effect of MR-HIFU on specific fibroid-related symptoms: bleeding or bulk symptom (study IV)

Patients with isolated bleeding or bulk symptom were identified from the general study population and the effect of MR-HIFU was analyzed more specifically in this subset. In all, 122 women only with bleeding and 41 only with bulk symptoms were treated with MR-HIFU. The efficacy of MR-HIFU on these symptoms was evaluated with the UFS-QoL questionnaire three and 12 months after the treatment.

The two groups were similar regarding age and BMI. Fibroid-specific medication (ulipristal acetate or relugolix) was used by 11% in the bleeding group

and 2% in the bulk group. The median fibroid volume in the bleeding group was 61 ml (IQR 25-116) and 189 ml (IQR 97-330) in the bulk group (non-significant difference). The fibroids in these two groups differed by FIGO type. In the bleeding group, 58% of the fibroids were submucous (FIGO type 0–2), 35% were type 3. There were no totally subserosal fibroids (FIGO type 6-7). In contrast, most (67%) of the fibroids in the bulk group were FIGO type 4–6, *i.e.*, intramural or subserosal.

There was a significant reduction in SSS in both groups at three months. In the bleeding group the median SSS at baseline was 56 (IQR 47–69), at three months 28 (IQR 16–44), and at 12 months 25 (IQR 13–31). The reduction in SSS was statistically significant between baseline and three months ($p < 0.001$) and between baseline and 12 months ($p < 0.001$). The change was not significant from three to 12 months. In the bleeding group the median QoL score at baseline was 43 (IQR 31–58), at three months 70 (IQR 53–82), and at 12 months 82 (IQR 69–91). The increase in QoL was statistically significant at all timepoints; baseline to three months and baseline to 12 months ($p < 0.001$) as well as from three months to 12 months ($p < 0.05$), Figure 15.

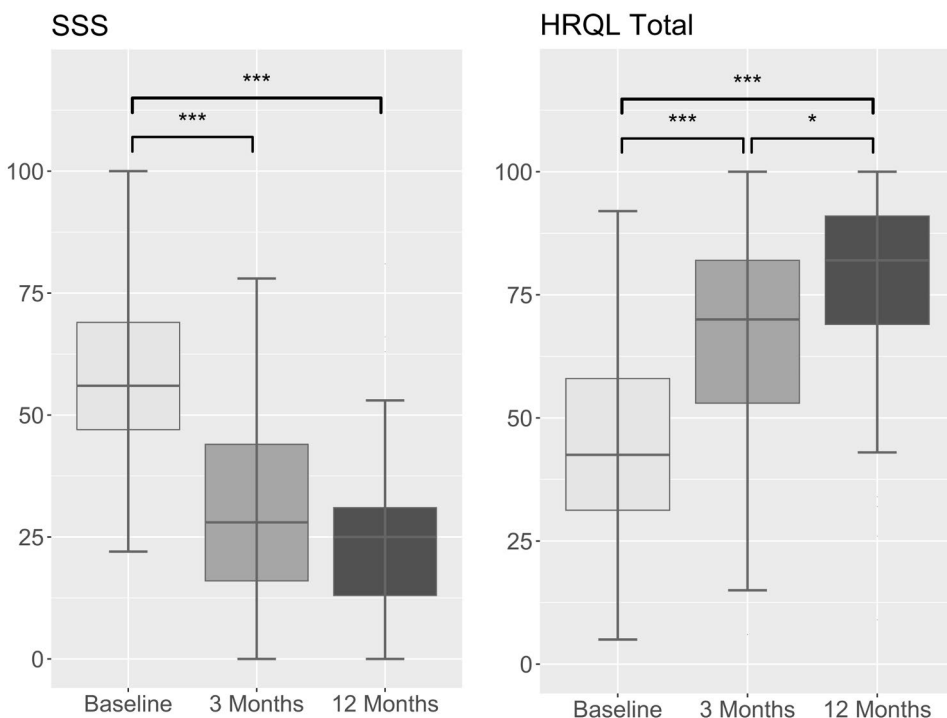


Figure 15. Median Symptom Severity Score (SSS) and Health Related Quality of Life (HRQL) among the bleeding patients. *** $p < 0.001$, * $p < 0.05$. In the bleeding group the change in SSS from 3 to 12 months was not significant (Modified from manuscript IV).

In the bulk group, results were similar. The median SSS at baseline was 46 (IQR 34–63), at three months 19 (IQR 6–30) and at 12 months 19 (IQR 6–41). The median QoL in the bulk group at baseline was 74 (IQR 45–83), at three months 89 (IQR 74–97) and at 12 months 82 (IQR 67–100). The reduction in SSS was statistically significant between baseline and three months ($p < 0.001$) and between baseline and 12 months ($p < 0.001$). It was not significant from three to 12 months. The increase in QoL was statistically significant from baseline to three months ($p < 0.001$) and from baseline to 12 months ($p < 0.01$) (Figure 16) but not from three to 12 months.

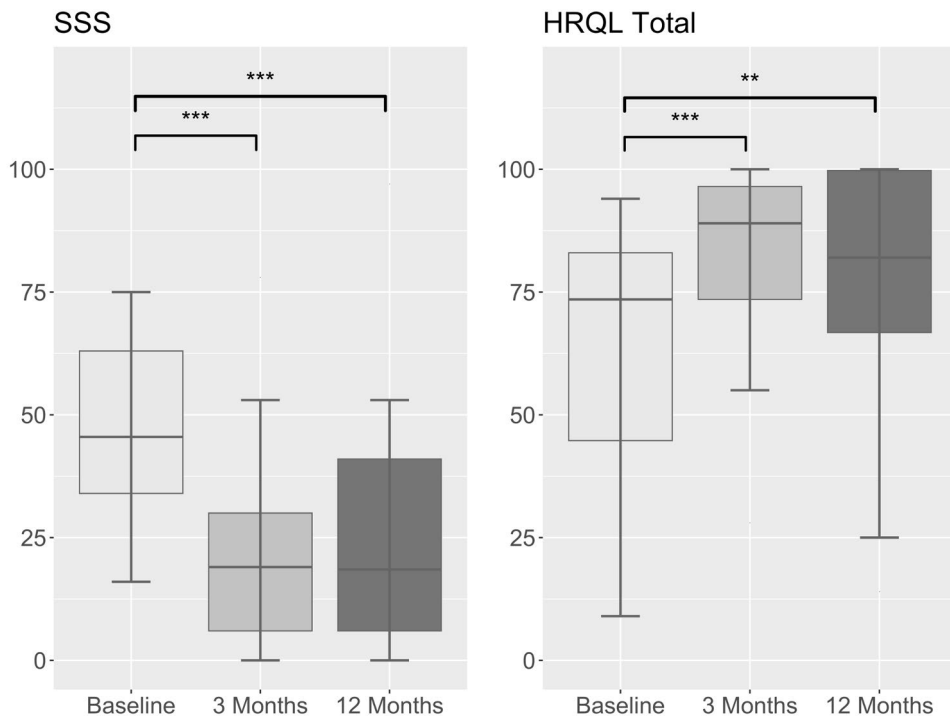


Figure 16. Median Symptom Severity Score (SSS) and Quality of Life (HRQL) of the patients in the bulk group. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$. Neither the change in SSS nor the change in HRQL was significant from 3 to 12 months (Modified from manuscript IV)

6 Discussion

Uterine fibroids constitute the most prevalent benign tumors among women of reproductive age, and their management therefore represents a substantial concern in healthcare. Owing to their high prevalence and potential impact on QoL, a comprehensive understanding of the available therapeutic modalities is important to optimize patient counseling and to support evidence-based clinical decision-making.

6.1 Oxytocin and uterine fibroids

In study I, the effect of oxytocin infusion on the blood flow of different types of uterine fibroids and surrounding tissues was analyzed and quantified with contrast enhanced MRI. Oxytocin reduced effectively the blood flow in the uterine fibroid tissue in every fibroid studied without affecting myometrial blood flow. A slight, yet statistically significant, increase in skeletal muscle blood flow was observed, but this change was considered clinically irrelevant, since the patients reported no subjective sensations and there were no changes in either blood pressure or heart rate.

The results are in agreement with a previous study, in which blood perfusion of uterine fibroids was assessed using contrast enhanced ultrasound (Wang et al. 2016). The use of oxytocin reduces blood loss during abdominal and laparoscopic myomectomies (Atashkhoei et al. 2017; R. Zhang et al. 2015; C.-J. Wang et al. 2007). Our results indicate that this might be due to the very strong decrease in the blood flow in the fibroids themselves rather than to an effect on the myometrium.

The underlying mechanism for this phenomenon is thus far unclear. Since there were no changes in myometrial blood flow or in the size of the uterus, the reduced blood flow in the fibroid is probably not caused by a reduction in the volume of fibroid tissue or by contractions of the myometrium. Therefore, it seems more likely that the effect is related to either the circulation supplying the fibroid or to the fibroid itself. It is possible that higher concentrations of oxytocin could also affect the blood flow of the uterus. None of the women reported any unpleasant sensations during oxytocin infusion, which may also reflect the relatively small contractive effect of the dose of oxytocin used.

Fibroids have their own hyperestrogenic hormonal environment and this might affect the amount of oxytocin receptors in the fibroid tissue. Evidence suggests that

estrogens increase the levels of oxytocin receptors in the myometrium (Bulun et al. 2015). Oxytocin stimulates also the proliferation of both myometrial and fibroid cells (Busnelli et al. 2010). On the other hand, oxytocin is also related to vasodilatation, and oxytocin receptors are present in blood vessels (Gimpl et al. 2001). More histopathological studies are needed to investigate whether oxytocin receptors are found in abundance also in the aberrant blood vessels of fibroids.

The main limitation of this study was the highly restricted study population, although the fibroids included were heterogeneous in terms of location, size, and Funaki classification. The sample size was too small to determine whether factors like location, size, or Funaki type, might influence the effect of oxytocin on fibroids. Furthermore, the interval between the first and second MRI examinations varied considerably, ranging from four to 207 days. It can be speculated that some alterations in fibroid size or structure could have occurred during this period. However, any substantial changes would likely have been detected on the MRI scans, and no such differences were observed. Nevertheless, based on the findings of this study and clinical observations from our group and others, the use of oxytocin during MR-HIFU treatments has now become standard practice. It seems to enhance heat accumulation, shorten the ultrasound pulses and the duration of MR-HIFU and increase also the NPV% achieved (Łoziński et al. 2021).

6.2 MR-HIFU and ovarian reserve

MR-HIFU is an effective but potentially tissue-damaging therapy if inaccurately targeted. Since MR-HIFU is a uterine-sparing treatment and considered suitable for women desiring future fertility or undergoing infertility treatment, it is crucial that it does not compromise the ovarian reserve. Since the timing of the menopause has significant implications for women's overall health (Muka et al. 2016), maintaining ovarian function is relevant for all patients treated for uterine fibroids.

MR-HIFU treatment has no significant effect on AMH levels. This finding is consistent with previous research, which has reported no adverse effects of US-HIFU on ovarian reserve when fibroids are treated (Ji et al. 2021; Qu et al. 2020; Cheung et al. 2016). Similarly, the randomized controlled FIRSST trial, which compared MR-HIFU and UAE, found no significant change in AMH levels 12 months after MR-HIFU. At 24 months, the median absolute change in AMH was significantly larger ($p=0.03$) after UAE ($-0.6\mu\text{g/l}$ (IQR $-1.2 - -0.4$)) than after MR-HIFU ($-0.2\mu\text{g/l}$ (IQR $-0.4 - 0.4$)) (Laughlin-Tommaso et al. 2019). Notably, the baseline AMH concentration in the present study was higher than in the FIRSST cohort ($1.2\mu\text{g/l}$ vs. $0.3\mu\text{g/l}$), thereby extending the evidence on the safety of MR-HIFU to women with higher baseline ovarian reserves.

A major strength of this study was the evaluation of AMH changes across different baseline ovarian reserve categories. Previous evidence suggests that ovaries with a diminished reserve may be more susceptible to damage (Dillon et al. 2013). However, we observed no difference between low, intermediate, and high AMH groups regarding the impact of MR-HIFU on ovarian reserve. Furthermore, neither fibroid location nor total treatment energy correlated with AMH changes, supporting the safety of the procedure in clinical practice.

The main limitation of the study was the lack of menstrual cycle data. Nonetheless, AMH is known to be a stable biomarker with minimal intracycle and intercycle variation (Van Disseldorp et al. 2010; La Marca et al. 2007). Another limitation was the lack of information regarding the use of hormonal medication during the follow-up period. Although baseline medication data were collected, consistent longitudinal data on the use of hormonal medication was not gathered.

6.3 MR-HIFU in treating fibroid symptoms

At the time this project was initiated, data on the clinical outcomes of MR-HIFU treatment for uterine fibroids was limited. Consequently, the primary objective of this gynecological research project was to study patient-reported outcomes and to evaluate this novel therapeutic approach to fibroid treatment within a Finnish patient population.

MR-HIFU reduced effectively fibroid-related symptoms and improved QoL. These findings are consistent with other recent studies (Bitton et al. 2023; Verpalen et al. 2019). The NPV% in our study was 69%. It was encouraging to find clinical efficacy, even when the NPV% was below the currently recommended threshold of 80% (Bitton et al. 2023). Some other studies on MR-HIFU in treating fibroids have also reported clinical improvement with lower NPV% (Kim et al. 2011; Funaki et al. 2009). The ongoing follow-up of our cohort will further clarify the influence of NPV% and other variables on long-term outcomes and re-intervention rates following MR-HIFU.

Health-related quality of life (HRQL) is a multidimensional concept that encompasses the physical, social, and psychosocial aspects of a certain disease. The assessment of an individual's general wellbeing can be divided into several subcategories. In a general French survey, the median two-thirds of fibroid patients reported moderate to severe impairment of QoL. The most affected areas of wellbeing were concern, energy, and self-consciousness (Hervé et al. 2018). In our study population, the baseline median total QoL-score was 48 (IQR 33–66), compatible with severely impaired QoL. In a study assessing the efficacy of various fibroid treatments on symptoms and QoL, the median QoL-score was 45, reflecting the fact that only severely decreased QoL drives patients to seek care (Anchan et al.

2023). The patients benefited significantly from MR-HIFU, as the total QoL-score improved to median of 78 (IQR 66–90) by 12 months. Somewhat better improvement has been reported following hysterectomy, myomectomy, and UAE with HRQL 89, 90, and 86.5, respectively (Anchan et al. 2023). MR-HIFU resulted in improvements of all subdomains of QoL, most noticeably in the areas of concern and control. In a study that compared QoL after myomectomy and UAE, improvement after both treatments were recorded regarding anxiety, activity, and energy, whereas the QoL related to control and sexual functions remained unchanged (Aktürk et al. 2023).

As the primary therapeutic goal in fibroid management is to alleviate the wide range of fibroid-related symptoms, understanding the efficacy of various treatments for specific symptom types is essential for individualized treatment strategies. In Study III, most patients (73%) experienced fibroid-related bleeding symptoms, suggesting that MR-HIFU may be particularly effective in managing such symptoms. Bulk symptoms were the predominant complaint of 29% of the patients, while 25% experienced multiple symptoms. To further assess the effect of MR-HIFU on bulk symptoms, Study IV focused on two separate patient groups, those with isolated bleeding symptoms and those with isolated bulk symptoms.

MR-HIFU effectively reduced both bleeding and bulk symptoms of patients with fibroids. Interestingly, symptom reduction was observed as early as three months after treatment in the overall cohort as well as in the bleeding and bulk subgroups. This is in agreement with previous studies that also demonstrated rapid symptom relief after MR-HIFU (Jacoby et al. 2016; Lozinski et al. 2022). Considering that fibroids are not physically removed and remain visible on MRI at the three-month follow-up, the improvement is apparently not only due to volume reduction but also to structural and tissue changes induced by MR-HIFU. Thermal ablation causes coagulative necrosis, which changes the consistency of the affected tissue (Viitala et al. 2023). The fibroid tissue maintains its own hormonal microenvironment and MR-HIFU probably alters this and may also influence uterine molecular signaling and endometrial homeostasis in a way that contributes to reduced bleeding symptoms.

A limitation of Studies III and IV was the relatively short follow-up period of 12 months. Continued monitoring of these patients will bring valuable information on the long-term efficacy of MR-HIFU. Another important consideration is that the study populations represented a carefully selected subgroup of women with uterine fibroids. This selective inclusion can be viewed as a limitation, as the findings may not fully reflect the effectiveness of MR-HIFU in the broader population of women with symptomatic fibroids. Estimating the proportion of fibroid patients ultimately eligible for MR-HIFU treatment remains challenging. Given the strict selection criteria applied at our center, it is likely that MR-HIFU will remain a therapeutic option for only a subset of the overall fibroid patient population.

The main limitations of Study IV were the overlap with the patients in Study III and the rather small sample size of the bulk symptom group. Because MR-HIFU is less suitable for patients with very large or numerous fibroids, patients predominantly with bulk symptoms are often excluded from MRI-HIFU treatment. This results in a study population with a relatively higher prevalence of bleeding symptoms. Still, our findings indicate that MR-HIFU is also effective for patients with bulk symptoms. To our knowledge, this symptom-specific analysis of MR-HIFU's efficacy has not been reported previously. Indeed, these results might aid clinicians in counseling patients and planning treatment.

In this study, the re-intervention rate was remarkably low, only 2%, compared with previously reported rates which have ranged from 6% to 67%, depending on the duration of follow-up (Peregrino et al. 2025; Mindjuk et al. 2015; Froeling et al. 2013; Gorny et al. 2011; Kim et al. 2011). This rate might rise as follow-up continues. Yet, careful patient selection and identification of risk factors for re-intervention should help to maintain the risk of symptom relapse and re-intervention low. There is a clear learning curve in achieving optimal technical outcomes, especially in maximizing NPV% (Okada et al. 2009). We strongly emphasize that multidisciplinary patient selection is crucial for maintaining high efficacy and low re-intervention rates; although its relationship to patient-reported outcomes and long-term results remains to be clarified. The learning curve and case selection differences also complicate direct comparisons between MR-HIFU and other minimally invasive therapies, such as UAE, particularly in randomized settings (Laughlin-Tommaso et al. 2019). Overall, UAE represents a treatment modality where fibroids are targeted indirectly through intervention on the uterus and its blood supply, whereas MR-HIFU constitutes a more selective approach, with treatment precisely focused on the fibroid itself. These mechanistic differences may account for the observed disparities in the effects of UAE and MR-HIFU on ovarian reserve and reproductive outcomes.

Symptom relief and QoL improvement remain the key outcome measures in fibroid management. In Finland, the proportion of hysterectomies performed for fibroids has declined markedly over the past three decades: In 1994–2001 the lifetime risk of having hysterectomy because of fibroids was 12.8% and in 2010–2017 it was 4.2%. This trend apparently reflects advances in alternative treatments for menstrual disorders and shifting patient preferences away from major surgery (Hakkarainen et al. 2021). The demand for minimally invasive procedures that provide durable symptom relief continues to grow.

6.4 Future considerations and possible implications for clinical practice

Regarding the use of oxytocin in fibroid treatments, several aspects remain to be clarified by future research. The underlying mechanisms of the action of oxytocin are still not fully understood. It also remains to be established whether the observed decrease in uterine blood flow correlates with the administered oxytocin dose. The potential use of longer acting agents like carbetocin or other uterotonic agents such as misoprostol for treating in fibroids warrants further investigation. Some studies have demonstrated the efficacy of carbetocin in treatments such as MR-HIFU and myomectomy. Given that carbetocin has a half-life nearly ten times longer than that of oxytocin and that it is administered as a single dose without the need for infusion, it appears to be a particularly attractive alternative (Anneveldt et al. 2022; Taher et al. 2021).

One of the primary indications for uterine-sparing fibroid treatments is the preservation of fertility. Given the continuing trend toward delayed childbearing, the prevalence of fibroids among women seeking pregnancy continues to rise. Consequently, the safety of fibroid treatments with respect to fertility issues, such as endometrial function, ovarian reserve, ovarian function, subsequent pregnancy results, and pregnancy-related complications, remains a crucial area for future investigation. Current evidence suggests that MR-HIFU is a safe alternative for women wishing to conceive; however, there is no data on its impact on fibroid-related infertility. Although addressing this question would require a large randomized controlled trial, such a study could provide invaluable information about the best treatment options for this challenging condition.

Based on clinical experience and the results of this study, MR-HIFU has an established role in fibroid management in Finland. Nevertheless, long-term follow-up is essential for obtaining further information on the durability of treatment outcomes, symptom recurrence, and re-intervention rates. Future research should also focus on the relationship between technical treatment success, patient-related factors, and clinical outcomes. Finally, the development of AI-based tools to assist clinicians in patient referral and selection could facilitate broader implementation of this therapy into routine clinical practice. Ultimately, the long-term vision is that MR-HIFU will become an integrated, clinically effective, and cost-efficient component of fibroid treatment in Finland.

7 Conclusion

The following conclusions can be drawn from the results of this thesis:

1. Oxytocin infusion significantly reduces the blood flow in uterine fibroids without affecting the blood of the myometrium or causing adverse effects for the patient. This finding suggests a potential role for oxytocin in enhancing the efficacy of fibroid treatments, such as MR-HIFU.
2. MR-HIFU treatment does not adversely affect the ovarian reserve, as indicated by stable AMH levels. This finding supports the safety of MR-HIFU for women with fibroids seeking fertility preservation or future pregnancy.
3. MR-HIFU alleviates effectively fibroid symptoms and improves quality of life within 12 months of treatment and is associated with a remarkably low re-intervention rate of 2%.
4. MR-HIFU reduces significantly both bleeding symptoms and bulk symptoms associated with uterine fibroids. Symptom improvement is evident as early as three months after the procedure and it is sustained through 12 months.

Acknowledgements

This study was conducted at the Department of Obstetrics and Gynecology and the Department of Radiology at Turku University Hospital and the University of Turku between 2018 and 2025. I wish to express my warmest gratitude to the following persons:

Professor, Head of Department Kaarin Mäkikallio, and Professor Päivi Polo at the Department of Obstetrics and Gynecology: I warmly thank you for your supportive attitude toward scientific work. Your openness and availability in both clinical and research-related matters have been invaluable.

My supervisor MD, PhD Kirsi Joronen. You have tirelessly answered my questions and encouraged me. At the beginning of this project, I could not have imagined that it would one day become an academic dissertation, but years ago I realized that you actually believed in it. You have had the patience to efficiently guide me forward, and in the most difficult moments you have quietly chosen not to hurry me. Beyond this scientific work, I want to thank you for being an excellent clinician. As I have often said to my colleagues and friends, I trust you a lot in many circumstances.

My other supervisors, Professor Roberto Blanco Sequeiros and Associate Professor Antti Perheentupa, I greatly appreciate your experience and guidance throughout this project. Your calm attitude has often helped me believe that “this has been seen before; just keep going and it will be completed.” Thank you, Roope, for initially bringing the whole MR-HIFU to Finland.

The reviewers of this thesis, Associate Professor Elina Holopainen and Associate Professor Päivi Rahkola-Soisalo. Your critical insights and the time you dedicated to reviewing this work are highly appreciated, and your comments significantly improved its quality.

All co-authors of the original publications and to the entire MR-HIFU team at Turku University Hospital, past and present: Gaber Komar, Teija Sainio, Antti Viitala, Anna Yanovskiy, Jani Saunavaara, Visa Suomi, Ina Lehtonen, Anna Laaksonen and Reetta Kälvälä . Your ideas and discussions formed the foundation of this project. Together, your multidisciplinary expertise is inspiring and has offered valuable perspectives.

The financial support by the State Research Funding from the Hospital District of Southwest Finland and the Finnish Society of Obstetrics and Gynecology.

My obstetrician colleagues, especially Outi, for being a mentor to me in everyday work, and Kaisa K., for originally being the example of the obstetrician I aspired to become. My supervisor, Associate Professor Eeva Ekholm: thank you for your support and for making it possible to combine clinical and academic work.

All the obstetricians in TYKS, I am grateful for being welcomed into your team; it is truly the place where I belong! And also, my cross-sectional urogynecological and oncological colleagues and friends for all the coffee breaks, conversations, consultations and many funny moments together. Linda and Hilla, thank you for helping me during this project and especially at the end of this!

To my friends from different stages of life. Thank you to my closest friends from the Helsinki French–Finnish School for allowing me to grow alongside you and to be myself throughout our school years. Your friendship inspired me to work hard and continue to long studies.

To all my wonderful medical school friends, including the “Candion hyeenat”. I am deeply grateful for those carefree years when we grew into adulthood together!

To Katri and Veera, for being a steady foundation and always offering new perspectives on life. I hope we never stop wandering through forests, sailing, and sitting on quiet rocks staring at the sea.

To my newest group of friends on our home island of Kuusisto. It has been a joy to find such a wonderful community during these intense last years. Especially Hanna and Samu: without you, our life would have been much more difficult, lonely, and far less joyful in recent years.

To my family, I am deeply grateful. My mother Katri, for raising me into who I am, for teaching me to believe in my dreams, and for gently guiding me toward my goals. Without your support, I would be far from where I am today. I am also profoundly grateful for your role as a beloved (and very helpful) grandmother to our boys. My father Lauri, thank you for giving me a critical way of seeing the world and for inspiring my interest in cultures, freedom of speech, and diverse perspectives. And finally, my sister Inari, my best friend and “mind reader.” You have influenced me more than anyone else in my life. Without the possibility to call you and talk everything whenever needed, I would never have finished this project. Together with Markus, you have also brought into my life three wonderful girls, my “borrow-daughters” Aava, Malla, and Selma.

My grandmothers, Pirkkomummi and Riittamummi, thank you for being lifelong role models and for caring for me from the very beginning. My “Turku family”: Ritva, for being the best grandmother to our boys, and Iiro, Petra, Miina, and Martta for all your support.

Atte, for your love, and for all our years together. You trust in my strength and believe in me no matter what. Thank you for standing by me, even when I fail to notice it.

And finally, to my sons Reino and Paavo: having you and living life with you is the greatest joy and our greatest achievement! Every day you remind me of what matters the most.

Kuusisto, December 2025

Saara Otonkoski

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**Otonkoski, S, Sainio, T, Komar, G, Suomi, V, Saunavaara, J,
Blanco Sequieros, R, Perheentupa, A & Joronen K (2020)
Oxytocin selectively reduces blood flow in uterine fibroids without an
effect on myometrial blood flow: a dynamic contrast enhanced MRI
evaluation.
International Journal of Hyperthermia**

Oxytocin selectively reduces blood flow in uterine fibroids without an effect on myometrial blood flow: a dynamic contrast enhanced MRI evaluation

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ABSTRACT

Introduction: Uterine fibroids are the most common benign neoplasms in women. The administration of intravenous oxytocin is known to increase the efficacy of a non-invasive thermal ablation method (MR-HIFU) for treating fibroids. However, it is not known whether this phenomenon is caused by the effect of the oxytocin on the myometrium or the fibroid itself. The objective of this study was to evaluate the influence of oxytocin on the blood flow of fibroids, myometrium and skeletal muscle using a quantitative perfusion MRI technique.

Materials and methods: 17 premenopausal women with fibroids considered to be treated with MR-HIFU and 11 women with no fibroids were enrolled in the study. An extended MRI protocol of the pelvis was acquired for each subject. Later another MRI scan was performed with continuous intravenous infusion of oxytocin. The effect of oxytocin was analyzed from quantitative perfusion imaging. The study was registered in clinicaltrials.gov NCT03937401.

Results: Oxytocin decreased the blood flow of each fibroid; the median blood flow of fibroid was 39.9 ml/100 g tissue/min without and 3.5 ml/100 g/min with oxytocin ($p \leq 0.0001$). Oxytocin did not affect the blood flow of the myometrium in either group. Oxytocin increased the blood flow of the skeletal muscle in both groups ($p = 0.04$).

Conclusion: Oxytocin is effective in decreasing the blood flow in fibroids while having minor or no effect on the blood flow of normal myometrium. Routine use of oxytocin in HIFU therapy may make the therapy suitable to a larger group of women in a safe manner.

ARTICLE HISTORY

Received 31 May 2020
Revised 27 October 2020
Accepted 30 October 2020

KEYWORDS

Fibroid; MR-HIFU; oxytocin; blood flow; contrast enhanced MRI

Introduction



Uterine fibroids are the most common benign neoplasms in women affecting 2/3 of women by the age of 50 years [1]. Symptoms caused by fibroids are menorrhagia, dysmenorrhea, abdominal pain, bladder dysfunction and pelvic pressure often resulting in a significantly decreased quality of life [1]. Furthermore, fibroids can have an adverse impact on fertility by interfering with fertilization and implantation and leading to recurrent miscarriages and adverse perinatal outcomes [2].

Magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) is a noninvasive thermal ablation method based on high-intensity ultrasound waves causing heating of the target tissue and leading to coagulative necrosis [3]. Real-time magnetic resonance imaging (MRI) is used for therapy guidance and temperature monitoring during the treatment.

Careful patient selection is important in treating fibroids with high intensity focused ultrasound (HIFU-therapy). The

therapy is generally considered to be best suited for fibroids up to 10 cm in diameter or one to three smaller fibroids [4]. Alongside anatomical factors such as fibroid location and thickness of the subcutaneous fat tissue, probably the most significant predictors of good treatment outcome are the structure and vascularization of the fibroid [5]. The thermal response of the fibroid can be predicted based on the signal intensity of the T2-weighted MR images of the fibroid. An MRI-based Funaki classification is generally used to evaluate the suitability of a fibroid for HIFU therapy. The fibroids are divided into three Funaki types according to their average T2-signal intensity compared to those of the myometrium and skeletal muscle [6].

Funaki type I–II fibroids are known to have a better thermal response and thus predict better treatment outcomes [3]. Funaki type III fibroids have higher moisture content, lower collagen density, and tend also to have higher blood perfusion than other Funaki type fibroids and thus are more challenging to ablate with MR-HIFU [7,8]. Because of this

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Patient	Age	BMI	Number of fibroids	Largest fibroid (mm)	FIGO type	Funaki type
1	41	25	1	79	2-5	3
2	44	22	4	57	2	2
3	49	20	1	44	1	2
4	26	21	1	46	3	2
5	43	27	1	63	1	2
6	45	20	4	71	7	3
7	31	28	4	44	2-5	2
8	31	22	1	50	2	2
9	35	34	1	128	2-5	3
10	36	29	1	40	2	2
11	31	21	2	68	2-5	3
12	28	19	1	88	6	2
13	38	23	1	71	2-5	2
14	42	31	1	59	2-5	3
15	42	23	1	60	2-5	2
16	38	28	1	61	2-5	2
17	38	33	6	23	4	2

Figure 1. Characteristics of the patients and the fibroids enrolled in this study.

heterogeneity, unfortunately not all fibroids are suitable for MR-HIFU treatment.

Oxytocin is a nonapeptide synthesized in the hypothalamus and it has many physiological functions [9,10]. It has an important role in parturition and lactation and is widely used in obstetric care to induce labor, create contractions and to decrease postpartum hemorrhage [11–13].

The administration of intravenous oxytocin during the MR-HIFU treatment increases the efficiency of the therapy resulting in greater ablation volumes. It has also been shown that intravenous oxytocin administered before percutaneous microwave ablation can reduce blood flow in the fibroid and improve the therapeutic effect and that intraoperative infusion of oxytocin even reduces blood loss during myomectomy [9,14,15]. Wang et al. showed that oxytocin reduces blood flow in uterine fibroids which can be seen using contrast-enhanced sonography [16].

However, it has not been thoroughly investigated whether this phenomenon is caused by the effect of oxytocin on the myometrium or specifically on the fibroids.

Since the efficacy of oxytocin in improving the results of MR-HIFU treatments has also been observed in Turku University Hospital, we decided to evaluate this phenomenon in more detail. The objective of this study was to evaluate and quantify the influence of oxytocin on the blood flow of fibroids, normal myometrium and skeletal muscle of non-pregnant women using a quantitative perfusion MRI technique.

Materials and methods

Seventeen premenopausal women (age mean 38 ± 6 , BMI mean 25 ± 5) with one or several fibroids were enrolled in the study. These women were consecutive patients referred to the gynecological outpatient clinic for a potential MR-HIFU treatment, that is, they represented a selected subgroup of fibroid patients. 12 patients had a fibroid of Funaki type II, and 5 patients a fibroid of Funaki type III. Inclusion

criteria in this study were symptoms caused by fibroids, physical and mental health appropriate for an MRI scan, and premenopausal status. Exclusion criteria were a known allergy to the Syntocinon medicine or any of its adjuvants, high blood pressure, an ischemic heart condition, a long QT-syndrome, or medication that prolongs the QT segment. In addition, women with contraindications to an MRI scan were excluded. Details of the menstrual cycle and hormonal therapy were recorded for each woman. To evaluate whether the blood flow of the myometrium is affected by the presence of fibroids, additional 11 women (age median 26 [24–33]), (BMI median 21 [20–22]) without uterine fibroids were enrolled in the study.

Written informed consent for the MRI and oxytocin administration was obtained from all patients and healthy volunteers. This study was performed in accordance with the ethical regulations of the Ethics Committee of the Hospital District of Southwest Finland and the National Committee of Medical Research Ethics (T366/2017 25.1.2018). The characteristics of the fibroid patients are shown in Figure 1. The dominant fibroid was assessed if the woman had multiple fibroids.

All MRI images were acquired with the same MR scanner (Ingenia 3.0T, Philips, Best, The Netherlands). Women were positioned in a prone position during the MRI scan of the pelvis using a 32-channel torso coil. An extended scanning protocol was acquired for each woman. Among other sequences, the imaging protocol included dynamic contrast-enhanced (DCE) imaging for quantitative perfusion analysis. Later (median 58, range 4–207 days) another MRI scan was performed with the same imaging protocol under continuous intravenous infusion of oxytocin. 40 IU of oxytocin (Syntocinon 8.3 µg/ml, Sigma-Tau Industrie Farmaceutiche Riunite S.p.A) diluted to 500 ml of 0.9% NaCl was infused at the rate of 5 ml/min resulting in an oxytocin infusion rate of 0.4 IU/min with a volumetric infusion pump (Infusomat® Space, B Braun, Germany, Melsungen) placed in MRI compatible docking station (SpaceStation® MRI, B Braun, Germany,

Table 1. MR imaging parameters.

Parameter	T2W TSE	T2W TSE	T1W TFE SPAIR	T1W TFE SPAIR	Dynamic CE-T1W TFE SPAIR	CE-T1W TFE SPAIR	CE-T1W TFE SPAIR
Imaging plane	Sagittal	Axial	Sagittal	Axial	Axial	Sagittal	Axial
Repetition time (ms)	4844	3845	5.2	5.4	2.9	5.2	5.4
Echo time (ms)	95	80	2.6	2.6	1.3	2.6	2.6
Flip angle (°)	90	90	7	7	10	7	7
Number of slices	42	45	225	133	40	225	133
Number of dynamics	–	–	–	–	70	–	–
TSE/TFE factor	28	19	80	80	19	80	80
Section thickness (mm)	3	4	3	3	6	3	3
Matrix size M × P (mm)	344 × 267	272 × 241	168 × 232	172 × 298	112 × 145	168 × 232	172 × 298
Field of view AP × FH × RL (mm)	240 × 240 × 138	300 × 300 × 198	250 × 345 × 338	255 × 200 × 448	270 × 120 × 349	250 × 345 × 338	255 × 200 × 448

TSE: turbo spin echo; TFE: turbo field echo; SPAIR: spectral attenuated inversion recovery; CE: contrast-enhanced.

Meslungenen). The used dosage was considered safe since it's widely used in obstetric care for the treatment of postpartum hemorrhage and inducing uterine contraction. During the infusion of oxytocin, women were regularly asked about possible symptoms caused by the oxytocin. In addition, their blood pressure and heart rate were monitored and recorded. The MRI scan was started approximately 15 min after the initiation of the oxytocin infusion and DCE imaging was obtained 30 min after the start of the oxytocin infusion.

MRI protocol included a dynamic contrast-enhanced (DCE) T1-weighted sequence, the parameters of which are shown in Table 1. A single dose (0.2 ml/kg) of contrast agent (Dotarem, Guebert, Roissy, France) was manually injected at a constant rate followed by 10 ml saline flush after the acquisition of the first five time frames of the dynamic scans. The DCE-MRI data were analyzed with NordicICE software v. 4.1.1 (NordicNeuroLab AS, Bergen, Norway). The arterial input function was determined from the iliac artery by placing a circular region of interest (ROI) onto the artery lumen. Blood flow values were calculated by standard model-independent deconvolution technique by means of contrast bolus tracking [17]. Parametric blood flow values were obtained by T1 perfusion deconvolution arithmetic with the first pass of an AIF curve. Averaged blood flow values were obtained for the fibroids, myometrium and muscle. The fibroid ROIs were drawn within three middle slices of the fibroid to include most of the fibroid. The myometrium ROIs were drawn on the negative side of the fibroid in the three most representative slices of the myometrium and the muscle ROI's were drawn on the abdominal muscle within the three middle slices as the fibroid ROIs.

The Funaki type of the fibroids was determined by an experienced interventional radiologist (GK) by drawing the regions of interest (ROI's) on the sagittal T2 weighted image. A round ROI was placed to cover most of the fibroid. Elliptical ROI's were positioned on myometrium and skeletal muscle (abdominal muscle) so as not to include other tissues. Average signal intensity values for all three ROI's were obtained and compared in order to determine the Funaki type of each fibroid.

Statistical analysis was performed using JMP Pro statistical software version 13.1.0 (SAS Institute Inc.). A *p*-value less than 0.05 was considered statistically significant.

Each dataset was analyzed for normal distribution with the Shapiro–Wilk *W* test. Normally distributed numerical data were presented as a mean ± standard deviation and data with a skewed distribution were presented as the median [interquartile range (IQR)]. Normally distributed data were compared with the Tukey–Kramer test for all pairs and data with skewed distribution were compared with a nonparametric Steel–Dwass method for all pairs. A retrospective power analysis was performed using standard least squares to ensure a sufficient number of patients in the fibroid group.

The primary clinical outcome was the change of blood flow in the fibroid during the infusion of oxytocin as compared to the baseline state as well as the change of blood flow in the normal myometrium and skeletal muscle.

The secondary outcome was the evaluation of the side effects during the use of oxytocin on non-pregnant women.

Results

Oxytocin significantly decreased the blood flow of all the fibroids analyzed. All the women in our study tolerated the infusion without any reported symptoms and no side effects were observed. The oxytocin infusion had no marked effect on the blood pressure or heart rate of the women.

The baseline blood flow of the fibroids varied greatly. Based on MRI images, in our study group, we had 12 patients with a fibroid of Funaki type II and 5 patients with a fibroid of Funaki type III. In Funaki type II fibroids, the median baseline blood flow was 36.5 [21.1–173.5] ml/100 g tissue/min and in Funaki type III the mean baseline blood flow was 16.5 ± 19.4 ml/100 g tissue/min. Thus, the highest measured blood flow values were in the Funaki type 2 fibroids. The difference between the baseline blood flow of Funaki type II and type III fibroids was not statistically significant (*p* = 0.49).

The oxytocin infusion had no effect on the size of the fibroid or the uterus. Figure 2 shows MRI scans of a fibroid without oxytocin and with oxytocin.

Oxytocin decreased the blood flow of every fibroid analyzed (Figure 3). The median blood flow of all fibroids without oxytocin was 39.9 [21.9–134.5] ml/100 g/min. With oxytocin, the median blood flow was 3.5 [2.1–12.1] ml/100 g/

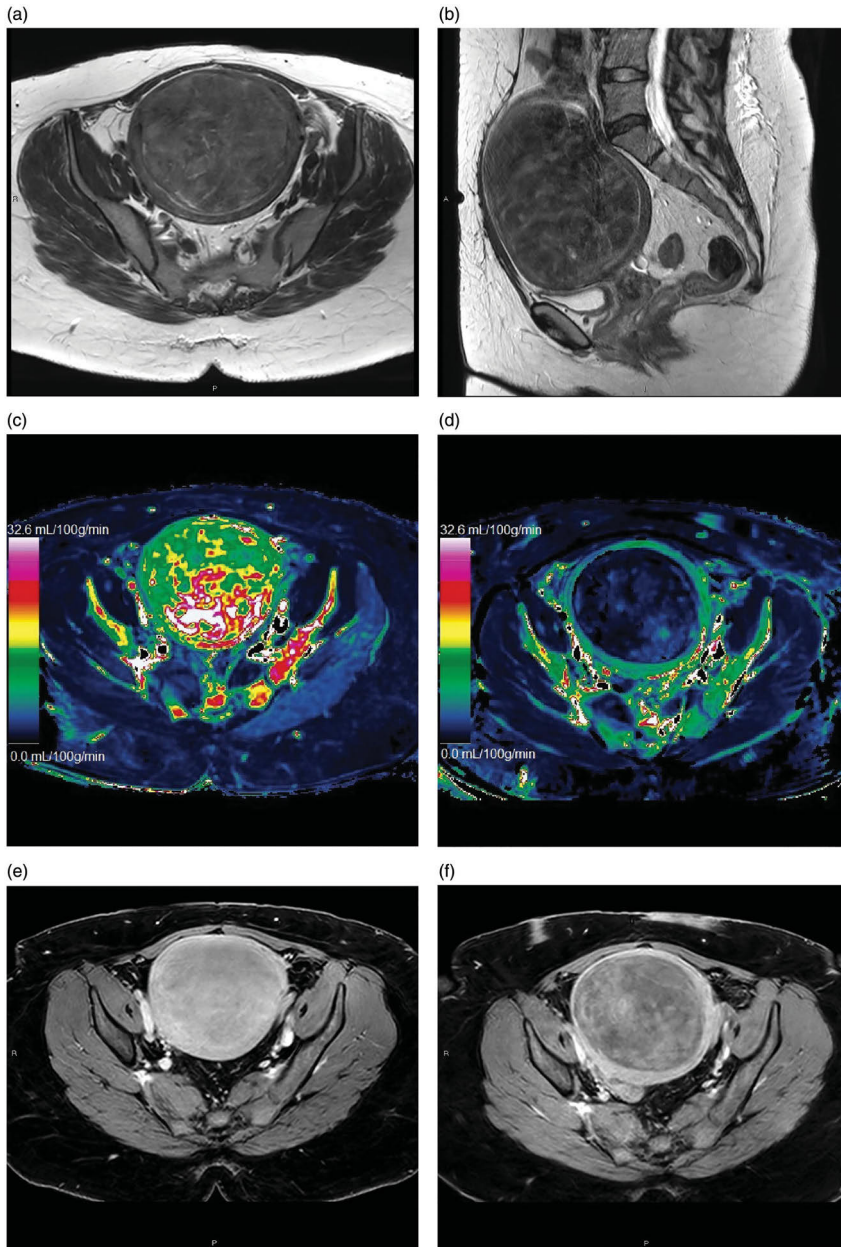


Figure 2. T2 weighted MR images of a uterine fibroid in (a) axial and (b) sagittal plane. Quantitative blood flow maps of the same fibroid in axial plane (c) without oxytocin and (d) with oxytocin. Contrast enhanced T1 weighted MR images of the same fibroid in axial plane (e) without oxytocin and (f) with oxytocin.

min, ($p \leq 0.0001$, power = 0.87). Oxytocin decreased the mean/median blood flow both in Funaki type II and type III fibroids. In Funaki type II the median blood flow with oxytocin was 3.4 [2.3–7.3] ml/100 g/min and Funaki type III the mean blood flow with oxytocin was 16.5 ± 19.4 ml/100 g/min. In Funaki type II fibroids the difference between the baseline blood flow and the blood flow with oxytocin was statistically significant ($p = 0.0004$ and power 0.65). Also in Funaki type

III fibroids the difference between the baseline blood flow and the blood flow with oxytocin was statistically significant ($p = 0.028$ and power 0.65). The difference in the blood flow with oxytocin between the type II and III fibroids was not significantly different ($p = 0.87$).

Oxytocin had no significant effect on the blood flow in the myometrium of the fibroid patients nor the control group (Figure 4a). In the fibroid group, the median

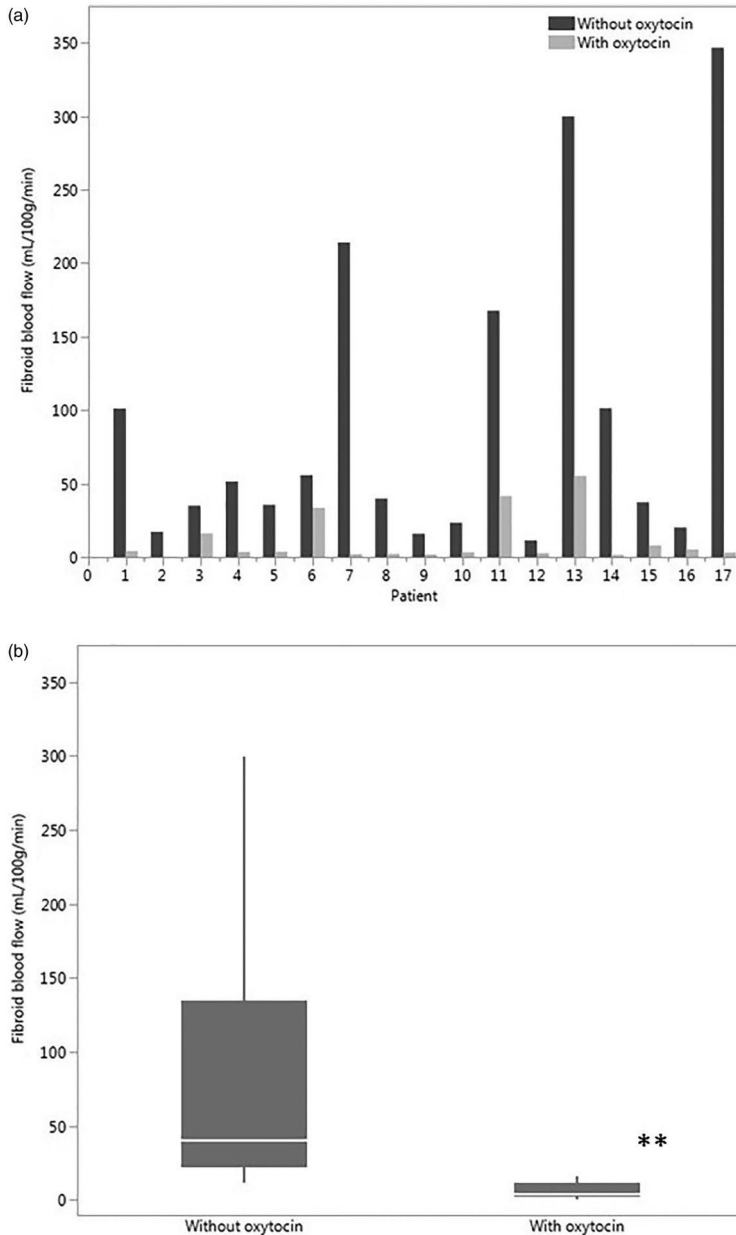


Figure 3. (a) Blood flow of the largest fibroid of every patient without oxytocin and with oxytocin (b) The median blood flow of all fibroids without oxytocin and with oxytocin, * p -value < 0.0001.

myometrial blood flow without the oxytocin was 61.1 [26.4–165.2] ml/100 g/min and 69.4 [21.5–134.6] ml/100 g/min during oxytocin infusion ($p = 0.81$), whereas in the control group the blood flow values were 59.4 [43.6–109.2] and 68.6 [30.8–101.4] ml/100 g/min ($p = 0.74$). No difference was observed when comparing the myometrial blood flow between the groups with fibroids and without fibroids, neither with nor without the oxytocin infusion.

In our study, oxytocin had a minor, yet statistically significant effect on the skeletal muscle blood flow by increasing it (Figure 4b). In the fibroid patients, the median blood flow of the skeletal muscle was 2.1 [1.6–2.8] ml/100 g/min at baseline and 3.7 [2.7–5.3] ml/100 g/min during oxytocin infusion ($p = 0.04$). In the control group, the skeletal muscle blood flow was 2.0 [1.6–4.4] ml/100 g/min without oxytocin and 4.9 [3.2–6.3] ml/100 g/min with oxytocin, ($p = 0.04$).

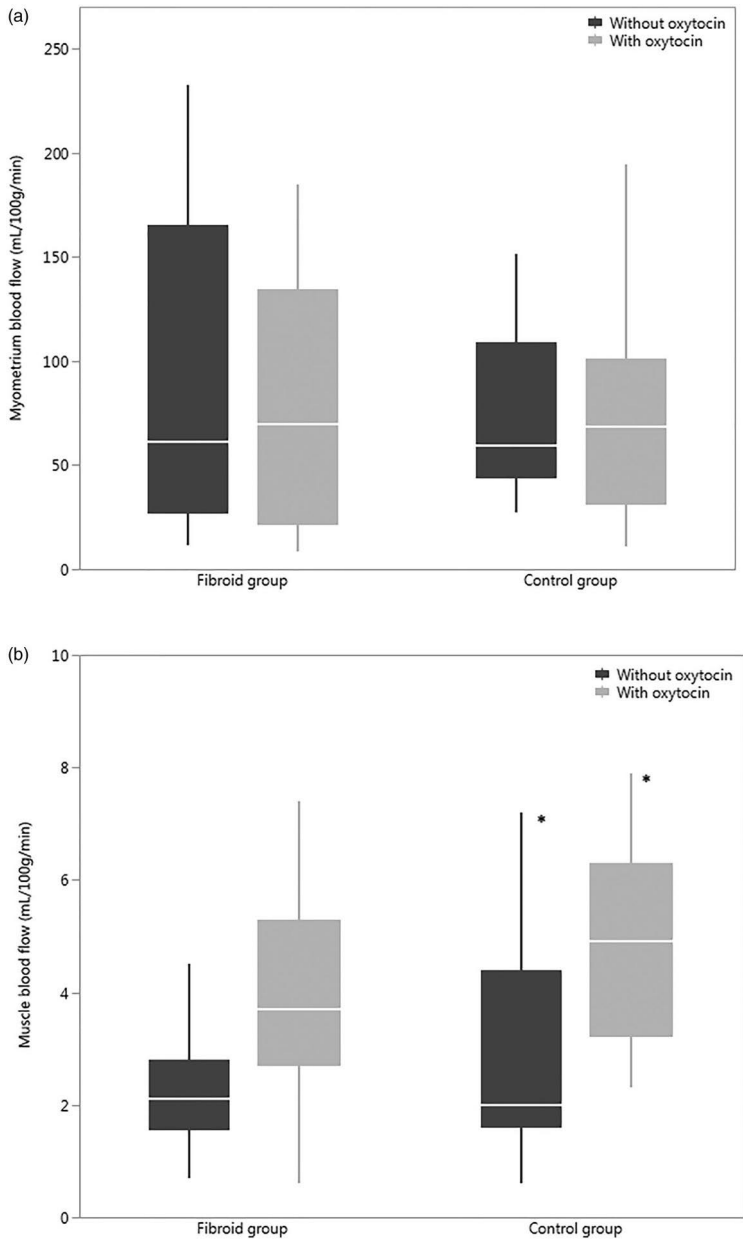


Figure 4. (a) Blood flow of the myometrium without oxytocin and with oxytocin in the fibroid patients and the control group (b) Blood flow of the skeletal muscle without oxytocin and with oxytocin in both groups, * $p < 0.05$.

Discussion

In this study, we demonstrated that oxytocin is very effective in decreasing the blood flow in the fibroid tissue; an effect that can be clearly demonstrated and quantified with MRI. Our results are in line with a previous study in which oxytocin was shown to decrease blood flow in fibroids with contrast-enhanced ultrasound and at the same time not affecting the uterine wall significantly [16].

Fibroids are monoclonal tumors that arise from the smooth muscle tissue of the uterus. They borrow their vascularization from surrounding structures, usually the myometrium. The vessels in the fibroid tissue lack the normal structure compared to the myometrial vessels and are more narrow in diameter [18]. Most fibroids are surrounded by a highly vascularized pseudocapsule which has its own gene expression profile and supplies the fibroid with peri- and intra-fibroid arteries [19].

Oxytocin mainly exerts its effects through the oxytocin receptor, which has a tissue-specific expression pattern. There is little and somewhat contradictory data on the expression of the oxytocin receptors in the myometrium of non-pregnant women or in fibroids. In a study by Sendemir et al. oxytocin receptors were mainly found in fibroid tissue whereas only scarcely in the healthy myometrium [20]. Lee et al., on the other hand, found oxytocin receptors to be more abundant in myometrium than fibroid tissue [13].

The fibroids have their own hormonal environment, which may influence the amount of oxytocin and its receptors in fibroids. For example, there is local hyperestrogenism in fibroids [21] and estrogens, in turn, have been demonstrated to increase the levels of oxytocin receptors and thus in part mediate the contractility of the myocytes. On the other hand, oxytocin receptors are also located in blood vessels, and commonly oxytocin is related to vasodilation [22]. However, it is not known whether the aberrant blood vessels in the fibroids have oxytocin receptors or how they respond to oxytocin.

It seems also that the expression of oxytocin receptors is somewhat dependent on the menstrual cycle with some reports suggesting that the blood flow is higher during the follicular and ovulatory phase compared to the luteal phase [23]. Despite our initial efforts, we could not assess this phenomenon in our study, since we were not able to synchronize the MR-imaging with the menstrual cycle of the women. However, the effect of oxytocin on the fibroid blood flow was strong in all women and it might be safe to speculate that the effect of oxytocin surpasses any possible effect of blood flow changes due to the menstrual cycle.

It must be kept in mind that the results of our study do not offer an explanation of the underlying mechanism for the rather dramatic decrease in blood flow in the fibroids in response to oxytocin. Since the blood flow in the healthy myometrium did not change during oxytocin infusion, it cannot be concluded that the decrease in blood flow in the fibroid is due to increased contractility of the uterus. Thus, it seems more likely that the effect is related to the fibroid itself or the supplying circulation. This, however, clearly needs to be explored in further studies.

Skeletal muscle was chosen as a negative control since during rest it exhibits constant blood flow levels. In our study, the infusion of oxytocin increased the blood flow of the skeletal muscle. Even though statistically significant, the rise in the perfusion value was fairly small in absolute terms (1.6 ml/100 g/min in the fibroid population and 2.9 ml/100 g/min in healthy volunteers) and may be explained by the small systemic vasodilative effect of oxytocin [22]. This effect was not strong enough to affect the blood pressure of the patients.

The study population comprised of women who were being evaluated for MR-HIFU therapy. Therefore, they represent a specific pre-selected subset of women with significant symptoms and fibroids initially considered treatable with MR-HIFU. Even though the fibroids were heterogeneous in size, location, Funaki type and blood flow, they represent a selected subgroup of fibroids and as such might not be

representative of the general fibroid population. On the other hand, the observed great variety in blood perfusion in fibroids potentially suitable for HIFU therapy only emphasizes the importance of perfusion imaging. Nine of the women enrolled in our study underwent the HIFU treatment later. The effect of oxytocin on the results of the HIFU therapy was not in the scope of this study.

The effect of oxytocin was significant in all the fibroids studied and the results observed rather robust. Regardless of this robustness of the results, the study population was too small to assess whether the localization, classification or the size of the fibroid have an influence in the magnitude of the response to oxytocin. Further studies are needed to characterize whether the blood flow of the fibroid and the Funaki type are correlated and whether oxytocin response differs in various types of fibroids. It also remains to be studied whether the decrease in blood flow of the fibroid could be enhanced by increasing the dosage of oxytocin.

Our data suggest that oxytocin has a significant influence on blood flow in a non-pregnant uterus with fibroids. It has been shown that the use of oxytocin decreases blood loss during abdominal and laparoscopic myomectomies [15,24,25]. Our results confirm that this is due to the very strong decrease in the blood flow of the fibroid rather than the myometrium itself. It is possible that with higher concentrations of oxytocin also the blood flow of the uterus would be affected. None of the women reported unpleasant sensations during oxytocin infusion, which may also reflect the relatively small contractive effect of the dose of oxytocin used.

MR-HIFU is an attractive non-invasive technology for treating symptomatic uterine fibroids. A major restriction of MR-HIFU, however, is that only a small proportion of fibroids respond to the therapy effectively. The Funaki classification is an important, yet often insufficient tool in predicting the efficacy of the MR-HIFU treatment. It is known that high blood flow in fibroids is one of the main predictors of a poor therapy outcome [26]. Keserci et al. found that parameters related to blood perfusion of the fibroid have a strong correlation to the HIFU treatment outcome [5]. Thus besides the Funaki type, also the blood perfusion of the fibroid should be measured for predicting the efficacy of MR-HIFU therapy. On the other hand, our results suggest that the effect of blood flow on the treatment efficacy can be overridden with the use of oxytocin during the MR-HIFU treatment, at least to some extent. It would be interesting to be able to define a threshold value for blood flow that would predict a good treatment outcome. Studying this would, however, require a much larger group of fibroids.

The results of our study demonstrate that oxytocin significantly and without side effects, decrease the blood flow of the fibroids, regardless of the Funaki type. This is probably why the administration of intravenous oxytocin during the MR-HIFU increases the efficacy of this treatment [9]. Routine use of oxytocin in HIFU therapy may therefore make this therapy suitable to a larger group of women in a safe and inexpensive manner as well as result in shorter sonication

times and overall duration of therapy in patients already suitable for HIFU.

Ethical approval and informed consent

This study was performed in accordance with the ethical regulations of the Ethics Committee of the Hospital District of Southwest Finland and the National Committee of Medical Research Ethics (T366/2017 25.1.2018). All the participants signed informed consent. The study was licenced by Finnish Medicines Agency (FIMEA) and reported to the EudraCT database (EudraCT: 2017-005022-38). The study was also registered in clinicaltrials.gov NCT03937401.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Funding for this study was received from the Government Research Foundation of Finland, The Finnish Cultural Foundation, TYKS Foundation, and Instrumentarium Science Foundation.

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Otonkoski, S, Sainio, T, Mattila, S, Blanco Sequieros, R, Perheentupa, A, Komar, G, & Joronen, K (2023)

Magnetic resonance guided high-intensity focused ultrasound for uterine fibroids and adenomyosis has no effect on ovarian reserve

International Journal of Hyperthermia

Magnetic resonance guided high intensity focused ultrasound for uterine fibroids and adenomyosis has no effect on ovarian reserve

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ABSTRACT

Introduction: Uterine fibroids are the most common benign tumors in healthy women. High Intensity Focused Ultrasound (HIFU) is a modern, noninvasive thermal ablation method for treating uterine fibroids. There is increasing evidence that ultrasound guided HIFU (US-HIFU) has no adverse impact on ovarian reserve but little data exists on magnetic resonance guided HIFU (MR-HIFU). There are different options to estimate ovarian reserve, perhaps the most reliable being the measurement of serum Anti-Müllerian hormone (AMH).

Material and methods: Seventy-four (74) premenopausal women with serum AMH 0.1 ug/L or over, aged 24–48 and with fibroids or adenomyosis treated with MR-HIFU were enrolled in our study. AMH levels were analyzed before and 3 months after the MR-HIFU treatment. Correlations between AMH level changes and position of fibroids, fibroid volume, non-perfused volume ratio, and treatment energies were studied.

Results: The median AMH level before the HIFU treatment was 1.20 (range: 0.1–7.75 ug/L) and after the treatment 1.23 (range: 0.1–8.51 ug/L). No significant change was detected ($p = .90$). The patients were divided in three subgroups depending on the baseline AMH levels. The changes were not significant in any of the subgroups. Neither did the location of the treated fibroid affect the change of AMH levels nor the total energy used during treatment.

Conclusions: MR-HIFU does not compromise the ovarian reserve. Neither the location of the treated fibroid nor the total energy used during MR-HIFU had any effect on the change of AMH levels.

ARTICLE HISTORY

Received 19 July 2022
Revised 16 November 2022
Accepted 29 November 2022

KEYWORDS

Fibroid; MR-HIFU; AMH; ovarian reserve; thermal ablation

Introduction



Uterine fibroids are the most common benign tumors in healthy women. It is estimated that about 70% of women get a fibroid by the age of 50. Most of the fibroids are asymptomatic but unfortunately the women suffering from symptoms caused by uterine fibroids have a severely compromised quality of life. Common symptoms caused by fibroids are menorrhagia, dysmenorrhea, lower abdominal pain and pelvic pressure. Fibroids can also have an adverse impact on fertility and interfere with pregnancy in multiple ways [1].

There are many different treatment options for symptomatic uterine fibroids. These are medical treatments (hormonal medication, selective progesterone receptor modulators, and medications aiming to reduce bleeding i.e., nonsteroidal anti-inflammatory drugs, tranexamic acid), surgical methods (hysterectomy, laparoscopic myomectomy, open myomectomy and hysteroscopic removal of fibroids) and non-surgical treatment methods (Uterine Artery Embolization, and HIFU) [1].

HIFU is a modern, noninvasive thermal ablation method for treating uterine fibroids. An external ultrasound energy source is used to create thermal ablation inside the body in the tissue to be treated. Either ultrasound (US) or magnetic resonance imaging (MRI) is used for treatment guidance. MRI is superior in providing excellent soft tissue contrast and real-time temperature measuring.

MR-HIFU treatments of uterine fibroids have been performed in Turku University Hospital since May 2016. Since MR-HIFU is considered to be a fertility preserving treatment suitable even for infertility patients, we have considered the safety of this treatment to be of paramount importance. In this context, the impact of the treatment on ovarian reserve has a central role. The close proximity of ovaries to the fibroid and the nature of the treatment (local heating) might cause concern about its effect on ovarian function and reserve.

Alongside its effect on fertility, the ovarian reserve and early onset of menopause are related to a broad spectrum of long-term health risks in women. The negative effects of early menopause include progression of cardiovascular

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 Supplemental data for this article is available online at <https://doi.org/10.1080/02656736.2022.2154575>

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disease, decreased bone density and risk of fracture, negative effect on mental health and cognition. It has been clearly documented that an early menopause increases the risk of frailty among women [2–4].

There are multiple methods for estimating ovarian reserve and function. Follicle stimulating hormone (FSH), antral follicle count (AFC) and Anti-Müllerian hormone (AMH) can be used [5]. AMH is a glycoprotein hormone produced by the granulosa cells of small, growing follicles in the ovary. Serum AMH levels strongly correlate with the number of growing follicles, and therefore AMH has received increasing attention as a marker for ovarian reserve [6,7]. It reaches its highest levels after puberty and decreases over time until it gets undetectable about 5 years before the menopause. AMH levels remain relatively stable during menstrual cycle, which is a major benefit compared to other possible markers [8]. AMH has little intra-cyclic variation although a small variation can be detected, and the plasma level is slightly higher during follicular than luteal phase. Also the inter-cyclical variation is known to be minor [9,10]. There is also some evidence that AMH levels decrease due to the use of oral contraceptives. However, this effect seems to be reversible [7,8,11,12].

There is increasing evidence that US-HIFU has no adverse impact on ovarian reserve but not many reports can be found about MR-HIFU [5,6,13]. Despite a strong argument in favor of its safety, we have in our center encountered one case in which the ovarian function was significantly decreased and AMH lowered after MR-HIFU treatment. This case has also undergone an investigation concerning our legal liability for the possible unfairly caused harm to the patient by the national Patient insurance center. Thus, we felt that it was of utmost importance to analyze the effect of the HIFU treatment on the ovarian reserve of all our patients in detail and this was done by analyzing AMH levels. The case report is presented in more details in the [Supplementary material](#).

Materials and methods

Seventy-four (74) premenopausal women with baseline AMH 0.1 µg/L and over were enrolled in our study. The age of the women was 24–48 years. 69 of the women had a symptomatic fibroid and five had adenomyosis evaluated to be suitable for MR-HIFU treatment. Criteria for MR-HIFU treatment were: diameter of fibroid primarily up to 10 cm (one patient with a fibroid diameter of 11 cm was also included due to lack of other treatment options), number of treated fibroids up to three, subcutaneous fat up to 4 cm, suitable fibroid structure on planning MR images (primarily Funaki type 1 or 2 with low to intermediate blood flow levels, but also some Funaki type 3 fibroids with higher blood flow levels were included), suitable anatomical position of the target making it MR-HIFU treatable and suitable positioning of ovaries making it possible to implement the treatment without damaging them. More detailed information about the study population is presented in [Table 1](#).

This study was performed in accordance with the ethical regulations of the Ethics Committee of the Hospital District

Table 1. More detailed information about the study population.

Characteristics	Value
Total number of patients	74
Mean age of the patients (y)	38 (24–49)
Total number of fibroids	72
Fibroid location	
Anterior	39
Posterior	27
Fundus	13
Lateral	14
Mean fibroid diameter (cm)	5.8 (2.2–11)
Funaki type	
Type I	6
Type II	60
Type III	6
Mean NPV ratio after HIFU (%)	59 ± 27
Mean total energy (kJ) per treatment	163 ± 110

of Southwest Finland and the National Committee of Medical Research Ethics (T366/2017 25.1.2018) and registered in clinicaltrials.gov NCT03937401. Written informed consent was obtained from all patients.

MR-HIFU system and treatment procedure

All treatment procedures were performed using an extracorporeal clinical tabletop MR-HIFU system (Sonalleve V2, Profound medical Inc., Mississauga Canada). The radiologist planned the treatment by positioning the ellipsoid treatment cells into the targeted fibroid one by one to cover the whole fibroid. Treatment power was selected based on test sonication to achieve best possible temperature rise in the target tissue. During the sonication, heating of the targeted area and possible undesired heating of surrounding tissue were monitored with real-time MR thermometry. After the treatment, a contrast-enhanced T1 weighted image was acquired by injecting the contrast agent (DOTAREM, Guerbet, Aulnay-Sous-Bois, France, 0.1 mmol/kg) to evaluate the non-perfused volume (NPV). NPV was used to calculate the non-perfused volume ratio (NPV%) for each patient, that is, non-perfused fibroid volume/total fibroid volume.

After the treatment, the total treatment energy was calculated from the treatment data by multiplying used power and sonication time for each sonication and summing up the energies for all sonications. To consider attenuation, the total delivered acoustic energy at the focus per treatment was calculated as described in a previous study published in 2021 [14].

Information about the ovarian reserve was gathered as a part of a larger study of the effectiveness and safety of MR-HIFU treatments. All patients were summoned for a control 3 months after MR-HIFU. Using a standardized manner the patients were interviewed about their fibroid symptoms, quality of life as well as recovery from the treatment and current gynecological health and symptoms (including menopausal symptoms). AMH levels were analyzed before the MR-HIFU treatment and 3 months after. For the AMH test, 5 mL of serum was collected and stored in a freezer. The assay was made with Elecsys AMH Plus which analytical imprecision is under 5% (Roche Diagnostics).

Statistical analysis

Statistical analysis was performed using JMP Pro statistical software version 16.2.0 (SAS Institute Inc.). A p -value less than .05 was considered statistically significant. The normal distribution of each dataset was analyzed with the Shapiro-Wilk W test. The correlation between normally distributed parameters was analyzed by Pearson product-moment correlation and non-normally distributed parameters were analyzed by Spearman's rank correlation analysis. Group means of normally distributed datasets were compared using Tukey-Kramer honestly significant difference (HSD) test for all pairs and non-normally distributed datasets were compared using the Steel-Dwass method for all pairs.

Results

The median AMH level before the HIFU treatment was 1.20 (range: 0.1–7.75 $\mu\text{g/L}$) and after the treatment 1.23 (range: 0.1–8.51 $\mu\text{g/L}$). No significant change was detected ($p = .90$).

These results are shown in Figure 1(a). None of the women reported any symptoms indicating loss of ovarian function.

In order to analyze possible effects in women with different initial ovarian reserve, the patients were divided into three different subgroups depending on the baseline AMH levels.

Group 1 (28 women) had the AMH 0.1–1 $\mu\text{g/L}$ before the MR-HIFU treatment. The median AMH level was 0.58 (range: 0.1–0.98 $\mu\text{g/L}$) before and 0.52 (range: 0.1–1.8 $\mu\text{g/L}$) after the treatment. The change was not significant ($p = .26$), Figure 1(b).

Group 2 (31 women) had AMH levels 1–2.5 $\mu\text{g/L}$. The median AMH was 1.62 (range: 1.05–2.5 $\mu\text{g/L}$) in the beginning and 1.68 (range: 0.22–3.7 $\mu\text{g/L}$) after treatment, Figure 1(c). No significant change was detected ($p = 1.00$).

Group 3 (15 women) had the highest AMH levels at the beginning, above 2.5 $\mu\text{g/L}$. The pretreatment median AMH level was 3.65 (range: 2.63–7.75 $\mu\text{g/L}$) and post treatment was 3.78 (range: 2.26–8.51 $\mu\text{g/L}$). The change was not significant ($p = 0.98$), Figure 1(d).

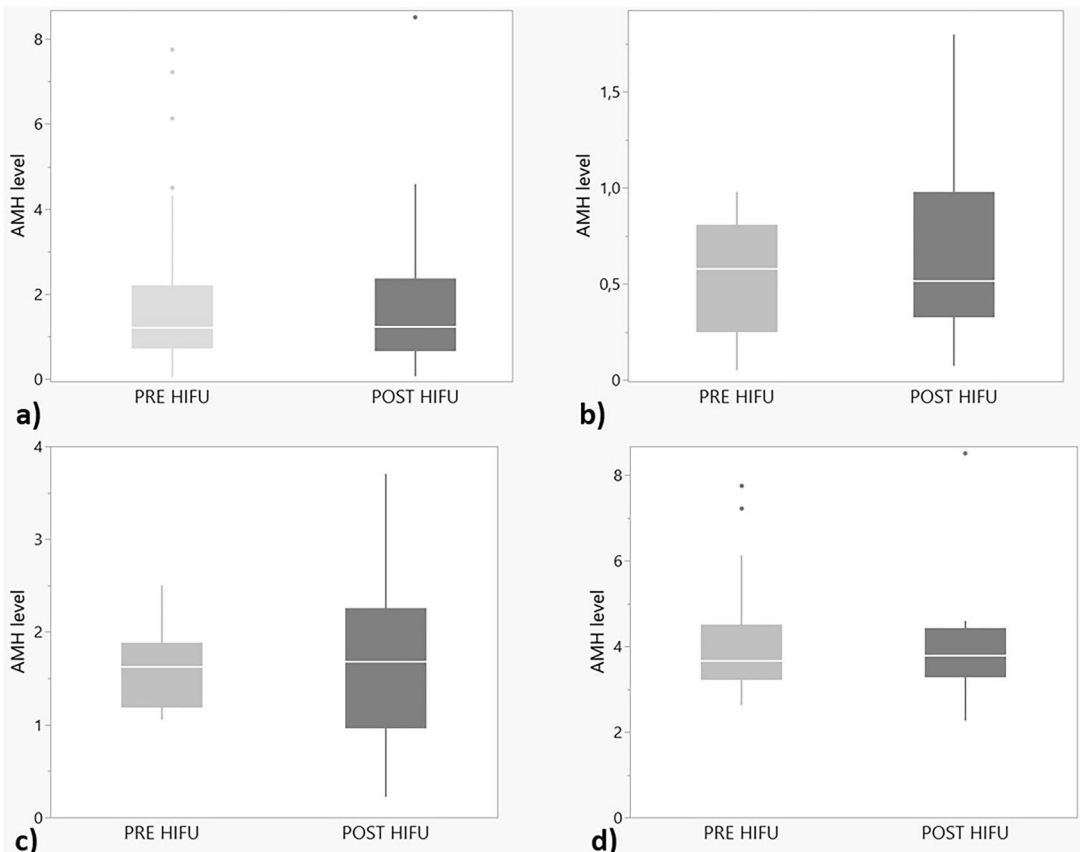


Figure 1. (a–d) Box Whisker plots (median and interquartile range) presenting AMH values before the treatment and 3 months after. (a) All AMH values before the treatment and 3 months after. No significant change was seen. ($p = .9$). (b) AMH values in the low AMH group (0.1–1 $\mu\text{g/L}$) before the treatment and 3 months after. No significant change was seen. ($p = .26$). (c) AMH values in the intermediate AMH group (1–2.5 $\mu\text{g/L}$) before the treatment and 3 months after. No significant change was seen ($p = 1.0$). (d) AMH values in the high AMH group (>2.5 $\mu\text{g/L}$) before the treatment and 3 months after. No significant change was seen ($p = .98$).

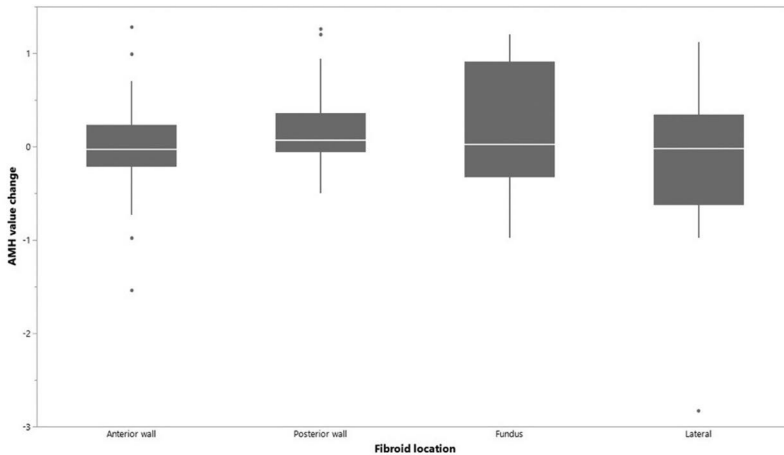


Figure 2. The change of AMH and fibroid location. There were no significant differences between the mean AMH level changes and different fibroid locations.

Table 2. The correlations between the AMH level changes, the total treatment energies, the total delivered acoustic energy at the focus and NPV ratios (%).

Variable	Spearman's ρ	<i>p</i> -value
The total treatment energy	-0.17	.14
The total delivered acoustic energy	-0.06	.61
NPV ratio (%)	0.03	.79

There were no statistically significant correlations between these parameters.

We also studied the AMH level change for different fibroid location: anterior wall, posterior wall, fundus and lateral. This was done because in one case (presented later), where the ovarian reserve was diminished after treatment, the ovaries were situated closely behind the uterus. There were no significant differences between the mean AMH level changes and different fibroid locations, [Figure 2](#).

The correlations between the AMH level changes, the total treatment energies, the total delivered acoustic energy at the focus and NPV ratios (%) are presented in [Table 2](#). There were no statistically significant correlations between these parameters.

Discussion

MR-HIFU treatments of uterine fibroids and uterine adenomyosis have been performed in Turku University Hospital since 2016. During this time, we have had one patient in which the loss of ovarian function was observed after MR-HIFU treatment.

Only women with significant ovarian reserve reflected in baseline AMH 0.1 or over were included in the analysis presented in this article, even though, we have, of course, treated also women with lower AMH levels. A case of decreased AMH level and typical climacteric symptoms evolving shortly after the HIFU treatment, however with a baseline AMH below 0.1 $\mu\text{g/L}$ is presented in the Supplemental material. Having encountered this patient case, it seemed important to investigate the effect of MR-HIFU treatment on the AMH levels. In this prospective cohort study, we have demonstrated that MR-HIFU does not compromise the ovarian

reserve. Our results are in line with earlier studies about the safety of US-HIFU on ovarian reserve and no significant change in the AMH levels was found [[5,6,13,15](#)]. Despite these results, it is also important to keep in mind that MR-HIFU is a treatment with potential risk of irreversibly damaging the ovaries.

AMH was chosen as a marker for ovarian reserve since it is widely used to detect the loss of ovarian reserve following surgery, chemotherapy and radiotherapy. These treatments are known to potentially affect ovarian function and reserve and cause premature menopause [[10](#)]. We measured serum AMH levels just before MR-HIFU and 3 months after the treatment. The time point of 3 months was chosen based on data from studies on the effect of ovarian surgery on ovarian reserve, that were available in 2016 when starting these treatments in Turku. There are many studies concluding that AMH levels drop immediately after cystectomy for benign ovarian cysts. It is suggested to be caused by the removal of healthy ovarian tissue containing the granulosa cells of small growing follicles, during the stripping of the ovarian wall [[10,16–20](#)]. It has been shown that recovery of the AMH levels takes place after surgery. Possible explanations about the mechanisms behind this are reperfusion of ovarian tissue and regathering and recruiting small antral follicles that then start releasing AMH [[17–21](#)].

MR-HIFU is a uterine sparing treatment for symptomatic uterine fibroids. It can be used to treat fibroid symptoms in women still hoping to conceive or even for infertility patients. It can be also offered to women wanting to avoid hysterectomy or to treat fibroid symptoms near menopause. For younger patients hoping for future pregnancy, it is of course crucial that the fibroid treatment has no negative effect on ovarian function and reserve. However, it is also important to consider the effects of treatments on the ovarian reserve as the age of reaching menopause has an impact on women's health in general. A systematic review and meta-analysis published in *JAMA Cardiology* in 2016 by Muka et al. showed that there is a higher risk of coronary heart disease, cardiovascular disease mortality and overall

mortality in women who experience premature onset of menopause (onset at under 45 years of age) [2].

Uterine artery embolization (UAE), another uterine sparing treatment for fibroid symptoms, appears to have a negative effect on ovarian reserve. In a retrospective cohort study published in 2014, Arthur et al. showed that AMH levels and antral follicle count (AFC) were significantly lower in women who underwent UAE compared to those with myomectomy at 12 months after treatment [21]. In a randomized controlled trial published in 2007 Hehenkamp et al. found that after UAE, the AMH levels were significantly decreased and remained so for the entire follow up period of 24 months [22].

Studies of the effect of hysterectomy on ovarian reserve have more complex and controversial conclusions. In 2012 Atebekoglu et al. published that the serum AMH levels in 22 women undergoing total abdominal hysterectomy (TAH) were decreased 4 months after surgery although the decrease was not statistically significant [23]. In 2010 Lee et al. showed that the AMH and ovarian arterial blood flow showed no difference at 1 week, 1 month or 3 months after laparoscopically assisted vaginal hysterectomy (LAVH) or TAH [16]. In 2013 Wang et al. published a study of the effect of hysterectomy and myomectomy on AMH levels. After both operations, the AMH levels were decreased at two days after surgery compared to the preoperative levels. At three months, in the myomectomy group the AMH levels had recovered being at the preoperative stage whereas in the hysterectomy group the AMH level stayed significantly lower at three months. These studies are interesting concerning the ovarian reserve, but of course hysterectomy should not be compared with MR-HIFU when the interest is in preserving the fertility of the patient.

The major strength of our prospective study is that we studied the possible changes in AMH levels also in subgroups of different base level AMH. There were no changes in AMH levels regardless of whether the baseline AMH was high ($>2.5 \mu\text{g/L}$), intermediate or already on lower side of the spectrum ($0.1\text{--}1.0 \mu\text{g/L}$). This is crucial since changes in baseline low levels of AMH can be difficult to detect and results can be unreliable. In the FIRSTT study published in 2019 by Laughlin-Tommaso et al. compared the two fibroid treating methods, MR-HIFU and UAE and also the effect on ovaries was studied by screening AMH levels. Compared to the FIRSTT study population, we had a higher AMH level median at the beginning. In the FIRSTT study the median was 0.3 ng/mL ($0.3 \mu\text{g/L}$), whereas in our population the median was $1.2 \mu\text{g/L}$. In this scope, our study gives new information about the effect of MR-HIFU on ovaries with higher AMH levels. In the subgroup with highest baseline AMH (over $2.5 \mu\text{g/L}$), the median baseline AMH was $3.65 \mu\text{g/L}$. It could be speculated that the risk of ovaries getting affected by the HIFU would be higher in ovaries with higher AMH levels as they usually are bigger in size and therefore often closer to the treatment field. In our study we have not been able to detect such an effect [24].

On the other hand, there is some evidence that an aging ovary with already declining ovarian reserve is more sensitive

to damage than a younger ovary with more reserve [25]. As mentioned before, UAE has been reported to have a negative effect on ovarian reserve and this effect seems to be more apparent in women over 40 years old [26]. It has also been reported that UAE predisposes women to earlier menopause [22]. We found no negative effect of MR-HIFU even in the subgroup of women, whose ovarian reserve was already compromised. There is no long-term accumulation of the heat or changes in the circulation of uterine or ovarian vessels with MR-HIFU. Whereas, in contrast, obliteration of the uterine arteries and possible drifting of the embolizing particles to ovarian vessels may cause long term changes in the circulation of the ovaries and thus have subtle effects on their function that manifest over long time.

Our study also reveals that the location of the treated fibroid has no correlation on the change of the AMH levels and neither the total treatment energy. These are important new results ensuring that treating fibroids with MR-HIFU has no adverse impact on ovarian reserve. We studied the correlation of the AMH and the location of the fibroid and the correlation between the AMH and the total treatment energy since usually a bigger fibroid requires more treatment energy in total. With higher total energy, the risk of causing non-target tissue damage might increase significantly. For this reason why we found it more relevant to investigate the correlation between AMH and total treatment energy than the size of the treated fibroid.

Although the location of the fibroid has no effect alone, it is very important to pay attention to the location of the ovaries when planning the fibroid treatment window and placing the treatment cells. The patient case presented in the supplement is an example of the possible adverse effect of MR-HIFU treatment on ovarian function. In a patient with a very low AMH level and thus poor ovarian reserve, even a minute effect on ovarian function may initiate amenorrhea and menopausal symptoms. This highlights the importance of appropriate patient counseling. Perhaps the ovarian reserve should routinely be evaluated with AMH measurement prior to the HIFU treatment so that the random occurrence of menopause and associated symptoms would not unduly be blamed on the treatment.

A limitation of our study is that information about the menstrual cycle was not recorded. On the other hand it is known that inter and intra-cyclic variation of AMH is low [27]. The strength is that AMH seems to be a stable marker compared to other markers. Another limitation is that no later AMH samples were gathered. In the case of a longer follow up, there should have been a control group enrolled in this study. Also, one limitation is the nature of the HIFU treatment which includes the acquisition of MR images of the pelvis, which provide detailed information on fibroid as well as on location of the ovaries. Patients with unfavorable location of ovaries that might lie in the treatment field, are therefore excluded in the selection process and, at least in our center, not treated with HIFU.

Based on our results and previous studies, it seems that MR-HIFU, in general, has no adverse impact on ovarian reserve nor function. However, we have encountered in our

center one case, in which MR-HIFU may have been an associated factor to the unfortunate premature failure of ovarian function and our patient was postmenopausal 3 months after the treatment. After this case we have become highly meticulous in addressing the position of the ovaries in the MR images and an individual assessment of the effect of HIFU treatment on the ovaries is made for each patient.

This study provides strong evidence in favor of the safety of MR-HIFU in regard to ovarian reserve. Based on these results, we consider it safe to recommend this treatment to women wishing future pregnancies. However, careful patient selection, treatment planning and monitoring are crucial in obtaining this safety.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Funding for this study was received from Government Research Foundation of Finland.

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**Otonkoski, S, Viitala, A, Komar, G, Sainio, T, Yanovskiy, A,
Blanco Sequieros, R, Perheentupa, A & Joronen, K (2024)
Magnetic resonance guided high intensity focused ultrasound
(MR-HIFU) effectively reduces fibroid-related symptoms and improves
quality of life- A single-centre 12-month follow-up study.
Acta Obstetrica et Gynecologica Scandinavica**



ORIGINAL RESEARCH

Magnetic resonance guided high intensity focused ultrasound (MR-HIFU) effectively reduces fibroid-related symptoms and improves quality of life—A prospective single-centre 12-month follow-up study

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Funding information

Finnish Government Research Funding

Abstract

Introduction: Uterine fibroids are the most common benign tumors among women, and it is estimated that approximately 70% of women have one or multiple fibroids by the age of menopause. About 30% of these women suffer from symptoms related to the fibroids. Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) is a novel, non-invasive treatment method for symptomatic uterine fibroids.

Material and Methods: In this prospective, single-centre follow-up study, 175 women with symptomatic uterine fibroids were treated with MR-HIFU. The effect of MR-HIFU on fibroid symptoms and quality of life was evaluated using a uterine fibroid-specific quality of life questionnaire (UFS-QoL). The main outcome measure was the symptom severity score and quality of life (QoL) before the MR-HIFU and 3 and 12 months after the treatment. This study was registered at clinicaltrials.gov (NCT03937401).

Results: The median symptom severity score decreased from 56 (IQR 44–69) at baseline to 28 (IQR 16–44) at 3 months ($p < 0.01$) and 25 (IQR 16–38) at 12 months ($p < 0.01$) after treatment. The QoL score increased from a median of 48 (IQR 33–66) at baseline to 73 (IQR 59–93) at 3 months ($p < 0.01$) and 78 (IQR 66–90) at 12 months after treatment ($p < 0.01$). The reintervention rate during the 12-month follow-up was 2%.

Conclusions: MR-HIFU significantly reduces the severity of fibroid-related symptoms in selected patients as early as 3 months after MR-HIFU. The effect persists at 12 months. There is also a significant improvement in the quality of life 3 months after treatment, which further increases at 12 months.

Abbreviations: MR, magnetic resonance; MR-HIFU, magnetic resonance-guided high-intensity focused ultrasound; NPV, non-perfused volume; SSS, symptom severity score; UAE, uterine artery embolization; UFS-QoL, Uterine fibroid-specific-quality of life.

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KEYWORDS

fibroid, MR-HIFU, quality of life, uterine fibroid

1 | INTRODUCTION

Uterine fibroids are the most common benign neoplasms in women, occurring in up to 70% of women by menopause.^{1,2} A third of these women develop symptoms, reducing their quality of life. The symptoms most commonly related to uterine fibroids are menorrhagia or other bleeding disorders and various pain or bulk symptoms. Uterine fibroids can interfere with fertility, being associated with miscarriages and infertility.^{2,3}

There are multiple ways to treat fibroid symptoms. Several types of pharmacological agents are available.⁴ Medical therapy, however, requires long-term compliance since the symptoms usually return if the medication is discontinued. Operative options include hysterectomy or myomectomy. Less invasive radiological treatment methods are uterine artery embolization (UAE) and high-intensity focused ultrasound (HIFU).⁵⁻⁸ Magnetic resonance-guided HIFU (MR-HIFU) is a non-invasive thermal ablation method based on the rapid heating of the target tissue. The procedure is performed under real-time magnetic resonance imaging, offering excellent image guidance and simultaneous temperature monitoring.^{6,9} Unlike UAE and hysterectomy, MR-HIFU is a viable option for women seeking future pregnancies. Earlier studies have shown that no negative effect on ovarian reserve is caused by MR-HIFU, and also normal pregnancies after HIFU treatment have been reported in several studies.^{10,11} The technical treatment success of MR-HIFU is assessed by calculating the non-perfused volume (NPV), which is the volume of the fibroid ablated during the treatment.

MR-HIFU offers several benefits in the treatment of symptomatic fibroids. However, the treatment is not suitable for all fibroids, and the histological structure and vascularisation of the fibroid, for example, affect treatment efficacy. Radiologically, fibroids are a heterogeneous group of tumors, and various parameters can be assessed from preoperative MR images and used to predict treatment efficacy. Most often, the so-called Funaki classification, in which the fibroids are classified into three classes by their signal intensity in a T2-weighted MR image, is used.¹² In addition, other parameters such as apparent diffusion coefficient and fibroid perfusion should be included in the preoperative analysis to improve the treatment success.^{12,13}

The modern concept of fibroid treatment highlights the clinical outcomes of the various therapies, since the main objective is to offer the patients sustainable symptom relief and improvement in quality of life by means of therapy that is the least invasive and safest possible. A commonly used clinical assessment tool is the validated uterine fibroid-specific symptom and quality of life questionnaire (UFS-QoL). It consists of questions both regarding the fibroid symptom severity (symptom severity score, SSS) as well as the effect of fibroid symptoms on different aspects of quality of life

Key message

Uterine fibroids are common benign tumors that cause symptoms decreasing the quality of life for many women. MR-HIFU is a non-invasive treatment method that significantly reduces the severity of fibroid-related symptoms in selected patients.

(QoL).¹⁴ Here we report the clinical outcome assessed with the UFS-QoL questionnaire of patients treated for uterine fibroids in Turku, Finland, since 2016.

2 | MATERIAL AND METHODS

A total of 175 women were recruited in this prospective, single-center follow-up study between May 2016 and November 2023. All patients had at least one symptomatic uterine fibroid, as evaluated in the gynecological department of Turku University Hospital, and were deemed suitable for MR-HIFU treatment. Written informed consent was obtained from all patients. The patients were initially referred to the gynecological department for evaluation of symptoms and their relation to the fibroid. All available treatment options were carefully discussed with the patients. Patients considered clinically suitable for MR-HIFU were referred for MR imaging to evaluate the technical suitability of the treatment. For each patient, a team consisting of experienced practitioners, one gynecologist, and one radiologist (KJ and GK) carried out the evaluation of suitability for MR-HIFU. A significant proportion of the patients were found to be unsuitable for the treatment. However, no record of these rejected patients was kept, and the exact proportion is not known. Our screening protocol for assessing the patients' suitability for MR-HIFU treatment is written in more detail in [Appendix S1](#).

The primary outcome of this study was the effect of MR-HIFU treatment on the patient's fibroid-related symptoms. The secondary outcome was the reintervention rate.

Planning MR images were obtained shortly before the treatment, and control images were obtained after the treatment to confirm the results. The NPV was defined immediately after the treatment. NPV values were determined by our radiologist (AY), who manually outlined the non-enhancing part of the treated fibroid on contrast-enhanced T1 weighted MR images and compared that to the whole volume of the fibroid, which was determined using T2 weighted MR images. Volumes were calculated using GE AW server 3.2 (GE HealthCare, Chicago, Illinois, USA).

The patients filled in the UFS-QoL questionnaire before the treatment, and this is taken as the baseline in our study. All patients were seen 3 months after the treatment, and this appointment included the UFS-QoL questionnaire, a clinical evaluation with a gynecological ultrasound, and an MRI. The same protocol was performed 12 months after the treatment. If a patient failed to make a follow-up visit and was not reached after two attempts from the hospital, the patient was considered as lost to follow-up.

All the treatments were performed using an extracorporeal tabletop MR-HIFU system (Sonalleve V2, Profound medical Inc., Mississauga, Canada). The treatment planning was conducted by positioning the ellipsoid treatment cells into the targeted fibroid. This was performed one by one to cover the whole fibroid. Test sonication was carried out, and the treatment power was selected based on it. The aim was to achieve the best possible temperature rise in the target tissue. The possible undesired heating of the surrounding tissues and the heating of the targeted area were monitored with real-time MR thermometry. The technical objective of the treatment was to ablate as much of the fibroid tissue as possible in those fibroids considered relevant with respect to the symptoms. During the treatment, intravenous oxytocin (40 IU of oxytocin, Syntocinon 8.3 µg/mL, Sigma-Tau Industrie Farmaceutiche Riunite S. p. A, diluted to 500 mL of NaCl 0.9%) was infused at a rate of 5 mL/min to reduce the blood flow in the fibroids.¹⁵ After the treatment, the NPV was evaluated from a contrast-enhanced T1-weighted image acquired by injecting the contrast agent (DOTAREM, Guerbet, Aulnay-Sous-Bois, France, 0.1 mmol/kg). NPV% was calculated for each patient.

Clinical evaluation of the efficacy of MR-HIFU on fibroid-related symptoms was performed using the UFS-QoL questionnaire. The first part of the questionnaire is about the severity of the fibroid symptoms (SSS) and the second part about the fibroids effect on the quality of life (the quality of life questionnaire, QoL). The quality of life questionnaire is also divided into subgroups; Concern (five questions); Activities (seven questions); Energy/Mood (seven questions); Control (five questions); Self-Consciousness (three questions); Sexual Function (two questions). The total quality of life score (HRQoL) consists of the sum of the subgroup results. All of the questions have responses on a five-point scale, the options being from 'none of the time' or 'not at all' to 'all of the time' or 'a very great deal'. The results are calculated with set formulas that provide the SSS and QoL. With the SSS, the minimum score is 0 and the maximum 100, a higher score indicating greater severity of symptoms. With the QoL, the minimum is 0 and the maximum 100, a higher score indicating a better quality of life. The analyses were conducted by using all of these questionnaires, even if one patient did not have responses for all of the timepoints. In addition, we made supplementary analyses using the patient series with responses to all of the timepoints, and gained similar results. These are shown in Figures 1 and 2.

Statistical analysis was conducted in RStudio 2022.07.2 Build 576 (RStudio, PBC, Boston, USA) using R version 4.2.2 (R: A language and

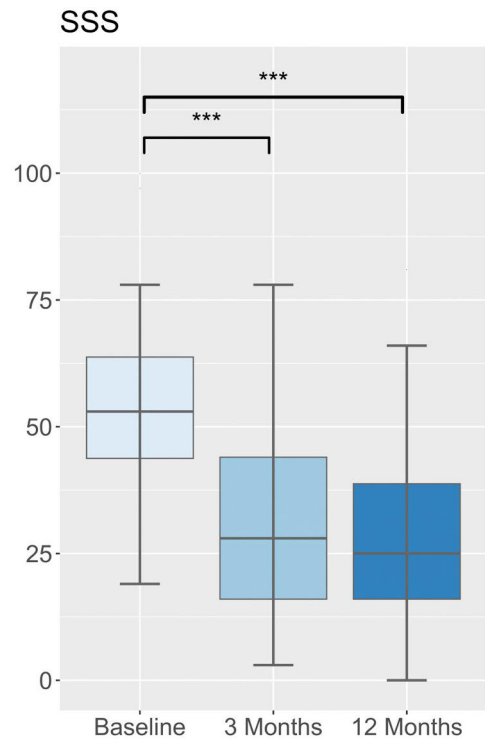


FIGURE 1 Symptom Severity Score (SSS) at baseline, 3 months, and 12 months based on the patient series with responses to all of the timepoints. *** $P < 0.001$.

environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

For all the outcome parameters, we used the Shapiro-Wilk test and visual density distribution evaluation to assess whether the data was normally distributed. Since the majority of the parameters were found not to be normally distributed, a paired Wilcoxon signed-rank test was used to calculate the statistical significance of parameter changes between time points. The full R is available online.¹⁶

3 | RESULTS

All the women included in this study were premenopausal. The median age of the women was 39 years (range 24–57) and the median body mass index (BMI) was 24 (range 18–39). At baseline, 55 (31%) of the women were using hormonal contraception, and they continued with the same medication throughout the follow-up. Eight women were using ulipristal acetate medication at the outset and four were on relugolix/estradiol/norethisterone acetate. All of these women continued their medication until at least the first follow-up at 3 months. Information was obtained about the medication potentially increasing bleeding (two patients with warfarin

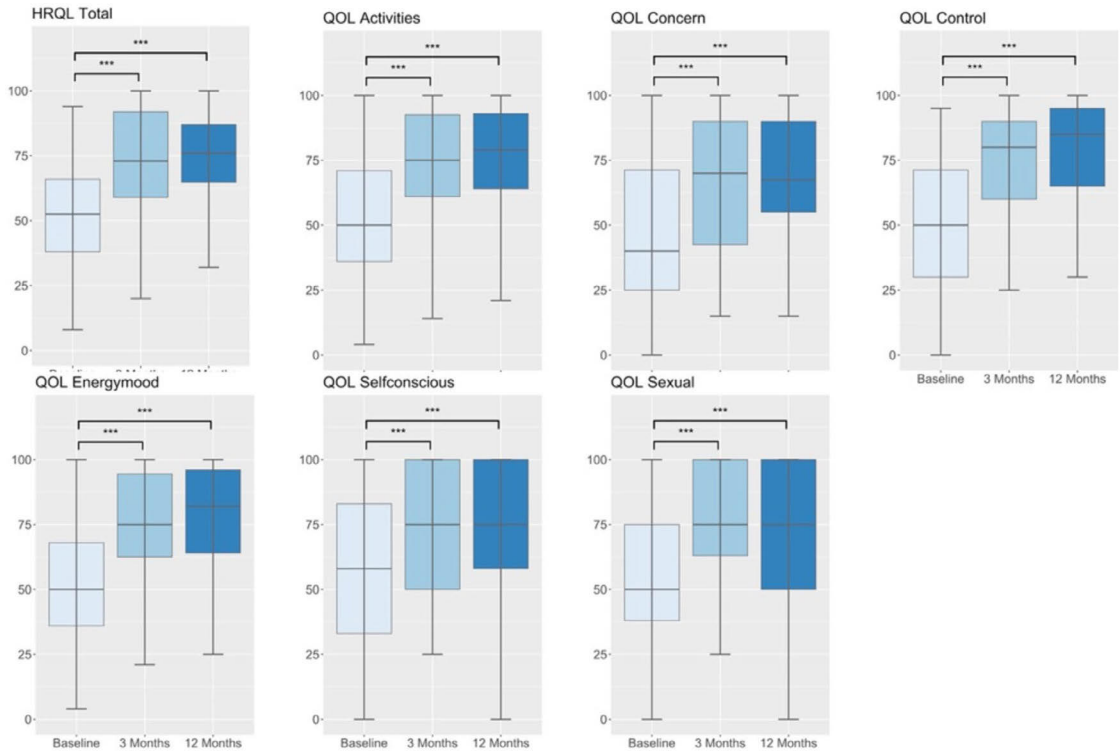


FIGURE 2 Total quality of life score (HRQoL) at baseline, 3 months, and 12 months based on the patient series with responses to all of the timepoints. *** $P < 0.001$.

and one mini-heparin) or decreasing bleeding (27 patients using tranexamic acid). Sixty-four women (38%) had had earlier successful pregnancies.

Detailed information about the leading symptom was gathered. 42 (25%) women had more than one leading symptom. A total of 127 (73%) women had a leading symptom related to menstrual bleeding: menorrhagia or menometrorrhagia. Fifty women (29%) had bulk symptoms such as a feeling of abdominal pressure or frequent urination. For 33 (19%) women, the leading symptom was pain, that is, abdominal pain, dysmenorrhea, or dyspareunia. Infertility was the leading symptom for eight (5%) patients. The women in this group had experienced unsuccessful in vitro fertilization or recurrent miscarriages, for instance. 22 (13%) women had had an earlier hysteroscopy for the fibroid, and five had had multiple hysteroscopies. Five (3%) women had had a myomectomy by either laparoscopy or laparotomy. Only three (2%) women needed reintervention during follow-up at 12 months: one myomectomy and two hysterectomies.

The parameters regarding the patients and the fibroids are shown in Table 1.

The fibroids treated were of various sizes, locations, and vascularization. In some patients, multiple fibroids were treated, but no data was kept on the number of fibroids treated per woman.

In clinical practice and studies, the FIGO classification is used to classify fibroid location.⁴ In our study population, the fibroids were divided into FIGO groups as follows: seven fibroids (4%) of type FIGO 0; 24 (12%) of FIGO 1; 52 (26%) of FIGO 2; 64 (32%) of FIGO 3; 20 (10%) of FIGO 4; 17 (9%) of FIGO 5; and 15 (8%) of FIGO 6. A total of 109 (54%) of the fibroids were located in the anterior wall of the uterus, 20 (10%) in the fundus, 20 (10%) in the lateral wall and 51 (25%) in the posterior wall. In addition, there was one fibroid (0.5%) located in the cervix, and the location of one (0.5%) was unclear. In addition, the signal intensity of the fibroids was assessed: there were 22 (11%) fibroids of Funaki group 1, 159 (80%) of Funaki group 2, and 17 (9%) of Funaki group 3. Before the treatment, the median volume of the fibroids was 63 mL (IQ range 18–134), corresponding to a diameter of approximately 4.9 cm.

In these MR-HIFU treatments, the median NPV% was 69 (IQ range 47–89). There were five complications: two first-degree skin burns treated with a topical agent and anti-inflammatory medication (group B according to SIR criteria), one pulmonary embolization that was diagnosed 2 weeks after the MR-HIFU, and two nonspecific inflammatory reactions (group C according to SIR criteria). One of the two resulted in fever, leukocytosis, and a high C-reactive protein and was similar to post-embolization syndrome. This patient recovered

TABLE 1 Parameters regarding the patients and the fibroids included in the study.

Parameters	
Number of patients	175
Age (median, range)	39 (24–57)
BMI (median, range)	24 (18–39)
Hormonal contraception	
Yes	55 (31%)
No	120 (69%)
Fibroid medication	
Ulipristal acetate	8 (5%)
Relugolix	4 (2%)
Medication affecting blood coagulation	
Warfarin	2 (1%)
Mini-heparin	1 (0.6%)
Tranexamic acid	27 (15%)
Earlier fibroid treatments	
Hysteroscopy	22 (13%)
Myomectomy	5 (3%)
Leading symptom	
Bleeding symptom	127 (73%)
Bulk symptom	50 (29%)
Pain	33 (19%)
Infertility	8 (5%)
More than one leading symptom	42 (25%)
Earlier fibroid treatments	
Hysteroscopy	22 (13%)
Myomectomy	5 (3%)
FIGO groups (number of fibroids)	
FIGO 0	7 (4%)
FIGO 1	24 (12%)
FIGO 2	52 (26%)
FIGO 3	64 (32%)
FIGO 4	20 (10%)
FIGO 5	17 (9%)
FIGO 6	15 (8%)
Funaki groups (number of fibroids)	
Funaki 1	22 (11%)
Funaki 2	159 (80%)
Funaki 3	17 (9%)

after a short hospital stay. The other patient had low fever, bleeding, and abdominal pain for 2 weeks after the treatment but also recovered and did not need further treatment. Three women needed a reintervention: one myomectomy and two hysterectomies. The reintervention rate at 1 year was 2%.

A total of 129 patients answered the baseline questionnaire, 118 the questionnaire at 3 months, and 91 the questionnaire at 12 months. The clinical follow-up demonstrated a significant

SSS

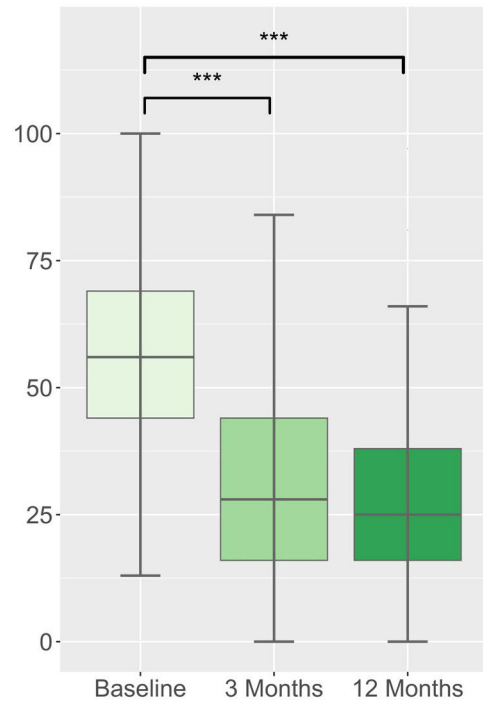


FIGURE 3 Symptom Severity Score (SSS) at baseline, 3 months, and 12 months. *** $P < 0.001$.

reduction in fibroid-related symptoms as well as an improvement in quality of life. The median SSS decreased from 56 (IQR 44–69) at the baseline to 28 (IQR 16–44) 3 months and to 25 (IQR 16–38) 12 months after treatment. The change was significant from the baseline to 3 and 12 months ($p < 0.01$ and $p < 0.01$ respectively) but not from 3 to 12 months ($p = 0.3$). The SSS at the baseline, 3 months, and 12 months is shown in [Figure 3](#).

Accordingly, the QoL score increased from a median of 48 (IQR 33–66) at the baseline to 73 (IQR 59–93) 3 months ($p < 0.01$) and 78 (IQR 66–90) 12 months after treatment ($p < 0.01$). Unlike SSS, the change in the QoL was also statistically significant between 3 and 12 months after treatment ($p = 0.02$). The QoL at the baseline, 3 months, and 12 months is shown in [Figure 4](#).

The QoL results were also analyzed according to subgroups.

In the subgroup Concern, the median QoL score at the baseline was 35 (IQR 20–65), at 3 months 65 (IQR 45–90), and at 12 months 70 (IQR 55–90). The change was statistically significant between the baseline and 3 months ($p < 0.01$) and between the baseline and 12 months ($p < 0.01$).

In the subgroup Activities, the baseline median QoL score was 46 (IQR 29–71), at 3 months 75 (IQR 57–96) and at 12 months 82 (IQR 64–93). The change was statistically significant between the baseline and 3 months and between the baseline and 12 months ($p < 0.01$ and $p < 0.01$ respectively).

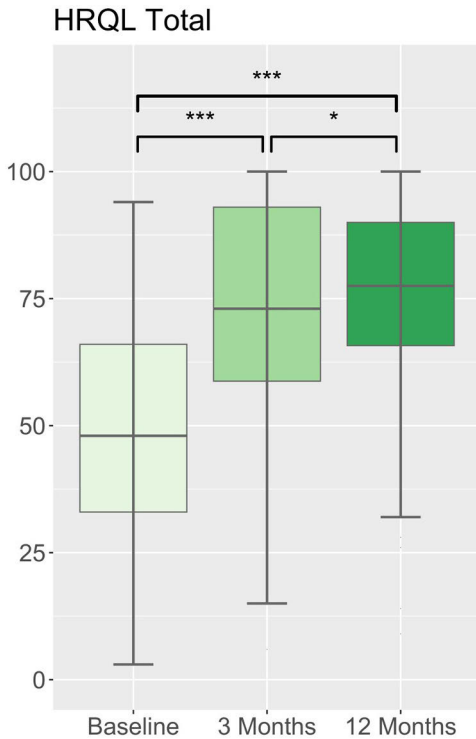


FIGURE 4 Total quality of life score (HRQoL) at baseline, 3 months, and 12 months. * $P < 0.05$, *** $P < 0.001$.

In the subgroup Energy/Mood, at the baseline the median QoL score was 46 (IQR 31–68), at 3 months 77 (IQR 61–95) and at 12 months 82 (IQR 64–100), with the change also statistically significant at the timepoints of 3 months ($p < 0.01$) and 12 months ($p < 0.01$) compared to the baseline.

In the subgroup Control, the baseline QoL median was 50 (IQR 30–70), at 3 months 80 (IQR 56–95), and at 12 months 85 (IQR 65–100). The change was statistically significant at 3 months compared to the baseline ($p < 0.01$) and at 12 months compared to the baseline ($p < 0.01$).

In the subgroup Self-Consciousness, at the baseline the median QoL score was 58 (IQR 25–75), at 3 months 75 (IQR 54–100), and at 12 months 75 (IQR 58–92). The change was statistically significant at 3 months ($p < 0.01$) and 12 months ($p < 0.01$) compared to the baseline.

In the subgroup Sexual, at the baseline, the median QoL score was 50 (IQR 25–75), at 3 months 75 (IQR 50–100) and at 12 months 75 (IQR 50–100), the change being statistically significant between the timepoints baseline to 3 months ($p < 0.01$) and baseline to 12 months ($p < 0.01$).

In all the subgroups, the QoL scores were significantly higher at both 3 months and 12 months compared to the baseline. The QoL subgroups Concern, Activities, Energy/Mood, Control, Self-Consciousness, and Sexual are shown in Figure 5.

4 | DISCUSSION

In this paper, we present the results of our prospective single-center study demonstrating the effectiveness of MR-HIFU in treating uterine fibroid-related symptoms over a follow-up period of 12 months. Uterine fibroids are the most common tumors in women of reproductive age, and even though benign, they are known to often significantly impact patients' quality of life. With an estimated annual cost of 34 billion dollars in the United States, they represent an important burden for healthcare systems all over the world.¹⁷ Since there are currently no effective methods to inhibit the development of fibroids, it is very important to attempt to develop minimally invasive or non-invasive treatments that are also cost-effective.

Uterine fibroids are a common benign indication for hysterectomy. However, recently there has been a major decrease in hysterectomies performed for uterine fibroids, and in Finland, the lifetime risk of undergoing hysterectomy for a uterine fibroid has decreased from 12.8% to 4.2% in the last 30 years.¹⁸ This is largely due to the development of treatment options for menstrual disorders (such as the hormonal intrauterine device, IUD). Nevertheless, this phenomenon may in part be attributed to the changing attitude of women regarding major surgery, with women increasingly opting for less invasive treatment options that offer effective and sustainable symptom relief.

In our study, we have demonstrated that MR-HIFU is efficient in treating fibroid-related symptoms and improving the quality of life of patients. For both of the parameters measured, there was a clear improvement 3 months after treatment, and the response was maintained (SSS) or even improved (QoL) 12 months after treatment. Furthermore, comparing the baseline and the timepoint of 12 months, the change was significant.

According to a study published in 2002, in which the UFS-QoL questionnaire was established, the mean SSS of a healthy woman with no fibroid-related symptoms was 23, and the QoL was 86.¹⁴ Considering this, it is clearly unrealistic to aim for lower scores with any fibroid treatment. Considering this, an SSS of 28 at 12 months and a QoL of 73 at 12 months do not differ much from the results for healthy control women. This significant improvement in symptom severity was achieved despite the median NPV% being less than 80, which is often the target when planning HIFU treatments.

We were surprised by the fairly rapid effect of MR-HIFU on fibroid symptoms at 3 months after the treatment, considering that the fibroids were not physically removed. In a meta-analysis published in European Radiology in 2022 by Liu et al., similar results were found, but the first follow-up was at 6 months after treatment instead of our 3-month time point.¹⁹ A systematic review of minimally invasive approaches to uterine fibroids published in 2022 found a significant decrease in symptom severity from baseline to 6 months but not as early as 3 months. The rapid decrease in symptom severity could be explained by changes in the structure of the fibroid following the coagulative necrosis caused by the heating of the tissue. We speculate that this is the reason for

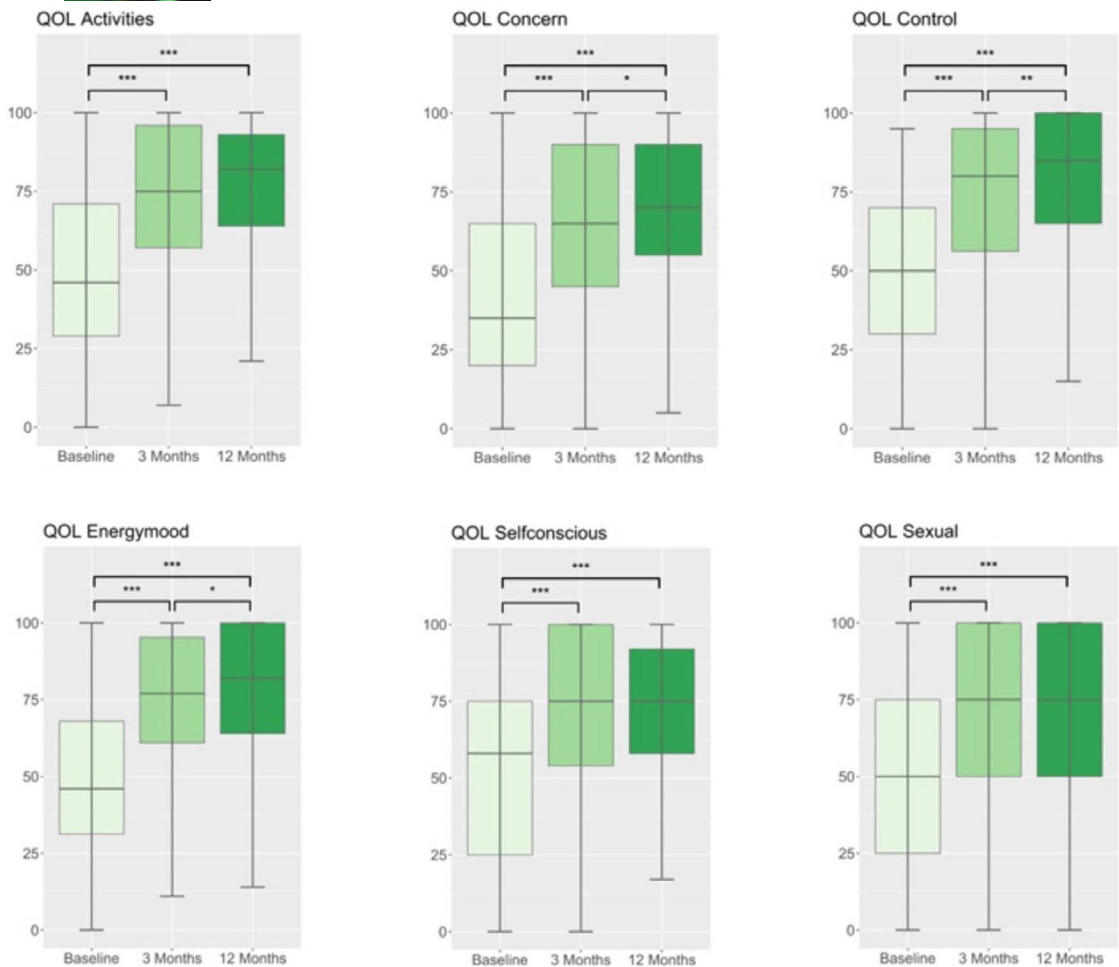


FIGURE 5 Quality of Life according to the subgroups. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

the rapid relief of bulk symptoms even when the fibroid has not yet significantly shrunk in the MRI at 3 months. On the contrary, fibroids are biologically active tumors producing hormones and cytokines, which may disturb endometrial homeostasis and contribute to bleeding disorders.²⁰ Thus, inactivation of the fibroid tissue can also affect the molecular environment of the uterus and the endometrium.

The relief of fibroid symptoms demonstrated in our study is in accordance with previously published studies. In a meta-analysis by Liu et al., published in 2022, MR-HIFU was found to be superior to surgery in treating uterine fibroid symptoms and increasing quality of life with a follow-up time of 6–12 months. Symptom recurrence, reinterventions, and adverse events were comparable for these two treatment methods.¹⁹ In an earlier review and meta-analysis published in 2018, HIFU was associated with the least favorable outcomes in decreasing fibroid symptom severity and increasing quality of life.²¹ Mindjuk et al. published a single-center study of the clinical

results of MR-HIFU and the factors affecting clinical success. They found that the NPV ratio was highly correlated with treatment success, with an NPV over 80 resulting in a clinical success for over 80% of patients. In their study, the reintervention rate was 12.7%, with a follow-up time of 19 months.¹² Despite similar, favorable results in the short term, the need for long-term results is emphasized by most of these studies.

Notwithstanding the relatively short follow-up time of 12 months, the reintervention rate for fibroid-related symptoms in our study was extremely low, only 2%. The previously reported reintervention rate for fibroid symptoms after MR-HIFU varies from 14% (24 months follow-up) to as high as 54% (60 months follow-up), depending on the duration of the follow-up.^{12,19,21,22} For any uterine-sparing fibroid treatment, there is the evident risk of reintervention, due either to possible fibroid recurrence or to other non-fibroid-related symptoms. The reintervention rate after UAE is reported to be 1% at a follow-up time of 13 months and 14% at a

follow-up time of 60 months. Considering myomectomy, the rates are 1% (12 months follow-up) and 12% (60 months follow-up) respectively.^{1,21} As we continue the follow-up of our patients, we expect the reintervention rate to increase. However, we do believe that identifying the risk factors for early or late reintervention is a crucial part of patient selection and treatment success in MR-HIFU. This has also been reported by other groups.^{23,24}

Being a non-invasive treatment, MR-HIFU is patient-friendly; it can be performed in an outpatient setting and there is usually no need for absence from work and other daily life. When comparing MR-HIFU with the widely used Ultrasound-Guided High-Intensity Focused Ultrasound (US-HIFU), MR-HIFU offers superior image guidance and soft tissue contrast. Another advantage of MR-HIFU is the ability to perform real-time temperature monitoring during the treatment. In contrast, higher costs and poorer availability are the disadvantages of MR-HIFU when compared to US-HIFU.

As a disadvantage, we have observed that there is a significant learning curve associated with this treatment. Since MR-HIFU is not suitable for all patients, we believe that, in order to achieve good results, meticulous patient selection performed by a well-coordinated multidisciplinary team is essential. On the contrary, this makes direct comparison of MR-HIFU with other treatments (e.g., UAE) difficult.⁵ Nevertheless, once the learning curve is overcome, MR-HIFU is able to offer a selected group of patients an effective treatment with very low complication and reintervention rates.

The strength of this study is its aim to demonstrate the effect of this relatively novel fibroid treatment on patients' symptoms instead of the pure technical outcome of MR-HIFU. Most of the data available on MR-HIFU consist of technical outcomes of the treatment instead of patient-centered outcomes such as symptom severity or quality of life. Fortunately, there are currently other studies focusing more on the patient-reported outcomes in various fibroid therapies.²⁵ Symptom relief is evidently the most important outcome parameter for the treating physician as well as the patient herself. Considering that MR-HIFU is a new treatment method in the Nordic countries, it is very important to publish the clinical results from the first 175 women treated with MR-HIFU in Finland. Another strength is that the study population is clearly over 100 women, which can be considered a fairly large group among MR-HIFU studies. The limitation of this study is the relatively short follow-up time of 12 months. It is clear that in the future, a longer follow-up is needed to evaluate the long-term symptom relief as well as to assess the reintervention rate after MR-HIFU. The patients in this study present a carefully selected subgroup of women suffering from fibroid symptoms. This can be seen as a limitation in the interpretation of our results since they may not necessarily correlate with the efficacy of MR-HIFU treatment in a general fibroid population. We do recognize the need for a randomized controlled trial (RCT) comparing different treatments, and it will be interesting to see whether the same kind of results will be provided in the currently running randomized trial studying the efficacy of various fibroid therapies including

MR-HIFU in a more unselected setting.²⁵ However, currently it is our belief that meticulous patient selection offers the best patient-related outcomes in MR-HIFU as well as other fibroid therapies and that RCTs might not be the best way to study the potential of each therapy since we do not know precisely what the strengths and weaknesses of each therapy are. We believe the results of our study will help shape future trials that will answer these questions.

This is the first report from MR-HIFU treatments in Finland, and our aim was to investigate the effect of this treatment on patients' symptoms in general. Our future goals are to study the effect of MR-HIFU treatment on various symptoms in more detail, as well as to perform a long-term follow-up to address symptom recurrences and reinterventions, as well as the cost-effectiveness of MR-HIFU. We also aim to study more closely correlations of technical success or patient-related factors to the reduction of the symptoms.

5 | CONCLUSION

MR-HIFU can offer rapid and sustainable symptom relief for selected symptomatic fibroid patients. In our study, the severity of fibroid-related symptoms had significantly reduced at 3 and 12 months, while quality of life had increased. In addition, the treatment can be offered to women planning future pregnancies, as no negative effect on future fertility or pregnancy has been reported.^{11,26} In the future, the sustained nature of the treatment response must be confirmed, and further tools for predicting treatment success need to be developed.

AUTHOR CONTRIBUTIONS

Saara Otonkoski was the main author, participated in recruiting the patients, and collecting and analyzing the data. Antti Viitala was responsible for statistical analysis, revised the paper, and approved the version to be published. Gaber Komar was the radiologist responsible for conducting the MR-HIFU treatments, collected the data, revised the paper, and approved the version to be published. Teija Saino was the physicist conducting the MR-HIFU treatments and participating in collecting and analyzing the data. Anna Yanovskiy was the radiologist participating in collecting and analyzing the data. Roberto Blanco Sequieros contributed to the design of the research and approved the version to be published. Antti Perheentupa contributed to the design of the research, revised the paper, and approved the version to be published. Kirsi Joronen contributed to the design of the research, recruited the patients, participated in the interpretation of the data, revised the paper, and approved the final version to be published.

FUNDING INFORMATION

Funding was received from the Government Research Foundation of Finland.

CONFLICT OF INTEREST STATEMENT

The authors report that there are no competing interests to declare.

ETHICS STATEMENT

This study was registered at clinicaltrials.gov (NCT03937401) and was performed in accordance with the ethical regulations of the Ethics Committee of the Hospital District of Southwest Finland and the National Committee on Medical Research Ethics (T366/2017; January 25, 2018).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Otonkoski S, Viitala A, Komar G, et al. Magnetic resonance guided high intensity focused ultrasound (MR-HIFU) effectively reduces fibroid-related symptoms and improves quality of life—A prospective single-centre 12-month follow-up study. *Acta Obstet Gynecol Scand*. 2025;104:1172-1180. doi:[10.1111/aogs.15086](https://doi.org/10.1111/aogs.15086)

Appendix S1. The screening protocol for assessing patient suitability for MR-HIFU treatment

The assessment of patient suitability for MR-HIFU consisted of both gynecological and radiological evaluation. The aim of the gynecological evaluation was to assess the suitability of the patients clinical characteristics for MR-HIFU treatment and the radiological evaluation assessed the likelihood of a significant technical success of the treatment. This depended somewhat on the patient's dominant symptoms and the number and the location of the fibroids. In general, however we considered a non-perfused volume ratio (necrotic part) of 80% and more as technical success. Characteristics considered favorable for MR-HIFU were:

- Patients hoping for uterus sparing fibroid treatment and motivated for the MR-HIFU treatment
- Fibroids causing typical symptoms
- Patients with preferably 1-3 fibroids
- Maximum diameter of treated fibroid less than 9 cm
- Suitable location of the fibroid within the pelvis, i.e. the fibroid potentially reachable with the HIFU beam
- Fibroids of Funaki type 1 or 2

Otonkoski, S, Viitala, A, Komar, G, Sainio, T, Yanovskiy, A, Lehtonen, I, Perheentupa, A, Blanco Sequieros, & Joronen, K (manuscript)
Magnetic resonance guided high intensity focused ultrasound (MR-HIFU) therapy of uterine fibroids effectively reduces both bleeding and bulk symptoms – A prospective single centre 12 month follow-up study

Magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) therapy of uterine fibroids effectively reduces both bleeding and bulk symptoms – a prospective single center 12-month follow-up study

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Conflict of interest statement

The authors report there are no competing interests to declare.

Funding information

Funding was received from the Government Research Foundation of Finland.

ABSTRACT

Introduction: Uterine fibroids are common benign neoplasms in women with a prevalence of up to 70% by the end of the reproductive age. It is estimated that 30-40% of fibroids cause symptoms such as heavy menstrual bleeding and bulk symptoms of the pelvis and these can severely decrease the quality of life of the patients. Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) is a non-invasive therapy for uterine fibroids which is based on rapid heating of the target tissue and coagulative necrosis and it has been shown to effectively reduce fibroid symptoms and enhance the quality of life. In this study, we aimed to clarify symptom reduction in the two different type of fibroid symptoms: bleeding and bulk symptoms.

Materials and methods: In this prospective, 12-month follow-up study, women with symptomatic uterine fibroids and evaluated suitable for MR-HIFU were enrolled between May 2016 and November 2024. From this group, patients with isolated bleeding symptoms or only bulk symptoms were collected for this study. This resulted in 163 women enrolled. Planning MR images were obtained before the treatment. All treatments were performed using an extracorporeal tabletop MR-HIFU system (Sonalleve V2, Profound Medical Inc., Mississauga, Canada). Control images were obtained after the treatment and the Non-Perfused Volume ratio (NPV%) was determined. The patients completed the Uterine Fibroid Specific Quality of Life questionnaire (UFS-QoL) before, 3 months and 12 months after the treatment.

Results: 122 women with bleeding symptoms and 41 women with bulk symptoms were included in this study. The median age of the women in the bleeding group was 40 years (range 24-55), and in the bulk group 38 years (range 24-57). The overall mean NPV% for all patients was 62%. In the bleeding group, the mean NPV% was 72%, and in the bulk group 59%. The

median volume of the treated fibroids was 61 ml (interquartile range, IQR 25-116) and 189 ml (IQR 97-330) for the bleeding and bulk group, respectively.

In the bleeding group, the median symptom severity (SSS) at baseline was 56 (IQR, 47-69), at 3 months 28 (IQR 16-44), and at 12 months 25 (IQR 13-31). The reduction of SSS was statistically significant between baseline and 3 months ($p < 0.001$) and between baseline and 12 months ($p < 0.001$).

The median of Quality of Life (QoL) in the bleeding group at baseline was 43 (IQR 31-58), at 3 months 70 (IQR 53-82), and at 12 months 82 (IQR 69-91). The increase in QoL was statistically significant between all the time points compared: baseline to 3 months and baseline to 12 months ($p < 0.001$), as well as from 3 months to 12 months ($p < 0.05$).

In the bulk group, the median SSS at baseline was 46 (interquartile range, IQR 34-63), at 3 months 19 (IQR 6-30), and at 12 months 19 (IQR 6-41). The reduction of SSS was statistically significant between baseline and 3 months ($p < 0.001$) and between baseline and 12 months ($p < 0.001$).

The median of QoL in the bulk group at baseline was 74 (IQR 45-83), at 3 months 89 (IQR 74-97), and at 12 months 82 (IQR 67-100). The increase in QoL was statistically significant from baseline to 3 months ($p < 0.001$) and baseline to 12 months ($p < 0.01$).

Conclusions: The fibroid symptoms decreased significantly at 3 months after MR-HIFU in both groups; patients with bleeding symptoms and those with bulk symptoms. For Quality of life, the biggest improvement was achieved in both groups three months after MR-HIFU. In the bleeding groups, the QoL continued to improve from 3 months to 12 months, whereas in the bulk group, the QoL remained the same. When the MR-HIFU is technically successful, it provides significant symptom relief shortly after treatment for both bleeding and bulk symptoms.

Keywords: MR-HIFU, Fibroid, Quality of Life, Bleeding, Bulk

Abbreviations:

MR-HIFU: magnetic resonance guided high intensity focused ultrasound

UFS-QoL: Uterine Fibroid Specific- Quality of Life

HRQL: health-related quality of life

SSS: symptom severity score

MR: magnetic resonance

UAE: uterine artery embolization

NPV: non-perfused volume

IQR: interquartile range

Key message:

Uterine fibroids are common benign tumors causing various symptoms decreasing the quality of life of many women. MR-HIFU is a thermal ablation therapy, which can be used in treating both fibroid related bleeding and bulk symptoms.

INTRODUCTION

Uterine fibroids are the most common benign neoplasms in women. They are hormonally dependent tumours with an estimated prevalence of up to 70% by the end of reproductive age (1).

The majority of women with fibroids are asymptomatic. However, it is estimated that 30–40% of fibroid patients suffer from symptoms that deteriorate their quality of life. The most common symptom reported by women suffering from fibroids is heavy, prolonged menstruation (2). This is especially associated with fibroids protruding into the uterine cavity, i.e., submucous fibroids. However, bleeding symptoms are also described by women with intramural fibroids. They may affect the contractility of the uterus and cause the uterine cavity to distend. Fibroids are also known to alter endometrial homeostasis by producing several hormones and cytokines (3). Another common symptom caused by fibroids is bulk symptoms (4). They can also present in various ways, such as a feeling of pressure or heaviness in the abdomen or multiple urinary symptoms. These are usually associated with larger fibroids, although there is no clear correlation between the size or location of a fibroid and presentation of bulk symptoms (5) (6). Besides bleeding and bulk symptoms, fibroids can also cause many other symptoms, such as lower abdominal pain, dysmenorrhea, and infertility (7). The FIGO classification is used to classify fibroids based on their location and impact on endometrium and uterine serosa: FIGO type 0, 1, and 2 fibroids are submucous, FIGO type 3 fibroids are intramural but in contact with the endometrium, and FIGO type 4–7 fibroids are purely intramural or subserous (8).

The modern concept of fibroid management is focused on reducing the symptoms caused by fibroids (3) (9). Since these are benign tumours, fibroids per se seldom require intervention. There are many different options available for treating fibroid symptoms (10). Medical therapy is readily available and often effective in controlling the excessive bleeding caused by fibroids (11). Uterine artery embolization is known to effectively reduce both bleeding and bulk symptoms caused by fibroids (12) (13). Myomectomy is a surgical option for those patients wishing to retain the uterus, and especially hysteroscopic myomectomy is often preferred for small, submucous fibroids. Hysterectomy is the definitive therapy for fibroid symptoms. Numerous studies have demonstrated that it provides efficient and long-term symptom relief, as well as an improvement in quality of life. However, it is a major surgery with a higher complication risk than the less invasive treatment modalities, and of course, not an option when preservation of the uterus is essential (14) (10).

Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) is a relatively novel, non-invasive, and radiation-free therapy for uterine fibroids. It produces coagulative necrosis in the fibroid through rapid heating of the target tissue. The procedure is performed under real-time MRI guidance, which enables the operator to constantly and precisely control the location and heating of the targeted and adjacent tissues. The technical result and early success of MR-HIFU treatment are assessed by determining the Non-Perfused Volume (NPV) from post-treatment contrast-enhanced T1-weighted MR images. The Non-Perfused Volume ratio (NPV%) is a parameter commonly used in evaluating MR-HIFU treatment outcomes. It is calculated by dividing the non-perfused volume by the total fibroid volume before treatment. In current literature, NPV% above 80% is generally considered to be associated with better short-term symptom relief and clinical outcomes, although individual responses may vary (16) (17). MR-HIFU is a safe and effective treatment for symptomatic fibroids (18) (19) (20). However, there is limited data on the impact of MR-HIFU on specific symptoms related to fibroids.

In our previous study, we demonstrated the effectiveness of MR-HIFU in reducing fibroid-related symptoms and improving quality of life 12 months after MR-HIFU therapy (21). In this

study, we aimed to clarify symptom reduction and changes in quality of life in patients experiencing either bleeding symptoms or bulk symptoms alone. To better advise patients and plan individual fibroid management, we also sought to determine the time frame of symptom relief for both of these specific symptoms.

MATERIAL AND METHODS

The study population in this prospective, 12-month follow-up study consisted of women with symptomatic uterine fibroids evaluated in the gynaecological department of Turku University Hospital and deemed suitable for MR-HIFU treatment between May 2016 and November 2024. Written informed consent was obtained from all patients. The patients were initially referred to the gynaecological department for evaluation of their symptoms and their relationship to the fibroids. All available treatment options were carefully discussed with the patient. Patients considered clinically suitable for MR-HIFU were referred for MR imaging to evaluate the technical suitability of the treatment. The criteria for suitability are presented in our previous publications (21). For each patient, a team consisting of experienced practitioners, one gynaecologist (KJ), and one radiologist (GK) carried out the evaluation of suitability.

For each patient, the primary fibroid symptom was recorded, and patients for whom the leading symptom was either bleeding disorders or bulk symptoms were recruited for this study. Urinary symptoms, such as urge and frequency, were categorized as bulk symptoms if the fibroid was found to cause a pressure effect on the urinary bladder. Patients with both bleeding and bulk symptoms or with other symptoms, such as pain or infertility, were excluded. This resulted in 163 women fulfilling the inclusion criteria.

The primary outcome was the effect of MR-HIFU treatment on the patient's fibroid symptom, ie, bleeding or bulk symptom. The secondary outcome was the effect on bleeding and pressure symptoms on the patient's quality of life, as well as the time frame of symptom relief for each symptom.

Planning MR images were obtained shortly before the treatment, and control images were obtained after the treatment to confirm the results. NPV values were determined by our radiologist (A.Y.), who manually outlined the non-enhancing part of the treated fibroid on contrast-enhanced T1-weighted MR images and compared that to the whole volume of the fibroid, which was determined using T2-weighted MR images.

The Uterine Fibroid Symptom and Quality of Life (UFS-QoL) Questionnaire was introduced by Spies et al. in 2002 to evaluate the effect of various therapies on fibroid-related symptoms and quality of life (15). It assesses both symptom severity (Symptom Severity Score, SSS) and health-related quality of life (HRQL) using a five-point Likert scale. Scores are calculated using standardized formulas. The SSS ranges from 0 to 100, with higher scores indicating more severe symptoms. The HRQL score also ranges from 0 to 100, with higher scores indicating a better quality of life (15).

The patients completed the questionnaire before treatment, which was considered the baseline in our study. All patients were seen three months after the treatment, and this appointment included the UFS-QoL questionnaire, a clinical evaluation with a gynaecological ultrasound, and an MRI. The same protocol was performed 12 months after the treatment. If a patient failed to

make a follow-up visit and was not reached after two attempts to contact her from the hospital, she was considered a loss to follow-up.

All treatments were performed using an extracorporeal tabletop MR-HIFU system (Sonalleve V2, Profound Medical Inc., Mississauga, Canada). The treatment planning was conducted by positioning the ellipsoid treatment cells into the targeted fibroid. This was performed one by one to cover the whole fibroid. Test sonication was performed, and the treatment power was selected accordingly. The aim was to achieve the best possible temperature rise in the target tissue. The potential undesired heating of surrounding tissues and the targeted area was monitored in real-time using MR thermometry. The technical objective of the treatment was to ablate as much of the fibroid tissue as possible in those fibroids considered relevant with respect to the symptoms. During the treatment, intravenous oxytocin (40 IU of oxytocin, Syntocinon 8.3 µg/ml, Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., diluted to 500 ml of 0.9% NaCl) was infused at a rate of 5 ml/min to reduce the blood flow in the fibroids (22). After the treatment, the NPV was evaluated from a contrast-enhanced T1-weighted image acquired by injecting the contrast agent DOTAREM (Guerbet, Aulnay-sous-Bois, France, 0.1 mmol/kg). NPV% was calculated for each patient.

Statistical analysis was conducted in RStudio 2024.10.0+467 (RStudio, PBC, Boston, USA) using R version 4.4.2 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). For all the outcome parameters, we used the Shapiro-Wilk test and visual density distribution evaluation to assess whether the data were normally distributed. Since the majority of the parameters were found not to be normally distributed, a paired Wilcoxon signed-rank test was used to calculate the statistical significance of parameter changes between time points. To evaluate differences in patient characteristics between the bleeding and bulk symptom groups, a two-sided exact Wilcoxon test was used for continuous variables and Fisher's exact test for categorical variable.

RESULTS

In our study, a total of 122 women suffered from bleeding symptoms and 41 women from bulk symptoms. The median age of the women in the bleeding group was 40 years (range, 24-55), and in the bulk group, 38 years (range, 24-57). The overall mean NPV% for all patients was 62%. In the bleeding group, the NPV% was 72%, while in the bulk group, it was 59%.

Hormonal contraception was used by 28% of women in the bleeding group and 39% in the bulk group. Medication specifically indicated for the control of fibroid symptoms (ulipristal acetate or relugolix combination therapy) was used by 11 % and 2%, respectively. 16% of women in the bleeding group had previous surgery for fibroids; for the bulk group, the number was 5%. Especially in the bleeding group, a majority of these previous surgeries were hysteroscopic myomectomies, which had resulted in incomplete fibroid removal.

The majority of the women in both groups were treated for a single symptomatic fibroid only. As could be expected, the bleeding and bulk groups differed when analysed for treated fibroids. In the bleeding group, the median volume of the treated fibroids was 61 ml (IQR 25-116). In the bulk group, the median volume was 189 ml (IQR 97-330). 58% of the dominant treated fibroids in the bleeding group were FIGO 0-2, 35% were FIGO 3 fibroids, and only 6% of fibroids were FIGO 4-5. There were no totally subserosal fibroids (i.e., FIGO 6 or 7 fibroids) in the bleeding

group. In the bulk group, 23% of the fibroids were classified as FIGO 0-2, 10% were classified as FIGO 3, and the majority, 67%, were classified as FIGO 4-6. The distribution of fibroids by FIGO-type in both groups are illustrated in Figure 1.

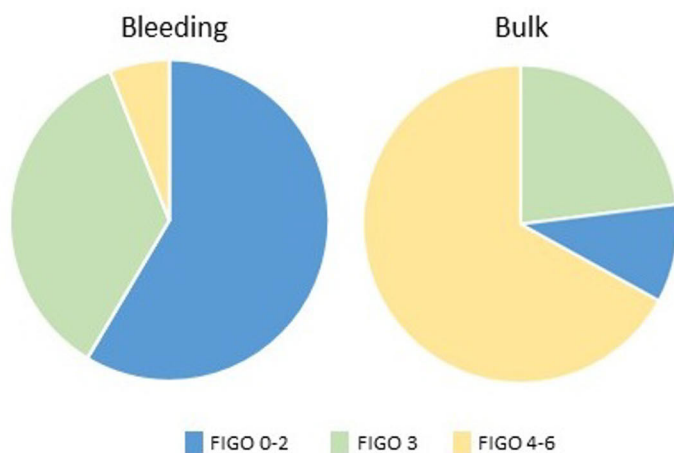


Fig 1. The distribution of fibroids by FIGO-type in the bleeding group and in the bulk group.

Five patients in our study underwent clinical follow-up; however, the imaging data for the fibroids of these patients was incomplete in our records. Since the primary scope of the study was in the relief of symptoms and quality of life, we chose to include these patients in the study. The characteristics of the patients and the fibroids treated are shown in Table 1.

Table 1. Patient and fibroid characteristics

	Bleeding	Bulk	p-value
N	122	41	
Age [Median (Range)]	40 (24, 55)	38 (24, 57)	ns
BMI [Median (Range)]	24 (19, 39)	24 (18, 37)	ns
Hormonal contraception			ns
Yes (N)	34	16	
No (N)	88	25	
Fibroid medication (N)	13	1	ns
Prior gyn surgeries (N)	20	2	ns
Dominant myoma volume at baseline [ml] [Median (IQR)]	61 (25-116)	189 (97-330)	ns
Dominant myoma NPV % [Median (IQR)]	79 (54-96)	64 (42-78)	0.05
Dominant myoma location anterior N (%)	61 (50%)	25 (61%)	ns
Dominant myoma location posterior N (%)	36 (30%)	5 (12%)	ns
Dominant myoma location fundus N (%)	10 (8%)	3 (7%)	ns
Dominant myoma location lateral N (%)	12 (10%)	6 (15%)	ns
Dominant myoma location unknown (imaging data incomplete) N (%)	3 (2%)	2 (5%)	

Ns= Non significant

In the bleeding group, the median SSS at baseline was 56 (IQR 47-69). Three months after MR-HIFU, the median SSS was reduced to 28 (IQR 16-44), and 12 months after MR-HIFU further to 25 (IQR 13-31). The reduction of SSS was statistically significant between baseline and three months ($p < 0.001$) and between baseline and 12 months ($p < 0.001$).

The median of Quality of Life in the bleeding group was 43 (IQR 31-58) at baseline. Three months after MR-HIFU, the median QoL increased to a median of 70 (IQR 53-82), and 12 months after MR-HIFU to a median of 82 (IQR 69-91). The increase in QoL was statistically significant between all the time points compared: baseline to 3 months and baseline to 12 months ($p < 0.001$), as well as from three months to 12 months ($p < 0.05$). The SSS and HRQL of patients with bleeding are shown in Figure 2.

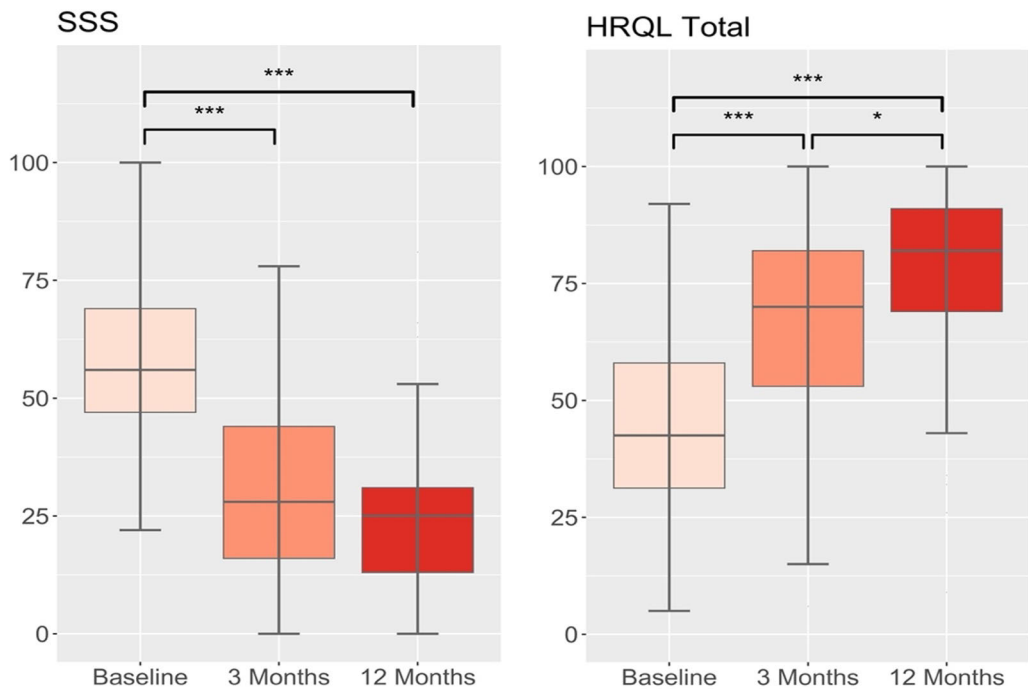


Fig. 2. The median symptom severity score (SSS) and health related quality of life (HRQL) of patients with bleeding symptoms 3 and 12 months after MRI-HIFU.

In the bulk group, the median SSS at baseline was 46 (interquartile range, IQR 34-63). Three months after MR-HIFU, the median SSS was reduced to 19 (IQR 6-30), and 12 months after MR-HIFU, the median SSS was also 19 (IQR 6-41). The reduction of SSS was statistically significant between baseline and three months ($p < 0.001$) and between baseline and 12 months ($p < 0.001$).

The median of Quality of Life in the bulk group was 74 (IQR 45-83) at baseline. Three months after MR-HIFU, the median QoL increased to 89 (IQR 74-97), and at 12 months, the median QoL score was 82 (IQR 67-100). The increase in QoL was statistically significant from baseline to three months ($p < 0.001$) and baseline to 12 months ($p < 0.01$). The SSS and HRQL of the bulk patients are shown in Figure 3.

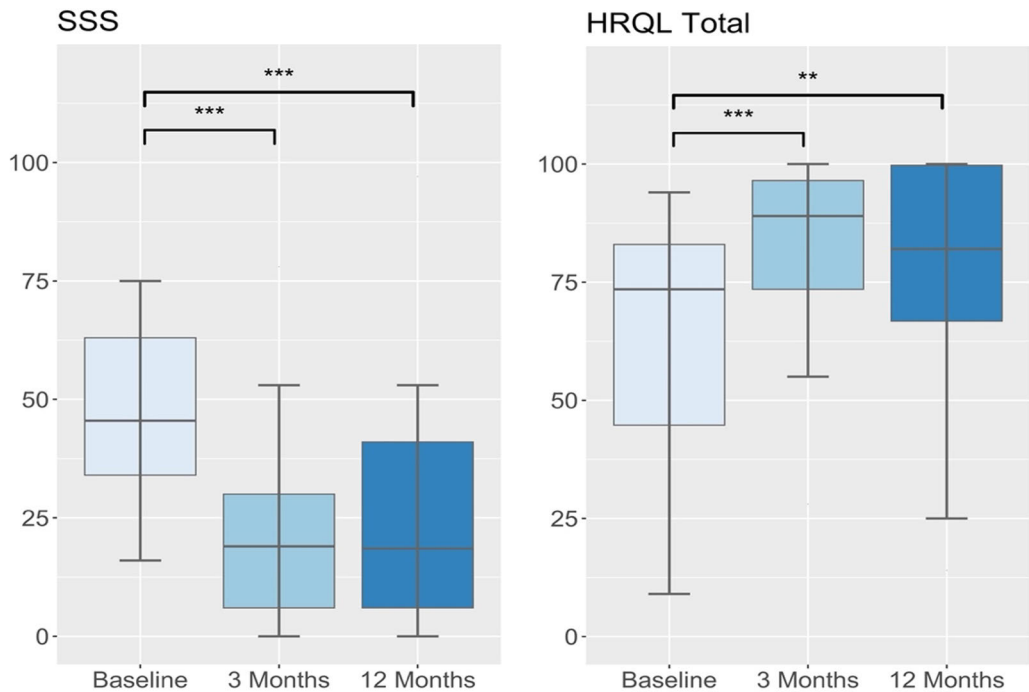


Fig. 3. The median symptom severity score (SSS) and health related quality of life (HRQL) of patients with bulk symptoms 3 and 12 months after MR-HIFU.

DISCUSSION

In this prospective non-randomized cohort study, we aimed to understand better the impact of MR-HIFU treatment on uterine fibroids, particularly in relation to the most common fibroid-related symptoms, the bleeding and bulk symptoms. To our knowledge, there are no previous studies investigating the effect of MR-HIFU on different types of baseline symptoms. As expected, the two study groups, comprising patients with bleeding and bulk symptoms, differed significantly in fibroid characteristics. In the group of women with bleeding symptoms, the fibroids were more often submucous and smaller in size, whereas the group of women with bulk symptoms had larger fibroids. This is in line with earlier findings, as it is known that large fibroids tend to cause pressure on the lower abdomen and pelvis and lead to urinary and bowel symptoms (5) (6). On the other hand, there was an overlap between the fibroid characteristics in these groups and the smallest treated fibroid in the group with bulk symptoms was only 24 ml (diameter approximately 3.6 cm). In the group with bulk symptoms, the majority (61%) of the fibroids was located in the anterior wall of the uterus and thus possibly caused pressure on the urinary bladder which is one of the typical pressure symptoms.

FIGO type 0-3 fibroids cause bleeding symptoms more often. This is thought to be partly because they distend the endometrium, thus increasing the surface area and causing distortion of the endometrial vessels (3).

In our study population, a significant number of bleeding patients had had earlier surgical interventions for their fibroids, especially unsuccessful hysteroscopic myomectomies. This

highlights the importance of selecting the most suitable treatment modality for each patient and their specific fibroid. Especially in cases of large FIGO type 0-2 fibroids, MR-HIFU is an applicable treatment option, as the complexity of hysteroscopic myomectomy for these types of fibroids is significantly increased.

In our study, the NPV% for all patients was 62%. For the bulk patients, the NPV% was smaller compared to the bleeding patients (64% vs. 79%). This can be explained by the fact that the fibroids of the bulk patients were larger than in the bleeding group. For large fibroids, the treatment time is usually longer, which at least partly may explain the lower NPV%. Large fibroids may also partly be out of reach of the HIFU beam. For these reasons, it's probably more difficult to achieve as large NPV% compared to bleeding patients with smaller fibroids.

Although NPV% is commonly used as a technical marker of treatment success, its correlation with symptom relief is not always linear (24). Some patients may experience significant symptom improvement even with moderate NPV%, while others with high NPV% may report persistent symptoms. This highlights the complexity of fibroid-related symptomatology, which is influenced not only by fibroid volume ablation but also by other fibroid characteristics. The overlap in fibroid characteristics between the bleeding and bulk groups further highlights that no clear correlation has been identified between fibroid size and symptom manifestation.

Our groups (bulk and bleeding) were not equal in size, as we had a larger number of bleeding patients. As MR-HIFU is recommended for fibroids less than 9-10 cm in diameter, it is likely that patients with difficult bulk symptoms and large fibroids were initially referred to other treatments than MR-HIFU. Thus, the group of patients with bulk symptoms was smaller compared to those with bleeding symptoms.

When comparing the bleeding and bulk groups, the quality of life was lower at baseline in the bleeding group compared to the bulk group. As it is known that heavy menstrual bleeding, irregular bleeding, and anemia are symptoms that significantly harm and lower the quality of life, it can be speculated that this is why we also saw a difference in the baseline score between our groups (3) (23). Additionally, the bulk symptoms are known to have severe effects on women's quality of life (5). However, we speculated that it might still be more challenging to cope with bleeding symptoms in daily life compared to bulk symptoms, which is reflected in lower quality of life scores.

We found that both the bleeding and bulk symptoms had already decreased by three months after treatment. It is reassuring that MR-HIFU provides significant symptom relief shortly after treatment. We didn't observe a substantial improvement in symptom severity in either group after three months. For QoL, the biggest improvement was achieved in both groups three months after MR-HIFU. In the bleeding groups, the QoL continued to improve from three months to 12 months, whereas in the bulk group, the QoL remained the same.

The major advantage of this study is that it is the first to publish an assessment of the effect of MR-HIFU on different types of baseline symptoms. As women with uterine fibroids present with a variety of symptoms, it is essential to be aware that both bleeding and bulk symptoms significantly decrease with this treatment when the criteria for MR-HIFU treatment are met.

A disadvantage of this study is that the bleeding and bulk groups were different in size. As this study was conducted as part of a larger study that included all patients assigned for MR-HIFU, no special recruitment was made for patients with different baseline symptoms. This is

also why these results cannot be generalized to all symptomatic fibroid patients, as our study group is a selected subset of fibroid patients initially deemed suitable for treatment with MR-HIFU. Further studies with symptom-stratified recruitment and larger sample sizes are needed to confirm these findings and to develop predictive models for MR-HIFU treatment response based on fibroid characteristics and symptom profiles.

In conclusion, when the MR-HIFU is technically successful (i.e., a high NPV% is achieved), this will translate into a clinically meaningful decrease in both bleeding and bulk symptoms. Patients with bleeding symptoms and early clinical response may expect continued improvement in quality of life up to 12 months after treatment. In contrast, patients with bulk symptoms who do not show improvement in by three months may benefit from reassessment and consideration of alternative therapies.

CONCLUSION

MR-HIFU can be considered as a treatment for patients with bleeding and bulk symptoms as it offers rapid and sustainable symptom relief for both symptoms types. Alleviation of both symptom types occurs already by three months after therapy. The quality of life also improves after MR-HIFU for patients with either bleeding or bulk symptoms at three months. The further improvement of QoL from three months to 12months highlight the lasting effect of MR-HIFU. This treatment modality is appealing also as it considered safe for women planning future pregnancies (25). In the future, the sustained nature of the treatment response must be confirmed and further tools for predicting treatment success need to be developed.

Author contributions

Saara Otonkoski was main author, participated in recruiting the patients, collecting and analyzing the data. Antti Viitala was responsible for statistical analysis and revised the paper. Gaber Komar was radiologist responsible for conducting the MR-HIFU treatments, collected the data and revised the paper. Teija Saino was the physicist conducting the MR-HIFU treatments and participated in collecting and analyzing the data. Anna Yanovskiy and Ina Lehtonen participated in collecting and analyzing the data. Roberto Blanco Sequieros contributed to the design of the research. Antti Perheentupa contributed to the design of the research and revised the paper. All authors above approved the study to be published. Kirsi Joronen contributed to the design of the research, recruited the patients, participated to the interpretation of the data, revised the paper and approved the final version to be published.

Ethical statement

This study was registered at clinicaltrials.gov (NCT02914704) and was performed in accordance with the ethical regulations of the Ethics Committee of the Hospital District of Southwest Finland and the National Committee on Medical Research Ethics (ETMK: 95/1801/2015 16.6.2015). Written informed consent was obtained from all patients recruited in the study.

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ISBN 978-952-02-0520-1 (PRINT)
ISBN 978-952-02-0521-8 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)