MR-HIFU: a choice to make for women suffering from uterine fibroids?

Effectivity and societal impact of uterine fibroid MR-HIFU

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The work described in this thesis was performed at the Isala Hospital, Zwolle, the Netherlands at the department of Radiology and Gynecology.

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MR-HIFU: een keuze voor vrouwen met myoomklachten?
Effectiviteit en maatschappelijke impact van myoom MR-HIFU
(met een samenvatting in het Nederlands)

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Toelichting voorkant

Zoveel vrouwen met vlees*boom*klachten, zoveel wensen en verwachtingen. Maar zijn er ook zoveel behandelkeuzes? Het doel van dit proefschrift is om bij te dragen aan het bieden van meer keuze voor al die verschillende vrouwen. Met op de voorkant deze boom als symbool voor de in dit proefschrift beschreven MR-HIFU behandeling voor vleesbomen. Een behandeling die, net als het daaromheen betrokken team de laatste jaren alsmaar is gaan groeien, dankzij het werk in o.a. dit proefschrift goed heeft kunnen wortelen en hopelijk bijna volwassen genoeg is om ook echt een behandelkeuze voor vrouwen te zijn.

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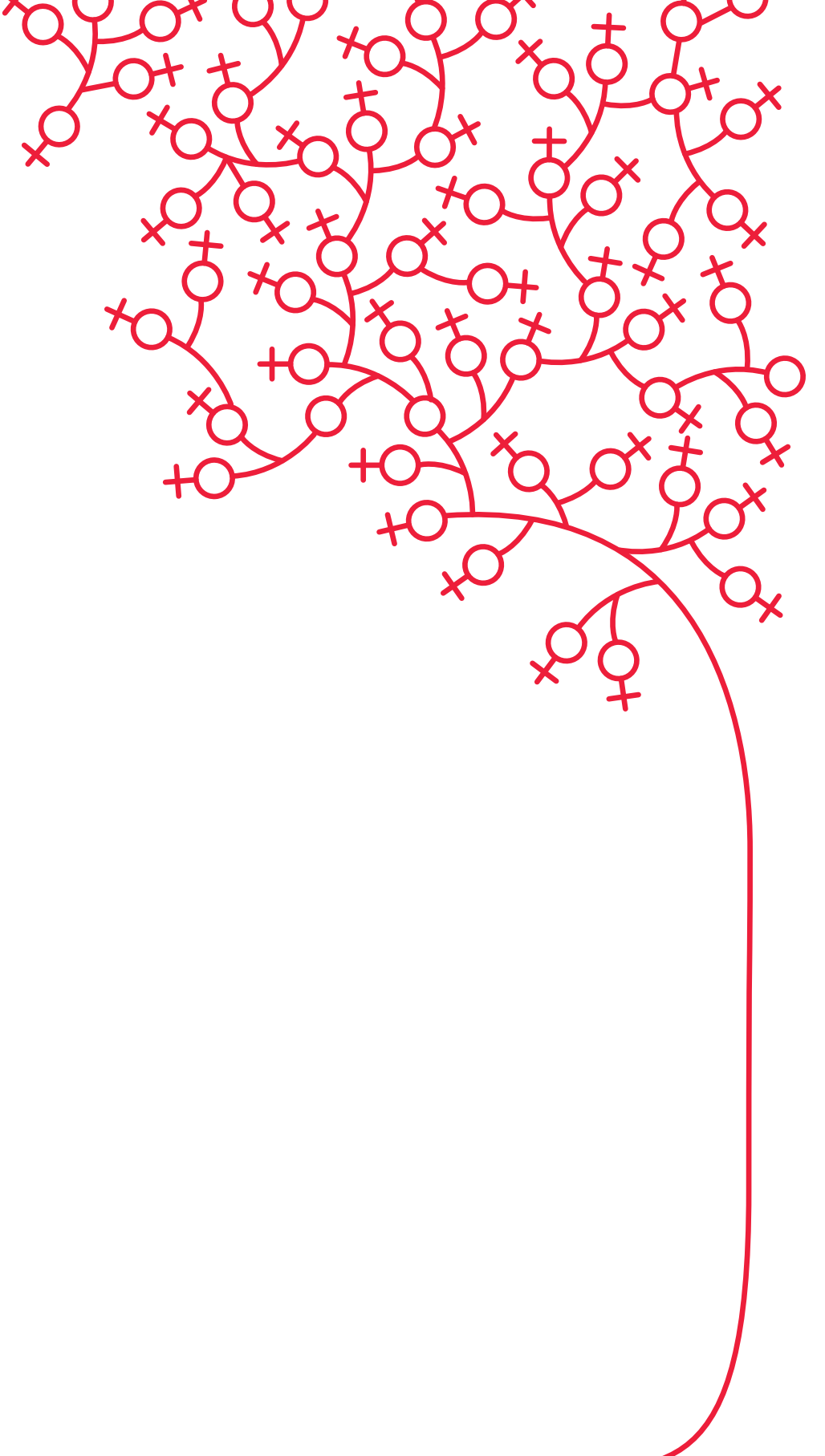

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General introduction and thesis outline

UTERINE FIBROIDS: SYMPTOMS AND DIAGNOSIS

Up to 70% of women develop uterine fibroids during their fertile lifetime. Not all women experience symptoms and in those cases treatment or regular check-ups are not necessary (1). The 25% of women who do suffer from their fibroids complain about mechanical pressure, sometimes leading to frequent urination or obstipation and/or heavy menstrual bleeding (HMB) with prolonged menstruation and loss of blood cloths (2). Another group of women experience difficulties becoming pregnant. In the case of submucosal fibroids, the presence of uterine fibroids might be the reason for their subfertility (3). Besides submucosal (abuts the endometrium), uterine fibroids can be located in the uterus wall or subserosal with distortion of the serosa (Figure 1). Most often the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) classification is used to distinguish the different locations of uterine fibroids in relation to the layers of the uterus (4).

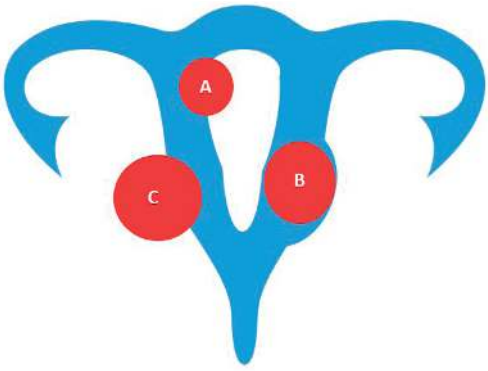

Figure 1: Uterus with different types of fibroids. A: Submucosal, B: Intramural, C: Subserosal.

Uterine fibroids can be found during (imaging) evaluation of not related symptoms (5). Simultaneously, symptoms caused by fibroids can be unspecific, resulting in women associating their symptoms with other conditions (1). Transvaginal ultrasound imaging has a sensitivity and specificity of 90% and 87% respectively. The gynecologist can easily perform this ultrasound examination and this is therefore the most cost-effective tool to diagnose fibroids. Infusion of saline into the uterine cavity (hysterosonography) during transvaginal ultrasound imaging can delineate submucosal fibroids and indicate the proximity of intramural fibroids to the endometrial cavity (6). With an accuracy of almost 100%, Magnetic Resonance Imaging (MRI) is superior to ultrasound imaging, however more expensive and less feasible in daily practice (1). MRI is therefore mainly reserved for women with a larger body habitus, in case of prior surgery or when a sarcoma is suspected (1,6). However, currently no preoperative non-invasive testing can definitively rule out sarcoma's (6).

UTERINE FIBROIDS: TREATMENT OPTIONS

When it comes to treatment options, a shift to less invasive options is seen (2). The removal of the uterus has been considered standard surgical treatment for women not wishing to conceive in the future and vaginal hysterectomies date back to ancient times (Figure 2) (6,7). Today, hysterectomies still account for 75% of the uterine fibroid related procedures in the USA (8). However, women do express their preference for a less invasive treatment and they desire a more proactive presentation by their health care provider of all treatment options available (2,8).

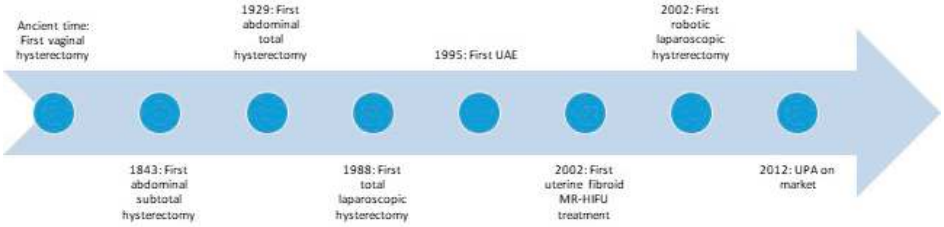

Figure 2: Timeline of uterine fibroid treatments.

First line treatment for HMB symptoms is medical therapy. This thesis does not focus on medical therapy of uterine fibroids. However, since many medical options are available and almost all women suffering from uterine fibroids are at some point advised to take medical therapy, a more detailed overview of the options will be given in this introduction. This will also make clearer why, although medical therapy is rather cheap and widely available, alternative options are preferable.

Medical therapy includes both hormonal and non-hormonal options (8). Two commonly used non-hormonal options are tranexamic acid and non-steroidal anti-inflammatory drugs (5). As hormonal alternative, contraceptives containing a combination of synthetic analogues of progesterone and estrogen are widely used and include both hormonal pills and intrauterine devices (1). The use of combined oral contraceptives can help to control HMB (1). Levonorgestrel devices inhibits the proliferation and induction of apoptosis in fibroid cells leading to a decrease of HMB, but no decrease of fibroid size is seen (1). To deal with both HMB and bulking symptoms, Gonadotropin-releasing hormone (GnRH) agonists are effective, gripping at another point on the hypothalamic–pituitary–gonadal axis (Figure 3). Due to side effects caused by the hypoestrogenism state, women are advised to not take them for a long period of time (6). GnRH agonists are therefore often advised as a pre-surgery treatment (6). Recently oral GnRH antagonists, have been developed and proven to be effective to suppress HMB compared to placebo. No long-term results

are available yet and at this point only approved by the FDA when combined with estradiol/ norethindrone acetate (9).

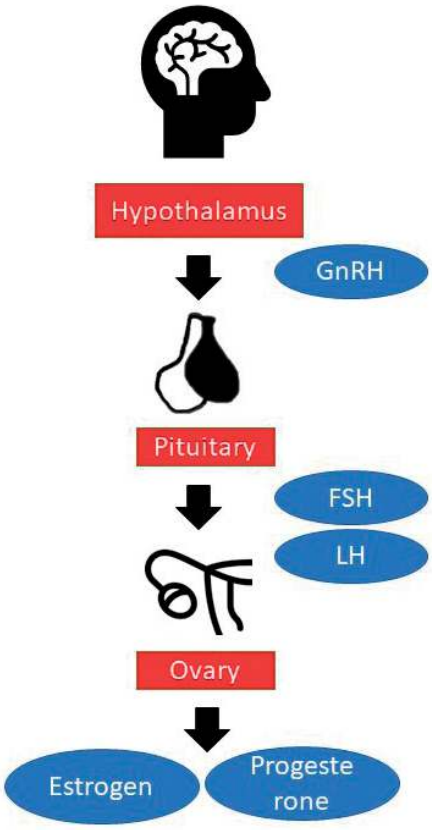

Figure 3: The female hypothalamic–pituitary–gonadal axis.

The crucial role of progesterone in the growth and development of fibroids has become clear in recent years and therefore modulating the progesterone pathway by use of selective progesterone receptor modulators (SPRMs) is seen as a treatment alternative (6). SPRMs are synthetic compounds that exert either an agonistic or an antagonistic effect on progesterone receptors (6). The most studied SPRM in large clinical trials, ulipristal acetate (UPA), showed uterine bleeding was controlled in more than 90% of patients receiving a three-month course of UPA, and the median time to control bleeding was shorter in the UPA group (5–7 days) compared to the GnRH agonist group (21 days) (6). This has led to the suggestion that UPA could not only postpone, but even avoid surgery (10). However, cases of drug-induced liver injury (DILI) while treated by UPA were brought to the attention of the European Medicine Agency. In five cases, DILI even resulted in liver transplantation (10). Recent evaluation of the DILI risks of UPA use, compared to other medication or

surgery, showed however that risk induced by UPA use is lower (10). A study on long-term clinical effect of UPA (MYOMEX-2 study) restarted recently (11). Other SPRMs include mifepristone, asoprisnil, telapristone actetate and vilaprisan, and are all-effective in reducing both fibroid volume and fibroid-related symptoms, although not FDA approved at this point (12). Finally, selective androgen receptor modulators (SARMs) are a new class of agonists and antagonist medication, acting on androgen receptors; however no SARMs have yet been approved for clinical use (12). Hence, several medical therapy options are available, but with women feeling more resistant to taking hormones in general or suffering from it side effects, availability (and development) of other treatment options is desirable.

NON-MEDICAL INTERVENTIONS IN THE TREATMENT OF FIBROIDS

Submucosal (FIGO type 0-2) located uterine fibroids (Figure 1) can be removed safely by hysteroscopic approach until a diameter of 3 cm (13). The procedure leads to significant decrease of HMB after six months and is performed under (local) anesthesia or conscious sedation. Women can leave the hospital the same day (14). Removal of submucosal fibroids is strongly indicated in case of otherwise unexplained subfertility and fibroids (15). When the fibroid is too large or intramuscular/subserosal located and a uterus preserving treatment is desired, a myomectomy can be performed. The approach depends on the exact location and size of the fibroid and can be performed by laparotomy, laparoscopy or robot assisted (5). When laparoscopy is possible, this is always preferred because of less severe post-operative morbidity, faster recovery and no significant difference of reproductive outcomes compared to a myomectomy performed by laparotomy (6). However, the possible advantages of fibroid resection for fertility reasons should be weighed against the risks of the treatment (16). Complications of myomectomy include major hemorrhage and intra-uterine and intra-abdominal adhesion formation. Additional limitations are the four to eight weeks convalescence and the general advice to extend any attempt to conceive for at least six months after treatment in order to facilitate proper wound healing of the uterus (17,18).

When women do not have a pregnancy wish and opt for a definitive solution, hysterectomy is the preferred treatment option. This surgery can be performed by vaginal or abdominal approach (5). The vaginal approach appears to be superior to an abdominal approach in case of a small uterus when it comes to faster return to normal activities (19). In case of a larger uterus the laparoscopic route or the laparotomy route should be considered, although total laparoscopic hysterectomy is associated with more urinary tract injuries. Preferably, the surgical approach of hysterectomy is the result of shared clinical decision-making (19).

In the ’90s of the previous century, an alternative treatment option performed by radiologists became available (Figure 2 and 4). Uterine artery embolization (UAE) is a minimal-invasive treatment option with a recovery of two weeks. The radiologist injects particles using a catheter inserted via the femur artery all the way up to the uterine artery (20). These particles will block the vascularization of the uterine fibroid and this will induce necrosis and therefore shrinkage of the uterine fibroid. Several fibroids can be treated in one session and both abnormal bleeding and bulking symptoms are treated effectively (20). A large randomized controlled trial, performed in the Netherlands with 10 years follow-up, showed that two third of the abdominal hysterectomies could be avoided due to clinical effective embolization (21). However, even with reimbursement, embolization is not implemented in all hospitals in the Netherlands and therefore not offered to all women suffering from uterine fibroids (21). Reasons for lack of implementation include insufficient knowledge of (effectiveness of) UAE, as described by gynecologists themselves, and therefore reluctant in counseling patients (22). Meanwhile, the laparoscopic hysterectomy has been implemented in Dutch healthcare, with a shorter recovery and admission compared removal by laparotomy, leaving embolization in an even more difficult position.

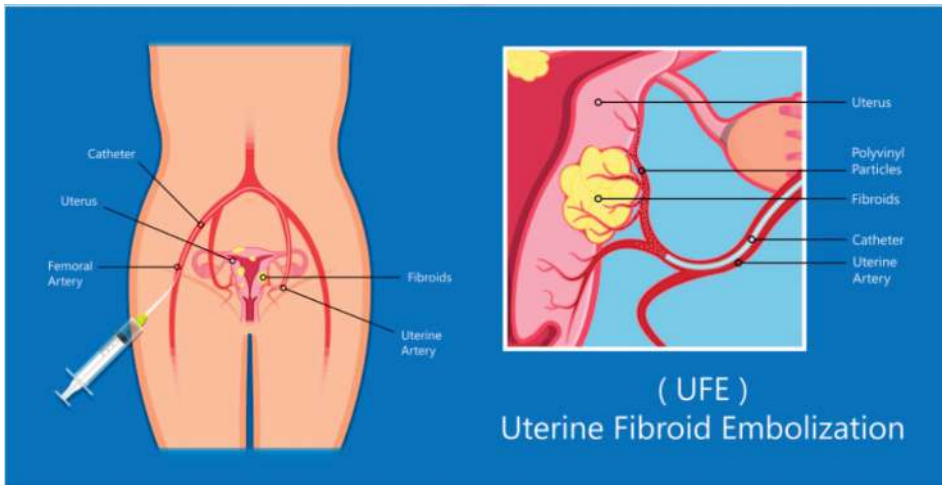

Figure 4: Uterine Artery Embolization (Shutterstock).

MR-HIFU TECHNIQUE: HISTORY AND TODAY

Another treatment option for uterine fibroids performed by the radiologist is the high-intensity focused ultrasound (HIFU) technique. Lynn et al. were the first to describe, back in the ’40s of the 20th century, how high-intensity focused ultrasound waves generated damage to paraffin blocks and fresh beef livers in a focus point, without damage to the surrounding tissue (23). In the decades following, this technique, able to heat and

damage tissue on purpose from the outside without the need of an incision, was tested on both animals and humans for mainly brain indications (24,25). First FDA approval was earned for the focused ultrasound surgery (FUS) of glaucoma in 1988 (26). Treatment of benign prostatic hyperplasia and malignant brain tumors were the clinical indications that followed (25,26). In the 90'of the previous century, first steps were taken towards MR guided HIFU, not only to provide better visual guidance, but for temperature monitoring as well (25,27). Furthermore, contrast enhanced MR-imaging could be used to evaluate treatment effect by showing the volume of non-perfused tissue directly after treatment. The first preclinical study demonstrating volumetric heating with MR-guided focused ultrasound and real time temperature feedback was performed in 2000 (28). Tempany et al. were the first to perform a clinical trial on uterine fibroids in 2002 using InSightec's MR-guided ExAblate 2000 system, which gained FDA approval in 2004 (24). In 2003, Stewart et al. published the first clinical results on safety and efficacy of uterine fibroid MR-HIFU treatment of fifty-five women (29). In a small sub analysis, the pathologic volumes of necrosis and hemorrhage of five women who underwent a planned hysterectomy after MR-HIFU, were compared to the treatment volumes and the non-enhanced tissue volumes on the MR images. MR-guided focused ultrasound surgery was proven feasible and caused safe thermo-coagulation resulting in necrosis of uterine fibroid tissue (24). Before 2004, the FDA only allowed 33% ablation (heating) of the uterine fibroid volume and women with a pregnancy wish were excluded (30). After April 2004, 50% of the fibroid volume could be ablated (31,32). Technical effectiveness is measured by the percentage of non-perfused volume (NPV) percentage compared to total fibroid volume as quantified on contrast-enhanced MRI (33). Clinical effectiveness is often measured by the Uterine Fibroid Symptom Quality of Life (UFS-QoL) questionnaire (31). Reasonable results were seen after MR-HIFU treatment but these results improved after FDA regulations were loosened in 2009 and 100% ablation was strived for (34).

In 2008, Philips Healthcare entered the Focused Ultrasound industry by introducing the MR-guided HIFU system Sonalleve (Figure 5). The device was CE approved by the European Union in December 2009 (30,35) after safety and feasibility was reported (36,37). In 2013, Philips released the V2 with several improvements compared to V1. Most importantly was the addition of a Direct Skin Cooling (DISC), resulting in continuously cooling of the abdominal skin, not only preventing skin burns, but also leading to a more comfortable sensation for patients (38). From 2017 on, Profound Medical acquired Philips's Sonalleve MR-HIFU business.

At this point, two manufacturers of MR-HIFU devices are active: InSightec Ltd. (Haifa, Israel) producing the ExAblate HIFU device requiring guidance by a GE MR-scanner, and Profound Medical (Mississauga, Canada) producing the Sonalleve HIFU device requiring guidance

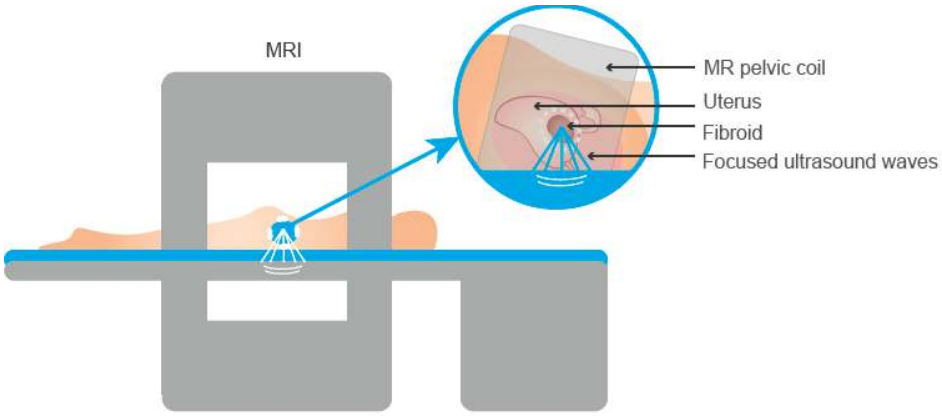

Figure 5: MR-HIFU treatment setting (Profound).

by a Philips MR-scanner (Figure 5) (30,35). Both companies have regulatory approvals in many countries for uterine fibroids and for palliation of painful bone metastases. In the Netherlands, the Sonalleve device is used for both the treatment of uterine fibroids and bone metastasis at the UMC Utrecht and Isala Hospital. Parallel to MR guided uterine fibroid HIFU, ultrasound guidance developed. Especially in China, ultrasound guidance became quickly the standard for HIFU treatment (39,40). Ultrasound guided HIFU (UsgHIFU) can be performed on an outpatient setting, there is no need for scarce and expensive MRI time and the procedure is often shorter (41,42). USgHIFU procedures allows real-time visualization of tissue ablation and provides continuous information about the acoustic beam path and potential obstructions (35). However, diagnostic ultrasound cannot obtain precise temperature information and therefore no information of the achieved absolute temperature or the thermal dose reached in the target tissue. MR-HIFU allows planning of sonications based on MR images with fine anatomic detail and MR-thermometry provides a near real-time temperature map to track the heating pattern in the focal point and surrounding tissue (35). As with MR-HIFU, USgHIFU treatment effect is often evaluated by an MRI-scan performed a couple of days after treatment. The use of contrast-enhanced ultrasound can indicate remaining enhanced tissue during treatment and seems to reduce treatment time and increase ablation efficiency (41).

With the recognition of the need to ablate as much fibroid tissue as possible back in 2009, not all challenges for uterine fibroid MR-HIFU disappeared. Especially the screening for eligible women remains a hurdle (43). A screening MRI-scan is in all cases necessary to evaluate amount, location and tissue type of the fibroid(s). Because of the technical aspects and precise planning of the treatment, MR-HIFU is not indicated for treatment of numerous small fibroids. Furthermore, there is a limit in the distance the sonication beam can reach and heating of other abdominal organs and structures like ovaries and bowels

should be avoided (35). Improvement of treatment devices have however taken place. For example, the amount of power that can be selected is increased, although still not all tissue types are a match for MR-HIFU treatment. Research is still necessary to optimize the screening process. Other remaining challenges include the place of MR-HIFU in case of future pregnancy wish. Although the FDA revised childbearing as contraindication in 2009, data on the benefit of MR-HIFU treatment is still lacking and therefore physicians cannot properly advise women on whether they should undergo MR-HIFU when having a future pregnancy wish (30).

REMAINING CHALLENGES

It has been over twenty years since the first uterine fibroid MR-HIFU treatment was performed. Ever since, multiple studies showed symptom improvement and increase of quality of life after women underwent the MR-HIFU treatment. Technical advancements led to decrease of adverse events and possibility to treat more challenging cases in terms of fibroid size, localization of the fibroid or women with abdominal scars. However, previous performed reviews on effectiveness often include data of studies with a limited treatment protocol. To be able to make a statement on outcomes like reintervention or fibroid shrinkage, one should at least include studies performing MR-HIFU with a non-restricted protocol. When providing information on the reproductive outcomes after (MR-) HIFU, at this point relevant factors as reached NPV percentage and maternal age are not considered. This makes it difficult to perform realistic comparison with other uterine fibroid treatments.

When it comes to implementing the treatment, several hurdles need to be taken. Since the treatment takes a couple of hours at this point, speeding up the procedure time by making the sonication more efficient, would benefit clinical adaptation. Previous literature showed that the use of a uterus stimulant could positively affect treatment efficiency. Furthermore, we noticed when implementing uterine fibroid MR-HIFU treatment in our own non-academic hospital, no practical guidelines or lessons learned are available and the expected learning curve is not known either. The most important hurdle however for clinical implementation, is the lack of reimbursement. This is mainly due to the fact that there is no data collected by randomized controlled trials (RCT) evaluating long-term effectiveness. These data are required to include MR-HIFU in clinical guidelines which is in the Netherlands conditional for reimbursement. Finally, when one wants to implement a new treatment, besides effectiveness and cost-effectiveness, environmental impact should be a future requirement as well and data on sustainability should become available.

THESIS OUTLINE

Part 1: Effectivity of gynecological and reproductive outcomes

Research questions:

- *What do we know of the effectiveness of uterine fibroid MR-HIFU treatment?*
- *What do we know about the reproductive outcomes after HIFU treatment?*

To get a broad overview of what is known on the effectiveness and reproductive outcomes after (MR-) HIFU treatment, we performed systematic reviews on the effectiveness and reproductive outcomes of uterine fibroid (MR-) HIFU treatment. In the effectiveness review we only including articles aiming for a full ablation (**chapter 2**). In a letter to the editor we reflected on a previous review on reproductive outcomes after several uterine fibroid treatment, however relevant contributors like maternal age, were not taken in consideration (**chapter 3**). In our own reproductive outcomes review, we did include these and other important contributors while we analyzed the effect of both MRI guided HIFU and US guided HIFU (**chapter 4**).

Part 2: Measures to improve effectivity

Research questions:

- *Can the use of a long-acting uterus stimulant improve treatment efficiency on a sonication level?*
- *What is the expected learning curve when starting performing uterine fibroid MR-HIFU treatments?*
- *What hurdles can one expect during clinical implementation of uterine fibroid MR-HIFU treatment?*

To further improve effectivity, we prospectively studied the effect of a long-acting uterus stimulant on the efficiency of sonication and on a sonication level to circumvent bias caused by external factors (**chapter 5**). Furthermore, we retrospectively analyzed our learning-curve of the first 70 performed MR-HIFU treatments and gave insights in the hurdles we needed to overcome when implementing the treatment in our non-academic hospital (**chapter 6**).

Part 3: Societal impact

Research questions:

- *How can we finally implement MR-HIFU treatment in standard and reimbursed care?*
- *How sustainable is a uterine fibroid MR-HIFU treatment?*

With all our previously gained knowledge on effectivity, it was now time to perform a multicenter randomized-controlled trial on long-term effectiveness and cost-effectiveness to eliminate the last hurdle of implementation: reimbursement. We published the MYCHOICE study protocol (**chapter 7**). Furthermore, we looked at the future and made the first step towards a life cycle assessment of uterine fibroid MR-HIFU treatment (**chapter 8**).

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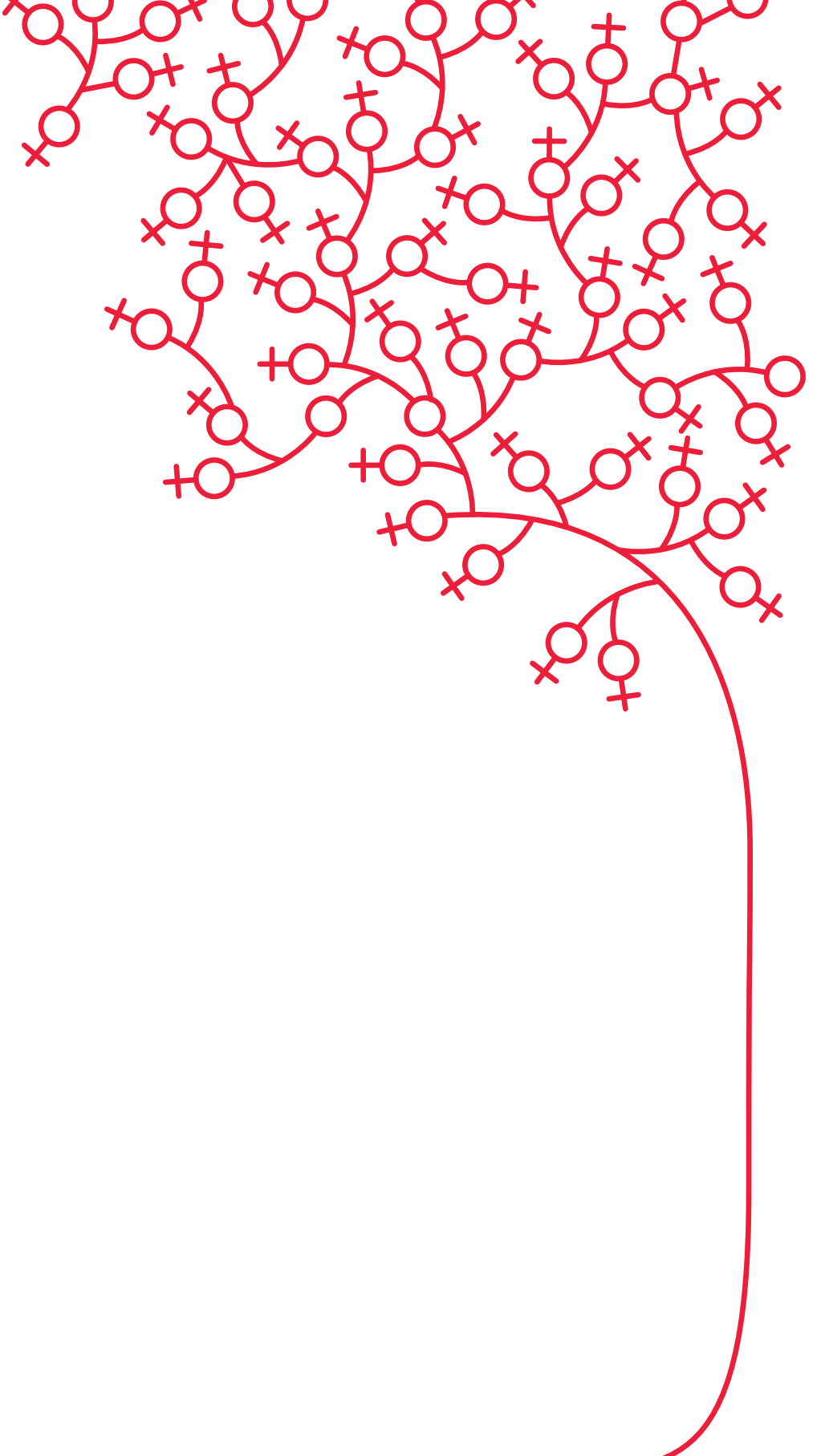
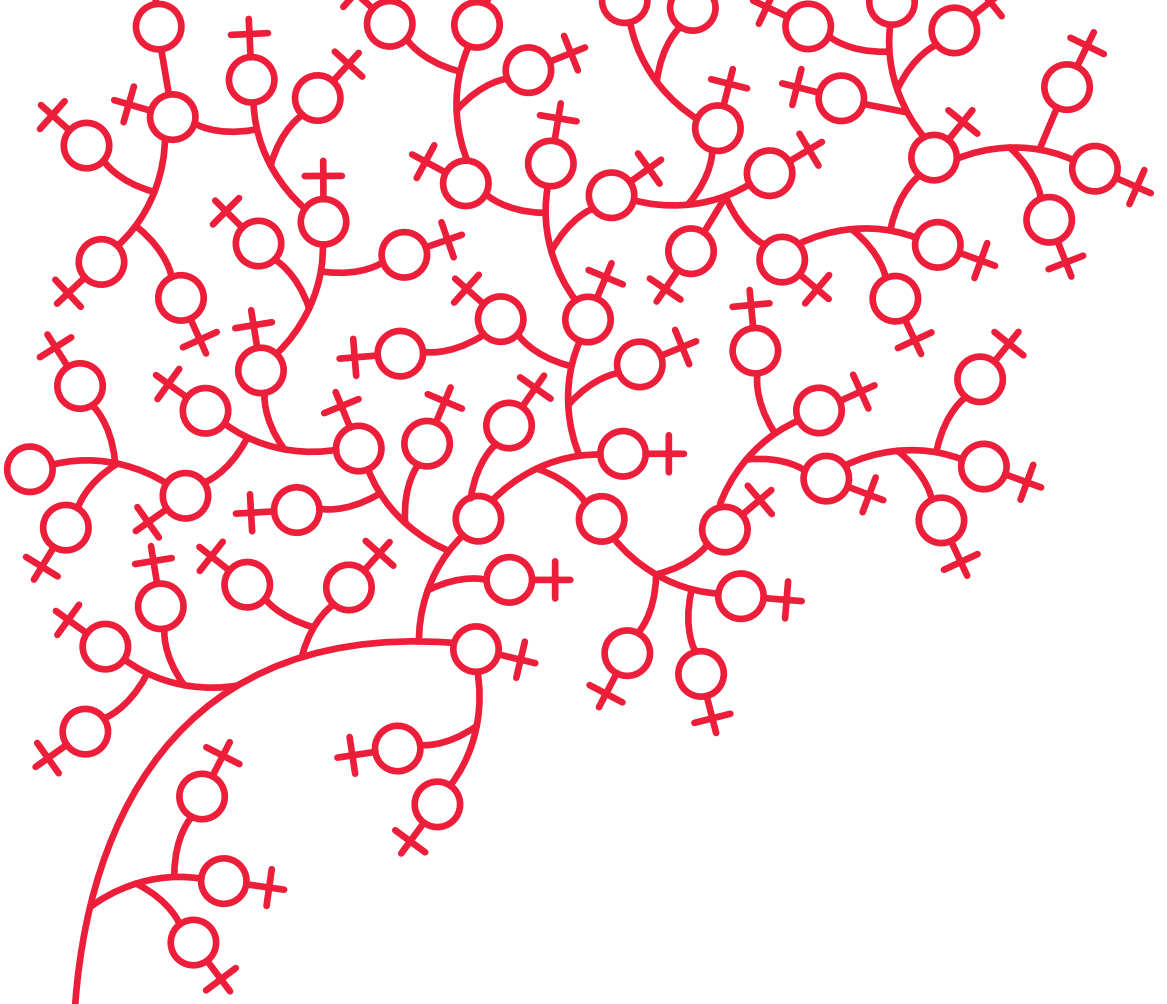
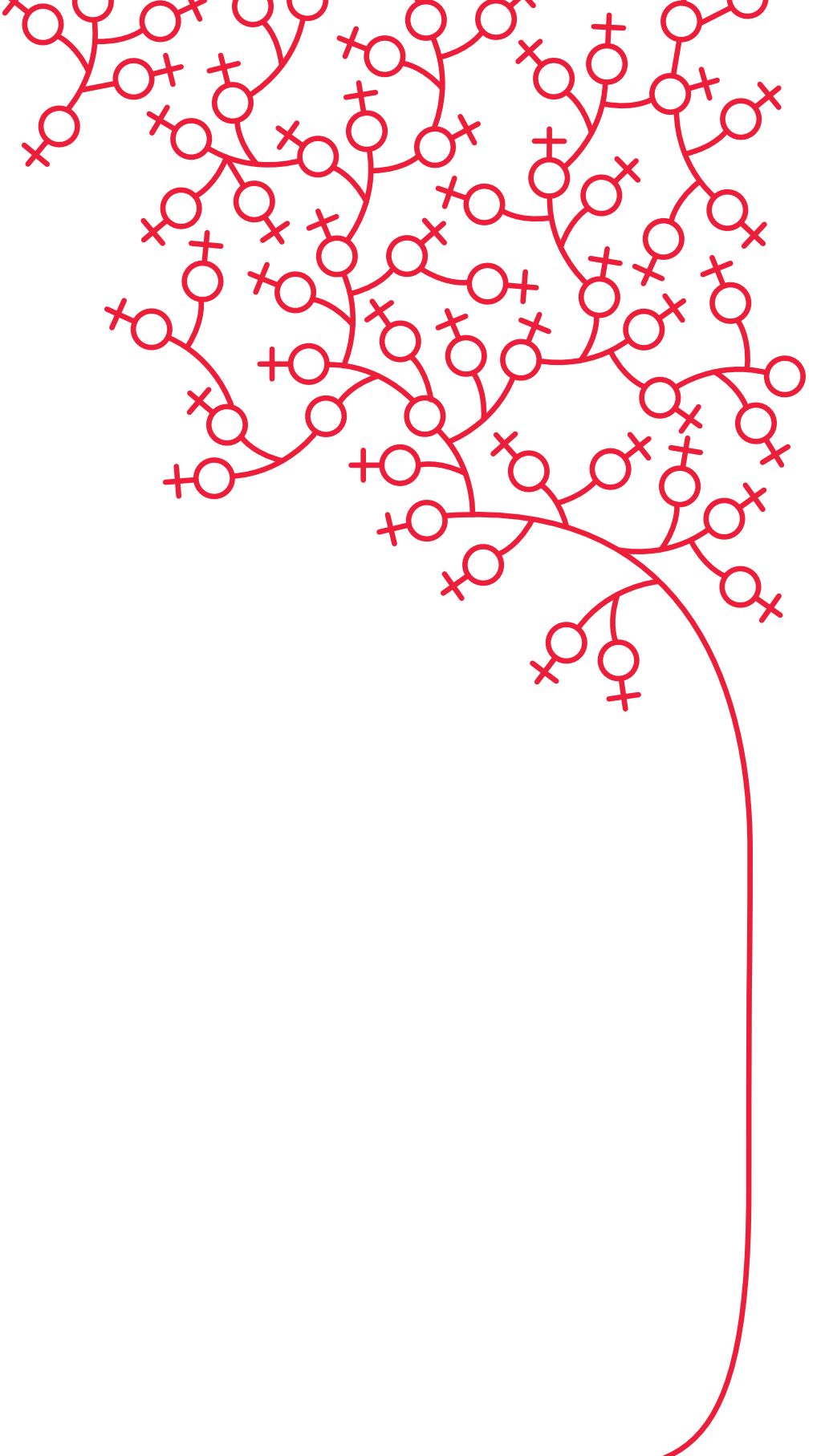




PART 1

EFFECTIVITY OF GYNECOLOGICAL AND REPRODUCTIVE OUTCOMES



2

Magnetic resonance-high intensity focused ultrasound (MR-HIFU) therapy of symptomatic uterine fibroids with unrestrictive treatment protocols: A systematic review and meta-analysis

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ABSTRACT

Objectives

Reevaluation of the effectiveness of Magnetic Resonance-High Intensity Focused Ultrasound (MR-HIFU) therapy for uterine fibroids by excluding studies with restrictive treatment protocols that are no longer used.

Methods

The National Guideline Clearinghouse, Cochrane Library, TRIP, MEDLINE, EMBASE and WHO International Clinical Trials Registry Platform (ICTRP) databases were searched from inception until the 22nd of June 2018. Keywords included “MR-HIFU”, “MRgFUS”, and “Leiomyoma”. Only studies about MR-HIFU treatment of uterine fibroids with at least three months of clinical follow-up were evaluated for inclusion. Treatments with ultrasound guided HIFU devices or protocols not aiming for complete ablation were eliminated. The primary outcome was the improvement in fibroid-related symptoms. Technical outcomes included screening and treatment failures, treatment time, application of bowel-interference mitigation strategies and the Non-Perfused Volume (NPV) percentage. Other secondary outcomes were the quality of life, fibroid shrinkage, safety, re-interventions, reproductive outcomes, and costs. Meta-analysis was performed using a random-effects model (DerSimonian and Laird).

Results

A total of 18 articles (1323 treated patients) met the inclusion criteria. All selected studies were case series except for one cross-over trial. Overall, the quality of the evidence was poor to moderate. The mean NPV% directly post-treatment was 68.1%. The use of bowel-interference mitigation strategies may lead to increased NPV%. The mean symptom reduction at 12- months was 59.9% and fibroid shrinkage was 37.7%. The number of adverse events was low (8.7%), stratification showed a difference between HIFU systems. The re-intervention percentage at 3-33.6 months follow-up ranged from 0-21%. Longer follow-up was associated with a higher risk at re interventions. Reproductive outcomes and costs couldn’t be analyzed.

Conclusions

Treatment guidelines aiming for complete ablation enhanced the effectiveness of MR-HIFU therapy. However, controlled trials should define the role of MR-HIFU in the management of uterine fibroids.

Keywords

Systematic review, Uterine Fibroids, MR Guided Interventional Procedures, High-Intensity Focused Ultrasound Ablation.

INTRODUCTION

Background uterine fibroids

Uterine fibroids are common benign gynecological tumors which develop from uterine smooth muscle cells. The cumulative incidence during the reproductive period ranges from 70-80% depending on the patient's ethnicity (1). Many women are asymptomatic, but in approximately 25% uterine fibroids cause clinically relevant symptoms (2). Main symptoms include pelvic pain, dysmenorrhea, menorrhagia, urinary frequency, dyspareunia and subfertility. Pharmacological agents are effective in alleviating symptoms, but adequate control may not be achieved, or significant side-effects occur. Overall, a high percentage of patients will eventually require intervention. Uterine fibroids are still the leading indication for a hysterectomy worldwide (3,4). Myomectomy is the therapy of choice for women who want to conceive. However, surgical approaches are associated with a high rate of short- and long-term morbidity, require a hospital stay and weeks to recover. Other minimally-invasive uterine-sparing treatment options are available including uterine artery embolization (UAE), hysteroscopic resection and Magnetic Resonance-High Intensity Focused Ultrasound (MR-HIFU). MR-HIFU is the only entirely non-invasive intervention and has several proven advantages such as a lower morbidity, less complications, no general anesthesia and shorter recovery time (5).

MR-HIFU technique

MR-HIFU is a thermal ablation technique and enables non-invasive treatment of uterine fibroids by selective tissue heating (6). The ultrasound transducer produces convergent high-intensity ultrasound waves. The targeted tissue absorbs the acoustic energy leading to a temperature rise which causes coagulative necrosis and apoptotic cell death (6). Magnetic Resonance Imaging (MRI) facilitates treatment planning and real-time monitoring by temperature mapping (7). Directly post MR-HIFU, a contrast enhanced MRI can visualize the ablated tissue, referred to as the non-perfused volume (NPV). Treatment result can be expressed as the NPV% which is the NPV divided by the fibroid volume. During MR-HIFU therapy, interference of bowel loops in the beam pathway could lead to treatment failure or untreated parts of the fibroid. Different mitigation strategies are developed to displace bowel loop. The BRB technique, which includes sequential applications of urinary bladder filling, rectal filling and urinary bladder emptying, is the most common technique. Three MR-HIFU devices are currently in clinical use. The ExAblate system (InSightec, Haifa, Israel) employs the conventional 'point-by-point' ablation technique. The Sonalleve system (Profound Medical Inc., Toronto, Canada) uses a volumetric ablation technology. The Chongqing system (Chongqing Haifu Technology, Chongqing, China) combines the 'point-by-point' treatment strategy with shot-sonication.

Background MR-HIFU

Since 2004, MR-HIFU treatment of uterine fibroids has been approved by the United States Food and Drug Administration (FDA). Initially, restricted protocols had to be used for safety reasons. However, over time it became clear that therapeutic outcomes are closely related to the NPV% (8, 9). Partially ablated fibroids tend to regrow, which may explain the relatively high re-intervention percentage reported in studies using a restricted protocol (10,11). Moreover, MR-HIFU treatment proved to be safe even when complete ablation was pursued (12). The FDA guidelines were modified in 2009, allowing operators to aim for complete ablation which has led improved outcomes in more recent studies (8,13). Although this might also be partially explained by increased experience of the HIFU centers with the technique (13). Furthermore, the safety guidelines were modified for women with symptomatic uterine fibroids and a desire for future fertility since uncomplicated pregnancies were reported after MR-HIFU therapy. Still, not all patients are eligible for MR-HIFU treatment. Exclusion criteria can be based on patient characteristics (BMI and MRI contraindications) or fibroid characteristics assessed by MR screening. Fibroids with a high T2 signal intensity are difficult to treat and therefore these fibroids, Funaki type 3, are generally excluded (14).

Rationale

To date, several reviews were published on the effectiveness of MR-HIFU treatment for uterine fibroids. Overall, they showed that MR-HIFU is effective in alleviating symptoms, but a relatively high re-intervention percentage is reported (15-17). However, these reviews included studies using restrictive treatment protocols that are no longer in clinical use which affected the results.

Objectives

The purpose was to reassess the effectiveness of MR-HIFU on reducing fibroid-related symptoms using treatment protocols aiming for complete ablation only. We also investigated the technical success measured by the post-treatment NPV% and treatment failures. Additionally, we evaluated the disease specific quality of life, the re-intervention percentage, safety, fertility, costs and fibroid shrinkage.

MATERIAL AND METHODS

In this review, we adhered to the standard guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (18). The review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42018100467.

Eligibility criteria

Studies about MR-HIFU treatment of women with clinically symptomatic uterine fibroids were evaluated for inclusion. Treatment protocols not aiming for complete ablation (except for a safety margin of five mm from the serosal surface) or ultrasound guided HIFU devices were excluded. Randomized controlled trials (RCT), prospective or retrospective non randomized studies and cross-over trials with at least three months of follow-up were evaluated for inclusion. Animal studies, case reports and ongoing trials were eliminated as well as studies not reporting on our primary outcome or NPV%. Gonadotropin-releasing hormone (GnRH) analogues prior to MR-HIFU were allowed.

Data search

We searched the following databases on the 22nd of June in 2018 (Appendix 1): National Guideline Clearinghouse, Cochrane Library, TRIPP, MEDLINE/PubMed, WHO International Clinical Trials Registry Platform (ICTRP) and Embase. Duplicate publications were detected by a reference manager (RefWorks) and removed. Two authors (IV and KA) independently completed the initial title and abstract screening for all six databases. Full texts were retrieved when studies possibly met our inclusion criteria. Reference lists of all retrieved full-text articles were manually searched to identify other relevant studies for full text screening.

Data extraction

The same two authors independently extracted data from all eligible studies. Data were collected in a summary of findings table containing (a) study characteristics: authors, year of publication, study design, MR-HIFU system, sample size, follow-up duration; (b) treatment parameters: NPV%, patient's eligibility percentage, the number of technical failures, the use of bowel interference mitigation techniques, sonication time; (c) primary outcome: reduction of fibroid-related symptoms preferably assessed by the validated disease-specific Uterine Fibroid Symptom and Quality of Life Questionnaire (UFS-QoL) (19); (d) secondary outcomes: Health-Related Quality of Life (HRQL) also assessed by the UFS-QoL questionnaire, fibroid shrinkage based on follow-up MR imaging, occurrence of any (serious) adverse events related to the MR-HIFU procedure, re-intervention percentage, evaluation of reproductive outcomes (fertility, pregnancy or obstetrical outcomes) and costs. The NPV% was calculated by the formula (20-22):

$$NPV\% = \frac{NPV}{fibroid\ volume\ pre-treatment} \cdot 100$$

This UFS-QoL questionnaire includes eight questions about symptom severity and 29 HRQL questions (19). All items were scored on a 5-point Likert scale. Subscale scores were transformed to a scale of 0-100 by the following formula:

$$Transformed\ score = \frac{actual\ raw\ score - lowest\ possible\ raw\ score}{possible\ raw\ score\ range} \cdot 100$$

Higher transformed Symptom Severity Score (tSSS) indicates greater symptom severity. Higher transformed HRQL (tHRQL) score is indicative of a better HRQL. Adverse events (AE) were categorized according to the Society of Interventional Radiology clinical practice guidelines (23). Minor adverse events were defined as skin burns, vaginal bleeding or abnormal discharge, cystitis, urinary retention, constitutional symptoms, nerve damage or pain longer than seven days. The re-intervention percentage was defined as patients undergoing an additional intervention due to fibroid-related symptoms (second MR-HIFU, hysterectomy, myomectomy or UAE).

Any disagreements were resolved by discussion or by consulting a third author. When multiple publications were available of one clinical trial, the most recent publication was used as the reference and additional details were derived from secondary papers. If outcomes were missing, we attempted to contact the corresponding authors by sending an email with request for additional data. If there was no response after seven days, a second email was sent.

Quality of evidence and risk of bias

Level of evidence of all articles was assessed independently by two authors (IV and KA) according to the Oxford Centre for Evidence-based Medicine (OCEBM) guidelines (24). The quality of case series was assessed by an 18- criteria tool developed through a Delphi technique (25). A score of 14-points or more indicated good quality. Discrepancies were identified and resolved through discussion. Where agreement couldn't be reached, a third author was consulted.

Data synthesis

The results of meta-analyses were presented in the form of tables and graphs. For continuous data using the same scale (e.g. difference in fibroid volume) the change from baseline (%) was reported. To combine data from eligible studies a random-effects model (DerSimonian and Laird) was used (26). If the results showed statistical heterogeneity (I2), we tried to explain the differences by stratification. We considered an I^2 value of greater than 50% indicative of substantial heterogeneity.

Outcomes were stratified by MR-HIFU device, the use of bowel-interference mitigation strategies and duration of follow-up: short-term (3-months), mid-term (4-6 months) and long-term (12-months or more). Explorative meta-regression was performed for all primary and secondary outcomes.

Missing data

Missing standard deviations were imputed by the arithmetic mean of all available standard deviations in the same category, unless reported otherwise. Sensitivity analyses were performed by comparison with point estimates when excluding studies with missing standard deviations (27). Regarding change scores, the correlation coefficient was imputed by 0.5, unless reported otherwise (27). The imputed correlation coefficients were used to calculate the SD of change scores using the following formula:

$$SD_c = \sqrt{SD_b^2 + SD_f^2 - 2 \cdot 0.5 \cdot SD_b \cdot SD_f}$$

When the SD of the change score was present (one study) correlation coefficient was calculated using the following formula:

$$r = \frac{SD_b^2 + SD_f^2 - SD_c^2}{2SD_bSD_f}$$

Software

Meta-analyses were performed using Comprehensive Meta-Analysis (calculations) and Open Meta-Analyst (figures and calculations) (28).

RESULTS

Literature search

The search revealed 568 potentially relevant studies (Appendix 1). After duplicates and textbooks were excluded 387 abstracts were screened and revealed 92 potentially relevant articles. By inspecting reference lists of these articles, no additional articles were identified. During full text screening, 55 studies appeared not to meet our inclusion criteria and 19 reviews were excluded. A total of 18 articles were finally selected (Figure 1) (20-22,29-43). These 18 articles included 16 different clinical trials. One study reported results of an extended patient population and one study published their results at two different time points.

Study characteristics

We composed a summary of findings table of all included studies (Table 1). The studies mostly applied similar inclusion criteria: age above 18 years old, a pre-or perimenopausal state and exclusion criteria: contraindications to MRI with gadolinium or pregnant patients. Nine studies excluded fibroids larger than 10-12 cm or uterine size larger than 20-24 weeks of gestational age (20,30,33-35,41,42). Another frequently reported exclusion criterion were Funaki type 3 fibroids (high T2W signal on MRI) (22,29,30,35,37,41). Only four studies, including the two oldest studies, excluded patients with a desire for future fertility (21,29,34,38). Three studies demanded a minimum tSSS at baseline of

41-points (33,34) or 21-points (38). Smart et al. studied the effect of GnRH agonists prior to MR-HIFU (38). Jeong et al. evaluated the effectiveness of MR-HIFU in patients with concomitant adenomyosis (35).

Data extraction

From all studies included, we retrieved the tSSS except from Morita et al., who reported subjective relief of symptoms instead of the tSSS (21). Therefore, we excluded this study from this part of the meta-analysis. Furthermore, the tSSS scores of Funaki type 3 patients could not be evaluated as reported by Funaki et al., thus these patients were not included in our data extraction (20). Jeong et al. reported that patients were not followed longer than 3 months if they experienced sufficient symptom relief, so only outcomes until 3-months were analyzed (35). Two authors were contacted for additional data. Unfortunately, we received no response.

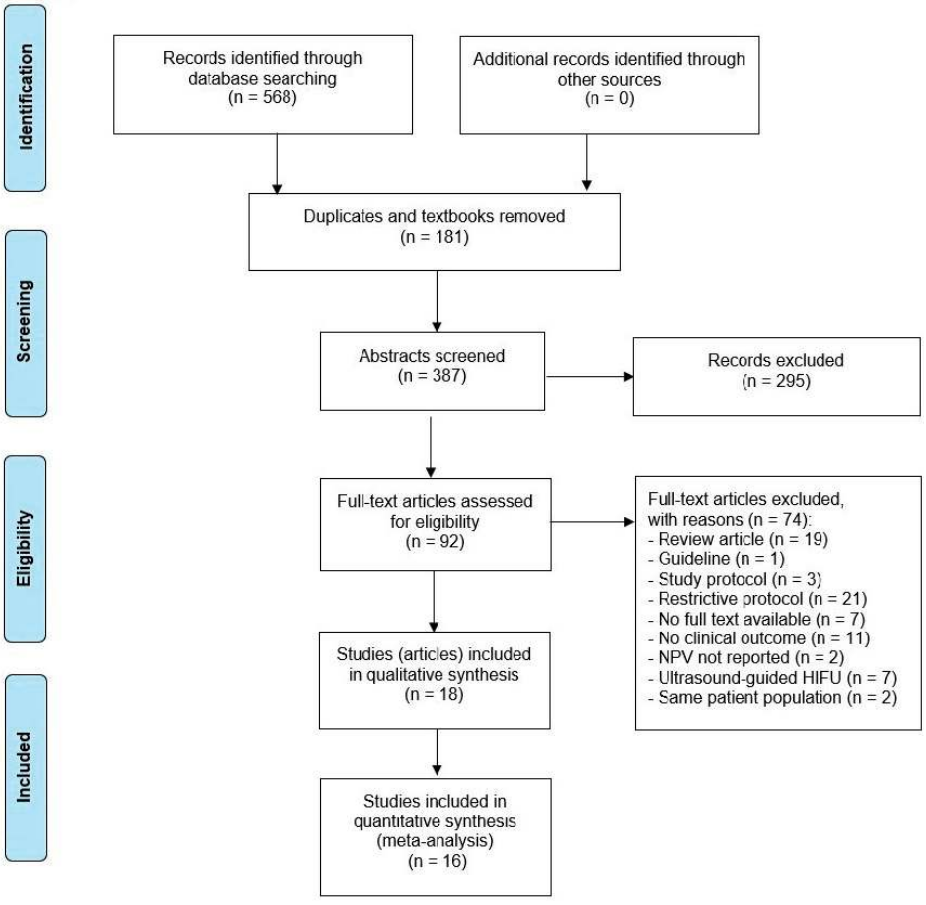

Figure 1: Flow chart shows summary of the literature review process.

Table 1. Summary of the included articles.

LoE	Quality	Author	Year	Study Design	Device	Follow-up	Patients	NPV% ± SD	FS%	tSSS↓	HRQL↑	RI%	(S)AE	Mitigation	Therapy time	TF	Eligiblity	Pregnancy
IV	14/18	Smart	2006	Prospective	ExAblate	12 months	49	51.0 ± 20.0	37.0	48.0%	NR	12.2	12.2%	No	183 minutes	NR	NR	0
IV	12/18	Morita	2008	Prospective	ExAblate	12 months	48	60.0 ± 18.0	33.0	NR	NR	4.0	8.3%	No	NR	NR	NR	1
IV	11/18	Funaki	2009	Prospective	ExAblate	24 months	80	54.3 ± 22.6	39.5	54.4%	NR	8.8	NR	No	170 minutes	NR	NR	4
IV	13/18	Gorny	2011	Retrospective	ExAblate	12 months	130	45.4 ± 22.5	NR	68.0%	NR	6.2	5.4%	Yes	NR	4.4%	NR	0
IV	12/18	Gorny	2014	Retrospective	ExAblate	33.6 months	138	45.5 ± 22.7	NR	NR	NR	21.0	5.1%	Yes	NR	4.2%	NR	0
IV	11/18	Desai	2012	Prospective	ExAblate	6 months	50	88.0 ± 6.0	30.0	49.7%	NR	0	8%	No	145 minutes	NR	NR	0
IV	12/18	Dobrotwir	2012	Prospective	ExAblate	12 months	51	67.0 ± 25.0	38.0	50.8%	NR	11.7	0%	Yes	NR	NR	NR	0
IV	12/18	Himabindu	2014	Prospective	ExAblate	6 months	32	70.0 ± 20.0	40.0	59.7%	NR	0	18.8%	No	NR	NR	NR	0
IV	14/18	Park	2014	Prospective	Sonalleve	3 months	74	62.7 ± 25.5	27.0	35.6%	NR	0	25.6%	Yes	165 minutes	6.3%	41%	0
IV	15/18	Jacoby	2015	Prospective	ExAblate	3 months	13	43.0 ± 20.0	18.0	55.4%	56.2%	0	0%	No	153 minutes	NR	NR	0
IV	10/18	Tan	2015	Prospective	ExAblate	12 months	100	65.0 ± 23.0	NR	61.8%	NR	9.0	4.3%	NR	NR	NR	47%	0
IV	16/18	Trumm	2012	Retrospective	ExAblate	6.5 months	115	88.0 ± 15.0	NR	40.0%	NR	NR	1.7%	Yes	198 minutes	6.5%	NR	0
IV	16/18	Mindjuk	2015	Retrospective	ExAblate	19.4 months	221	88.7 ± 15.0	NR	67.8%	NR	12.7	1.6%	Yes	180 minutes	3.2%	NR	15
IV	12/18	Xu CA	2015	Prospective	Chongquing	6 months	10	100	59.1	33.5%	NR	0	0%	Yes	25 minutes	NR	NR	0
IV	12/18	Xu PA	2015	Prospective	Chongquing	6 months	33	84.3 ± 15.7	40.1	45.5%	NR	0	2.3%	Yes	18 minutes	NR	NR	0
IV	14/18	Chen	2016	Prospective	Sonalleve	6 months	107	54.8 ± 21.2	50.2	30.2%	12.9%	0.9	6.5%	NR	NR	0%	43%	4
IV	9/18	Jeong	2016	Retrospective	Sonalleve	3 months	157	65.6 ± 22.7	35.3	55.0%	NR	5.7	12.7%	Yes	102 minutes	NR	NR	0
IV	9/18	Tung	2016	Retrospective	ExAblate	6 months	40	64.5 ± 11.4	31.7	43.7%	33.5%	0	0%	NR	NR	NR	31%	0
IV	13/18	Kerserci > 90	2018	Retrospective	Sonalleve	6 months	72	97.7 ± 3.2	54.0	86.0%	NR	0	26.4%	Yes	148 minutes	0%	46%	3
IV	13/18	Kerserci < 90	2018	Retrospective	Sonalleve	6 months	48	60.4 ± 27.3	14.0	26.0%	NR	0	22.9%	Yes	130 minutes	0%	46%	3

Abbreviations: LoE=Level of Evidence, NPV%=Non-Perfused Volume percentage, SD=Standard Deviation, FS%=Fibroid Shrinkage percentage, tSSS=transformed Symptom Severity Score, HRQL=Health Related Quality of Life, RI%=Re-intervention percentage, (S)AE=(Serious) Adverse Events, TF=Treatment failures, NR=Not Reported, Xu CA or PA=Complete Ablation or Partial Ablation of the uterine fibroid, Kerserci > 90=Treatments NPV% > 90%, Kerserci < 90=Treatments NPV% < 90%.

Quality of the evidence

All included studies were case series, except for one cross-over trial (34) of which only the first phase was included in our analysis. The level of evidence for all included studies was IV according to OCEBM levels of evidence. The quality of the evidence ranged from 9 – 16 points using the 18-criteria tool (25), indicating substantial differences in quality between the included studies. Only 6 of the 18 studies were of acceptable quality (29,34,36-38,40). Furthermore, the included studies poorly reported the different statistical parameters and thus, standard deviations often had to be estimated. However, excluding studies with imputed standard deviations for all different outcome parameters indicated that estimates were reasonably robust for standard deviation imputation.

Technical parameters

Screening and treatment failures

The number of screening and treatment failures were not reported in all studies. Eligibility percentage was reported by five studies (29,37,39,41,43) with a mean percentage of 42.0% and a screening failure percentage of 58.0%. Mean technical failure percentage was 3.5% based on seven studies (29,31,32,36,37,40,43). There was a slight decrease in the number of technical failures in the extended patient cohorts (31,32,36,40).

Bowel-interference mitigation strategies

Six trials stated that they used bowel-interference mitigation strategies if necessary (22,35-37,40,42,43). Seven trials explicitly said not to use mitigation techniques (20,21,30-34,38). In the other three studies it was unclear (29,39,41).

Treatment time

Sonication time was reported by 10 studies with a mean of 145,6 minutes (20,30,34-38,40,42,43). The shortest sonication time was reported by the study using the Chongqing system (42). More recent studies reported shorter treatment times and the average treatment time decreased in the extended patient cohorts (36,40).

NPV%

The point estimate (95% CI) of NPV% was 68.1% (59.9% – 76.0%) with I2 of 99.5%. The I2 of 99.5% indicates substantial heterogeneity, which could not be explained by stratification or meta-regression. One borderline difference between no mitigation (adjusted mean 58.9) and mitigation (adjusted mean 78.7) was found by meta-regression ($p = 0.016$), suggesting that the use of bowel-interference mitigation strategies results in a higher NPV% (Figure 2).

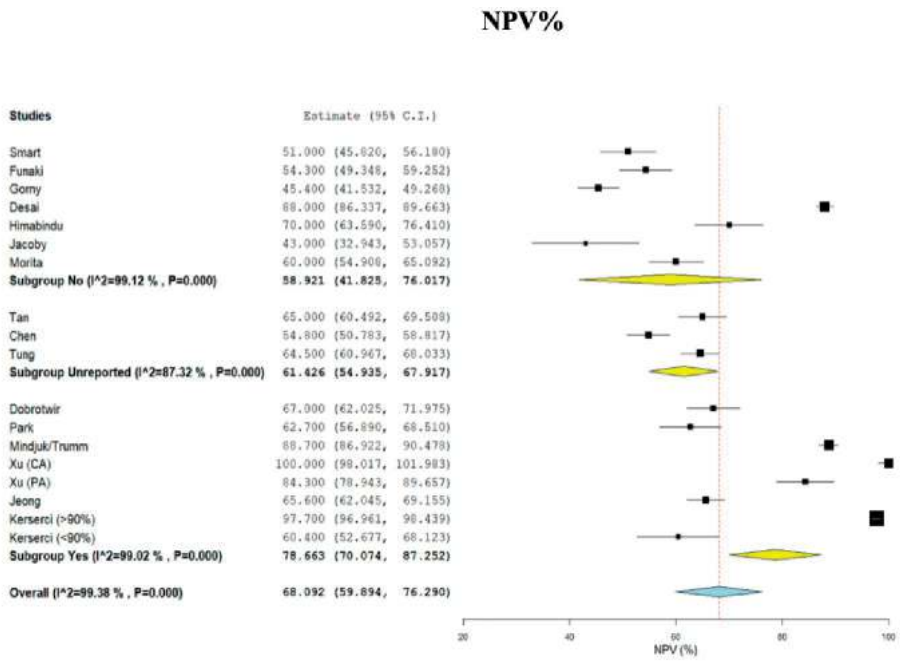

Figure 2: Forest plot of NPV% directly post MR-HIFU, stratified by the use of mitigation.

Symptom improvement

Baseline scores of tSSS were 46.1 (33.7 – 58.4) on 3-months, 56.1 (50.0 – 62.2) on 6-months and 53.6 (41.8 – 65.5) on 12-months follow-up, respectively. The combined estimates of the change percentages in the 3-month, 6-month and 12-month category showed symptom reduction following MR-HIFU treatment (decreased tSSS score; Figure 3). The I²'s indicate substantial heterogeneity in the 3-months and 6-months category. In the 12-months category the I2 was 75.35%. Explorative meta-regression analysis showed no association between NPV% and tSSS decrease. Similarly, there was no association between tSSS and fibroid shrinkage. Only Morita et al. did not report the tSSS, but asked patients about symptom relief and reported a success percentage of 85.4% (21).

HRQL

Only three of the included studies reported HRQL scores (29,34,41). The baseline scores of QoL were 61.0 (36.5 – 84.5) on 3-months and 55.5 (21.1 – 89.9) on 6-months follow-up, respectively. The combined estimates of the change percentages in the 3-month and 6-month category showed improved HRQL scores (Figure 4). The I²'s indicates substantial heterogeneity in the 3-month and 6-month category.

Fibroid shrinkage

All studies showed overall fibroid shrinkage after MR-HIFU treatment (Figure 5). Stratification by follow-up category showed only small differences. However, three studies reported a substantial effect of time on fibroid shrinkage percentage (22,29,38). The I^2's indicate substantial heterogeneity in the 3-months and 6-months category. This could be partly, although not significantly, explained by NPV%. In the 12-months category the I2 was 0%. Explorative meta-regression analysis showed that NPV% was not significantly associated with fibroid shrinkage (p=0.012; Figure 6). A borderline difference/trend was seen at 6-months follow-up, suggesting a positive relationship.

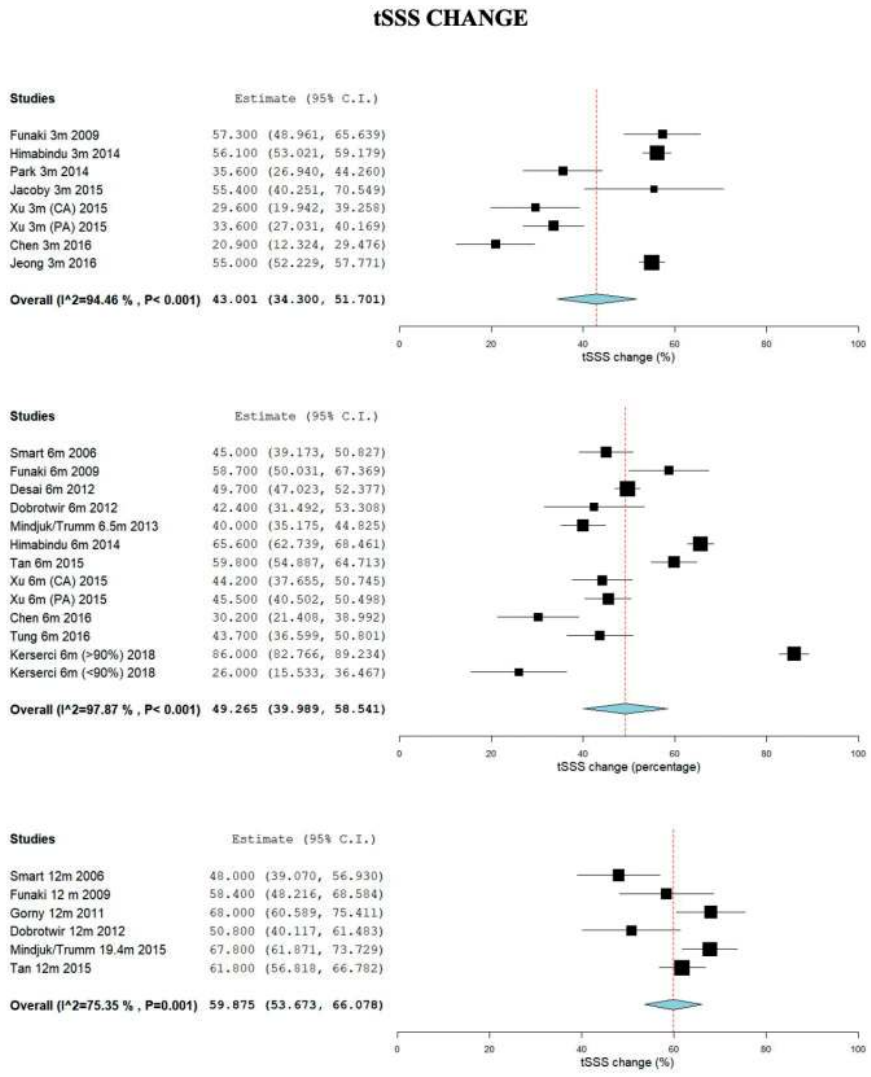

Figure 3: Forest plots of tSSS decrease percentage, stratified by follow-up category. Only Kerserci and Gorny reported the SD of the change percentage of the tSSS and all other SD had to be imputed.

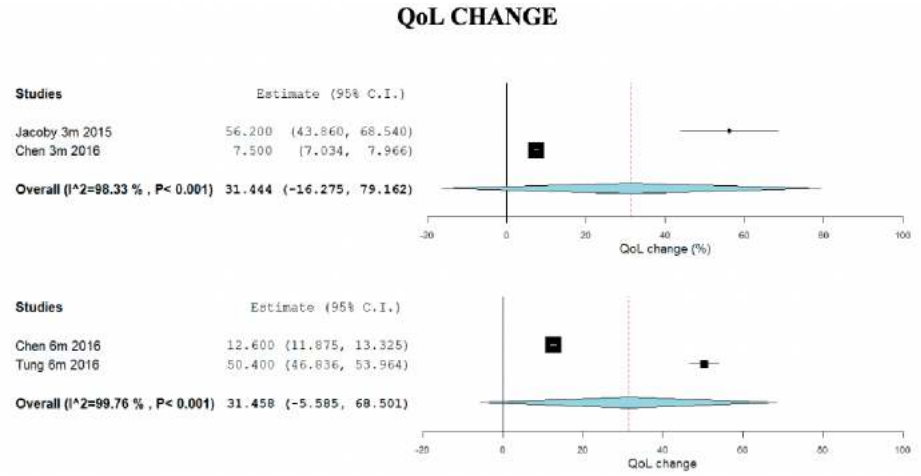

Figure 4: Forest plots of HRQL increase in change percentage, stratified by follow-up category.

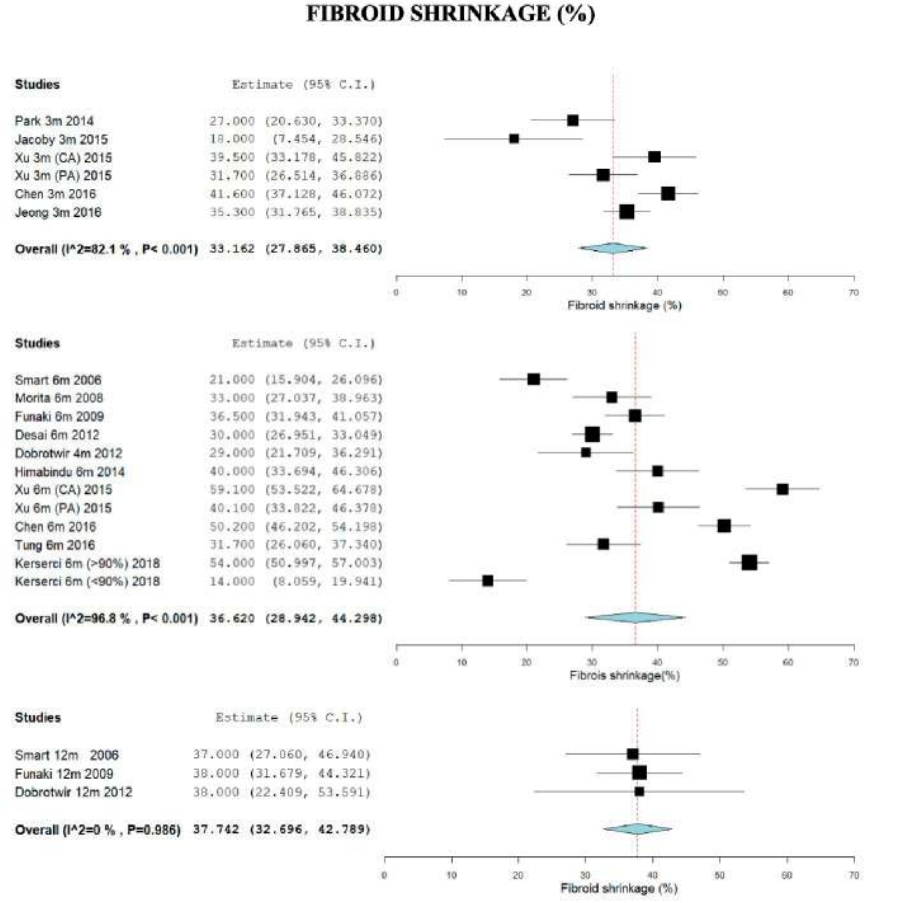

Figure 5: Forest plots of fibroid shrinkage in percentage, stratified by follow-up category.

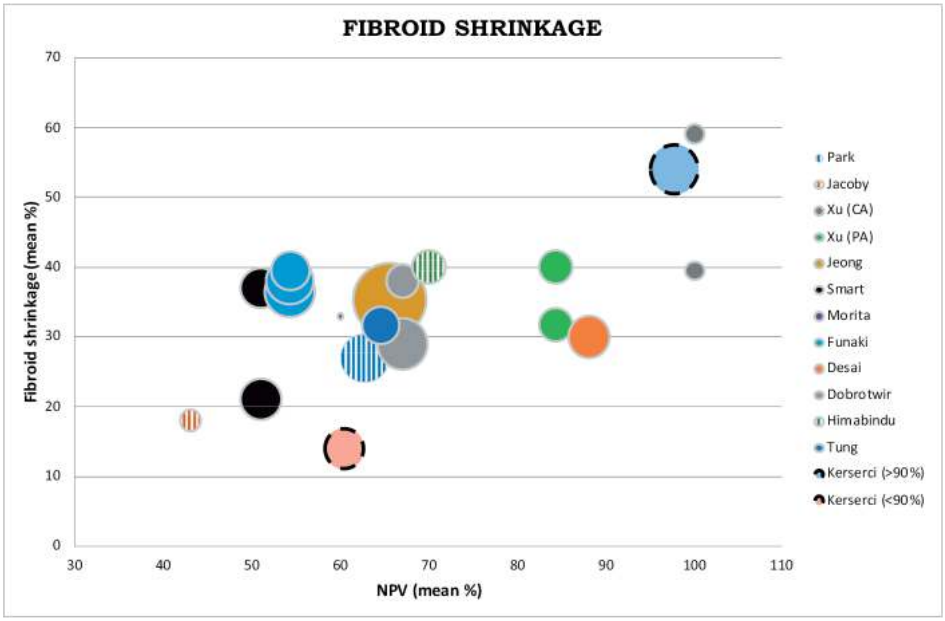

Figure 6: Association between fibroid shrinkage percentage and NPV% directly post MR-HIFU, not stratified by follow-up category. Every study has a dot with a different color and all different time-points are shown. The size of the dot represents the number of patients.

Adverse Events

Only one of the included studies did not report AE as outcome parameter (20). Of the 1330 treatments analyzed, 112 of 1330 (8.7%) patients experienced an AE (Figure 7). Importantly, 110 AEs were minor and self-limiting during follow-up. Only 2 patients (0.2%) experienced a serious adverse event (SAE), one deep venous thrombosis (DVT) and one third degree skin burn. These SAEs were reported in two of the most dated studies (patient enrollment between 2005 and 2009) (31,38). Stratification of (S)AE resulted in a substantial difference between Sonalleve and ExAblate, 17.6% versus 5.7%, respectively (Figure 7). The difference between Sonalleve and ExAblate was statistically significant as confirmed by meta-regression ($p<0.001$). None of the other investigated covariates (NPV%, sonication time) were associated with adverse events.

Re-intervention percentage

At the end of the follow-up from 16 different trials, data of 1323 treated patients were available. The re-intervention percentage at 3-33.6 months follow-up ranged from 0-21% (Table 2). A total of 97 re-interventions were reported of which 23 hysterectomies, 25 myomectomies, 7 surgical interventions (procedure not defined), 16 UAE, 15 repeat MR-HIFU, 1 thermal laser ablation, 1 transcervical resection and 9 unknown interventions. Results of three studies showed a substantial effect of time on re-intervention percentage

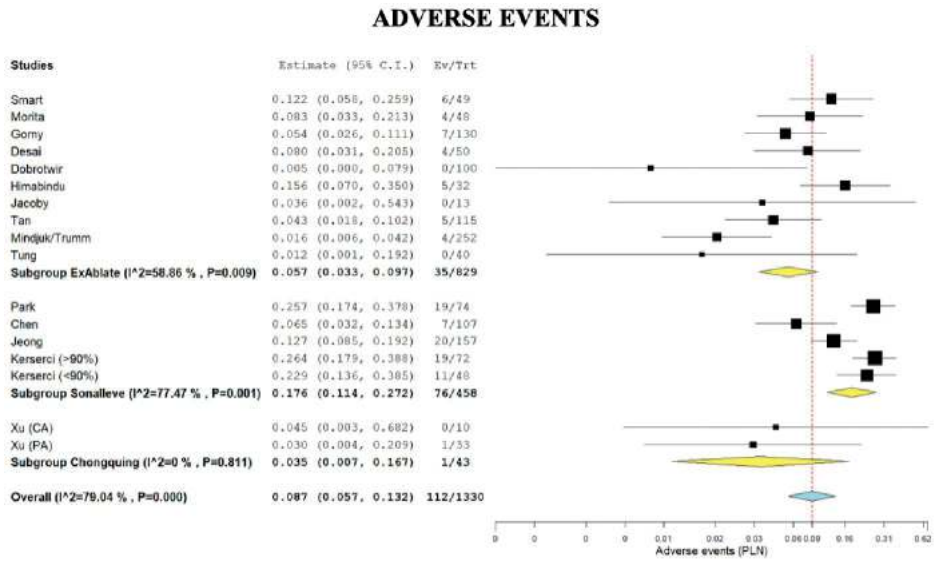

Figure 7: Forest plots of AE during follow-up, stratified by system. Ev/trt: the reported number of AE and the number of patients treated. In the studies that reported no AE a percentage of 0.5% had to be imputed. Therefore, all percentages shown in the figures below are higher than in reality. PLN (Natural logarithm transformed proportion) was used.

(Figure 8) (20,22,31,32). Funaki et al. calculated cumulative re-intervention percentages during follow-up (20).The reintervention rates at 6-, 12- and 24-months follow-up were 1.4%, 2.9% and 14.0%, respectively. Additionally, Gorny et al. reported the cumulative rates re-intervention percentages of 4% at 12-months, 13% at 24-months, 19% at 36-months and 23% at 48-months follow-up (31). Explorative meta-regression analysis showed no association with NPV% or tSSS decrease.

Reproductive outcomes

A total of 27 pregnancies were reported by five of the included studies (20,21,29,36,44). Interestingly, a desire for future pregnancy was an exclusion criterium in two of these studies (21,29) and four patients voluntarily terminated their pregnancies while enrolled in the trial (29). Morita et al. described one uncomplicated pregnancy and birth (21). Mindjuk et al. reported 12 uncomplicated cases (36), one spontaneous abortion occurred and two patients still pregnant at the time of publication. Kerserci et al. described three pregnant women loss to follow-up without further notice (44). Funaki et al. reported two live term births and two first-trimester miscarriages (20). Kerserci et al. considered the potential impact on the ovarian reserve because ovarian dysfunction is strongly associated with subfertility. The levels of the anti-Mullerian Hormone (AMH) were measured at baseline and 6-months follow-up, no significant changes were found, suggesting that the ovary and its vessels were not involved in the treatment area (43).

Table 2: Number of re-interventions and re-intervention percentage at the end of the follow-up.

Study, year, length of follow-up in months (m)	Number of re-interventions/ number of patients	Re-intervention percentage (%)
Smart 2006, 12 m	6/49	12.2%
Morita 2008, 12 m	2/48	4.0%
Funaki 2009, 24 m	7/57	12.3%
Gorny 2011, 33.6 m	29/138	21.0%
Desai 2012, 6m	0/50	0%
Dobrotwir 2012, 12 m	6/51	11.7%
Himbabindu 2014, 6 m	0/32	0%
Park 2014, 3 m	0/74	0%
Jacoby 2015, 3 m	0/13	0%
Tan 2015, 12 m	9/100	9.0%
Mindjuk 2015, 19.4 m	28/221	12.7%
Xu 2015, 6 m	0/43	0%
Chen 2016, 6 m	1/107	0.9%
Jeong 2016, 6 m	9/157	5.7%
Tung 2016, 6 m	0/40	0%
Kerserci 2018, 6 m	0/120	0%
Overall	97/1323	7.6%

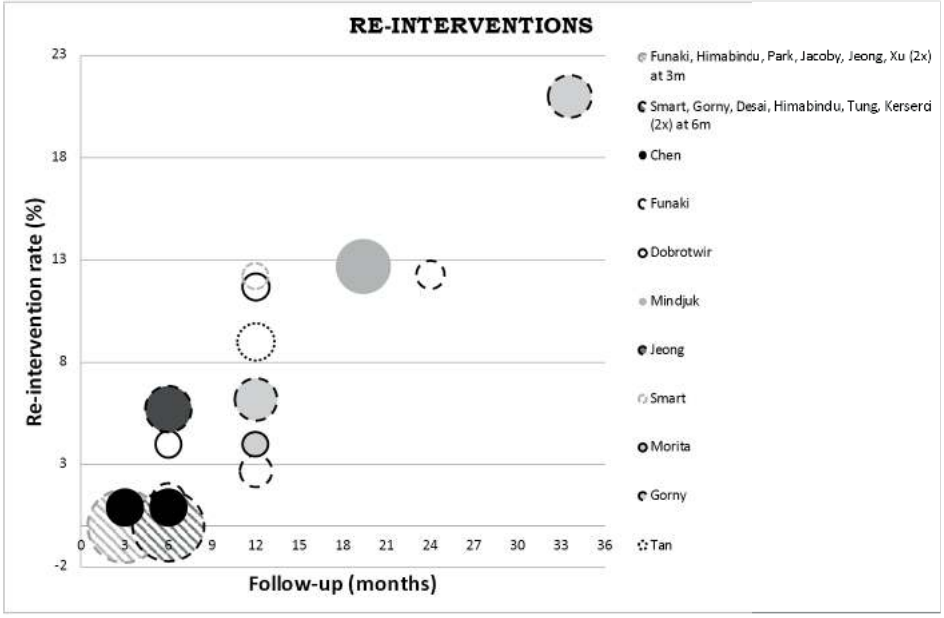

Figure 8: Bubble chart of re-intervention percentage at follow-up. The size of the dot represents the number of patients.

Costs

The authors did not report outcomes considering costs. Therefore, it is not possible to draw conclusions regarding cost-effectiveness on the included studies.

DISCUSSION

This systematic review reevaluated the effectiveness of MR-HIFU therapy of uterine fibroids only including treatment protocols aiming for complete ablation, because restrictive protocols are no longer in clinical use. The results showed that symptom severity and fibroid volume continued to decrease during follow-up. The number of (S)AE was low and the re-intervention percentage at 3-33.6 months follow-up ranged from 0-21%. Reproductive outcomes were encouraging. Costs and HRQL were under-reported. Importantly, the symptom improvement in this review was greater compared to other MR-HIFU reviews and retreatment rates were lower.(16,17) So, implementing unrestrictive treatment protocols has led to better clinical outcome.

Quality of evidence

In general, all outcome parameters discussed in this review were influenced by the overall level of evidence which was poor to moderate. Only non-randomized, non-comparative trials were available for inclusion (24). Sources leading to a high risk of bias were related to the specific study designs: inadequately reporting of loss to follow-up and potentially a selection bias. Weaknesses of the meta-analysis were caused by methodological limitations. Standard deviations often had to be estimated. Some studies were subject to loss of follow-up and some sub-studies were based on different sample sizes (27). Therefore, the results should be interpreted with care. Moreover, results are based on reported means instead of individual patient data, thus ecological fallacy may have affected outcomes. Heterogeneity for each outcome parameter was often substantial, and mostly unexplained, questioning whether we should generalize our results. However, this method is valid because we used a random-effects model for meta-analysis (26).

Technical parameters

Decreases in the number of technical failures and treatment time in the extended patient cohorts suggests that increased experience enhances treatment efficacy. The shortest sonication time was reported by Xu et al., so the Chongqing system might improve treatment efficiency.

The pooled NPV% directly post MR-HIFU was 68.1% which is higher than reported in other reviews (16,17), probably due to the exclusion of restrictive treatment protocols. Our results

revealed a remarkable asymmetry in the distribution of scattered points into two groups. Unfortunately, we were unable to fully explain this. Only one borderline difference was found with the use of bowel-interference mitigation techniques suggesting that this may lead to higher NPV%. Interestingly, like Peregrino et al. this review failed to show a statistically significant improvement in symptoms depending on different NPV% (16). However, two of the included studies divided their patients into two groups based on NPV% and showed that higher NPV% result in better clinical outcomes (42,43). One study showed that higher NPV% was associated with greater efficacy (36).

UFS-QoL

On average, the pooled tSSS was decreased and continued to improve during follow-up. There was no data available beyond 12 months. None of the included studies compared MR-HIFU to other treatment options. Jacoby et al. did compare MRgFUS to placebo (34) and reported a larger tSSS decrease in the MRgFUS group, -31 vs -13 points, at 3-months follow-up. To compare the tSSS of MR-HIFU to other treatment options (UAE, hysterectomy and myomectomy), we searched other uterine fibroid trials that used the UFS-QoL questionnaire. Spies et al. reported decreased tSSS: -40,2 for UAE, -40,5 for myomectomy and -57,3 for hysterectomy at 12-months follow-up (45). The tSSS in the Fume trial (46) was -37.6 for myomectomy and -30,4 for UAE after 12-months. In this review, the tSSS at 12-months was -30.5, which is comparable to UAE, but less improvement compared to myomectomy and hysterectomy.

HRQL was clearly under-reported in this review which is remarkable because the HRQL is part of the UFS-QoL questionnaire. Three studies did show improved HRQL after MR-HIFU treatment. Jacoby et al. showed greater HRQL improvement in the MRgFUS group compared to placebo, 27 vs 17-points.

Fibroid shrinkage

All studies showed fibroid shrinkage and the shrinkage percentage varied in time demonstrating that fibroids can continue to decrease in volume at least up to 1 year. A borderline significance was found between fibroid shrinkage and NPV% indicating that a higher NPV% could lead to more fibroid shrinkage. Please note that a follow-up MRI examination is expensive and often unnecessary.

Adverse events

The only two SAEs were reported in old studies (32,38) which could be explained by a small learning curve effect when MR-HIFU was implemented into clinical use (13). Stratification of AE by system showed significantly more AE in trials using the Sonalleve system compared to the ExAblate device (29,35,37,43). However, two ExAblate studies

reported 'no unexpected or significant AE', suggesting under-reporting (22,41). Moreover, there is no consensus on the definition of AE related to MR-HIFU. For example, abnormal vaginal discharge was often defined as AE, but one ExAblate study reported fibroid expulsion in 21% of their patients as normal finding (36). Interestingly, a Sonalleve study reported constitutional symptoms as AE while none of the other studies reported this (37).

Although the difference between Sonalleve and ExAblate in AE might be explained by a reporting bias, it remains important to investigate this in the future.

Re-intervention percentage

The overall re-intervention percentage ranged from 0-21% at the end at follow-up (3-33.6 months). Longer follow-up was associated with a higher risk of further interventions. Unfortunately, due to the lack of longer follow-up data, it remains unclear whether MR-HIFU provides symptom relief until menopause without the need for additional therapy. No association was found with NPV%, tSSS or fibroid shrinkage, this may be explained by the exclusion of patients undergoing re-interventions from further follow-up. The re-intervention percentage in our review at 24-months ranged from 13-14% as reported by two studies (218 patients) (20,31).This is comparable to the re-intervention percentage after UAE at 24-months. The EMMY trial (47) reported 23.5% re-interventions in the UAE group (48). A review comparing UAE with myomectomy and hysterectomy concluded that 15-32% will require further surgery within two years of UAE (49).

Reproductive outcomes

None of the included studies intended to investigate reproductive outcomes, but results were encouraging. Data is scarce since only one study investigated pregnancy outcomes after MR-HIFU treatment retrospectively (50). However, the available evidence is reassuring (51), but our results must be interpreted with caution due to the very small number of post MR-HIFU pregnancies and the relative rarity of the pregnancy complications one might expect because of MR-HIFU (i.e. abnormal placentation, placental abruption and fetal growth restriction). Compared to myomectomy, the noninvasive character of MR-HIFU is advantageous for women trying to conceive because patients can attempt pregnancy much sooner. How MR-HIFU affects one's ability to conceive is unknown, although the finding that AMH levels did not change in three studies (43,52,53) suggests that ovarian function is not compromised by MR-HIFU.

Costs

Based on the included studies, it was impossible to analyze the cost-effectiveness of MR-HIFU therapy compared to other uterine fibroid treatments. Five cost-effectiveness analysis are published, but not included in this review (54-58). They all suggested that

MR-HIFU may be a cost-effective strategy at commonly accepted willingness-to-pay thresholds.

Future perspectives

Although MR-HIFU treatment of uterine fibroids has been performed for 14 years now, there is still no wide-spread implementation of MR-HIFU or reimbursement worldwide. A randomized controlled trial is the gold standard to obtain reimbursement and one is currently ongoing to compare UAE and MR-HIFU (59). However, they experienced difficulties recruiting participants and some patients declined randomization. Thus, randomized trials are very hard to conduct and pose methodological challenges. To implement MR-HIFU treatment in regular clinical care, larger comparative controlled cohort studies with longer follow-up are warranted to define the role of MR-HIFU in the management of symptomatic uterine fibroids.

Core outcome set

Hitherto, there is no consensus on how to evaluate clinical outcome after MR-HIFU treatment. It is important to reach consensus, for example by developing a standardized Core Outcome Set (60), to improve the consistency of outcome reports in future MR-HIFU trials. Based on the outcomes identified via this systematic review we would recommend that clinical trials report the following outcomes: symptom improvement, QoL, NPV%, adverse events, fibroid shrinkage, re-intervention percentage, reproductive outcomes, recovery time and clinical efficacy. Symptom improvement and QoL should be assessed by a validated questionnaire such as the UFS-QoL (19). Clinical efficacy should be a combination of symptom reduction and no re-intervention during follow-up (36). Preferably, all patients are followed until menopause. Moreover, data of the patients undergoing an additional treatment should be published to identify risk factors for the need of re-interventions.

CONCLUSIONS

MR-HIFU therapy is a completely noninvasive safe therapy and is effective in alleviating fibroid-related symptoms for at least 12-months. Treatment protocols aiming for complete ablation led to better treatment outcomes. The re-intervention percentage is comparable to UAE at 24-months follow-up. Further trials should evaluate outcomes beyond 33.6 months and investigate reproductive outcomes. Moreover, controlled cohort trials are necessary to define the position of MR-HIFU compared to other treatment options for uterine fibroids.

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APPENDIX 1

Literature search

National Guideline Clearinghouse

Keywords contains:
1. “Leiomyoma”: 5 hits
2. “Myoma”: 2 hits
3. “Fibroid”: 13 hits
4. “Uterine fibroid”: 12 hits
5. #1 OR #2 OR #3 OR #4: 13 hits
6. “HIFU”: 6 hits
7. “FUS”: 34 hits
8. “High Intensity Focused Ultrasound”: 33 hits
9. “Magnetic Resonance-Guided Focused Ultrasound”: 50 hits
10. “Magnetic Resonance-Guided High-Intensity Focused Ultrasound”: 13 hits
11. #5 AND (#6 OR #7 OR #8 OR #9 OR #10): 12 hits

Cochrane Library

Title, abstract, keywords contains:
1. “Leiomyoma”: 796 hits
2. “Myoma”: 643 hits
3. “Fibroid”: 311 hits
4. “Uterine Fibroid”: 120 hits
5. #1 OR #2 OR #3 OR #4:1298 hits
6. “HIFU”: 133 hits
7. “FUS”: 50 hits
8. “High Intensity Focused Ultrasound”: 195 hits
9. “Magnetic Resonance-Guided Focused Ultrasound”: 38 hits
10. “Magnetic Resonance-Guided High-Intensity Focused Ultrasound”: 7 hits
11. #5 AND (#6 OR #7 OR #8 OR #9 OR #10): 43 hits

TRIP

Keywords contains:
1. “Leiomyoma”: 3671 hits
2. “Myoma”: 913 hits
3. “Fibroid”: 4746 hits
4. “Uterine Fibroid”: 1206 hits
5. #1 OR #2 OR #3 OR #4: 5514 hits
6. “HIFU”: 691 hits
7. “FUS”: 12.753 hits
8. “High Intensity Focused Ultrasound”: 618 hits
9. “Magnetic Resonance-Guided Focused Ultrasound”: 101 hits
10. “Magnetic Resonance-Guided High-Intensity Focused Ultrasound”: 34 hits
11. #5 AND (#6 OR #7 OR #8 OR #9 OR #10): 239 hits
12. #11 AND (“Magnetic resonance Imaging” OR “MRI”): 167 hits

Medline/PubMed

Keywords contains:
1. “Leiomyoma” [Mesh]: 19655 hits
2. “Leiomyoma” [tiab]: 9994 hits
3. “Leiomyoma”[tiab]) AND “Leiomyoma”[Mesh]: 7752 hits
4. “leiomyomas”[tiab]: 4488 hits

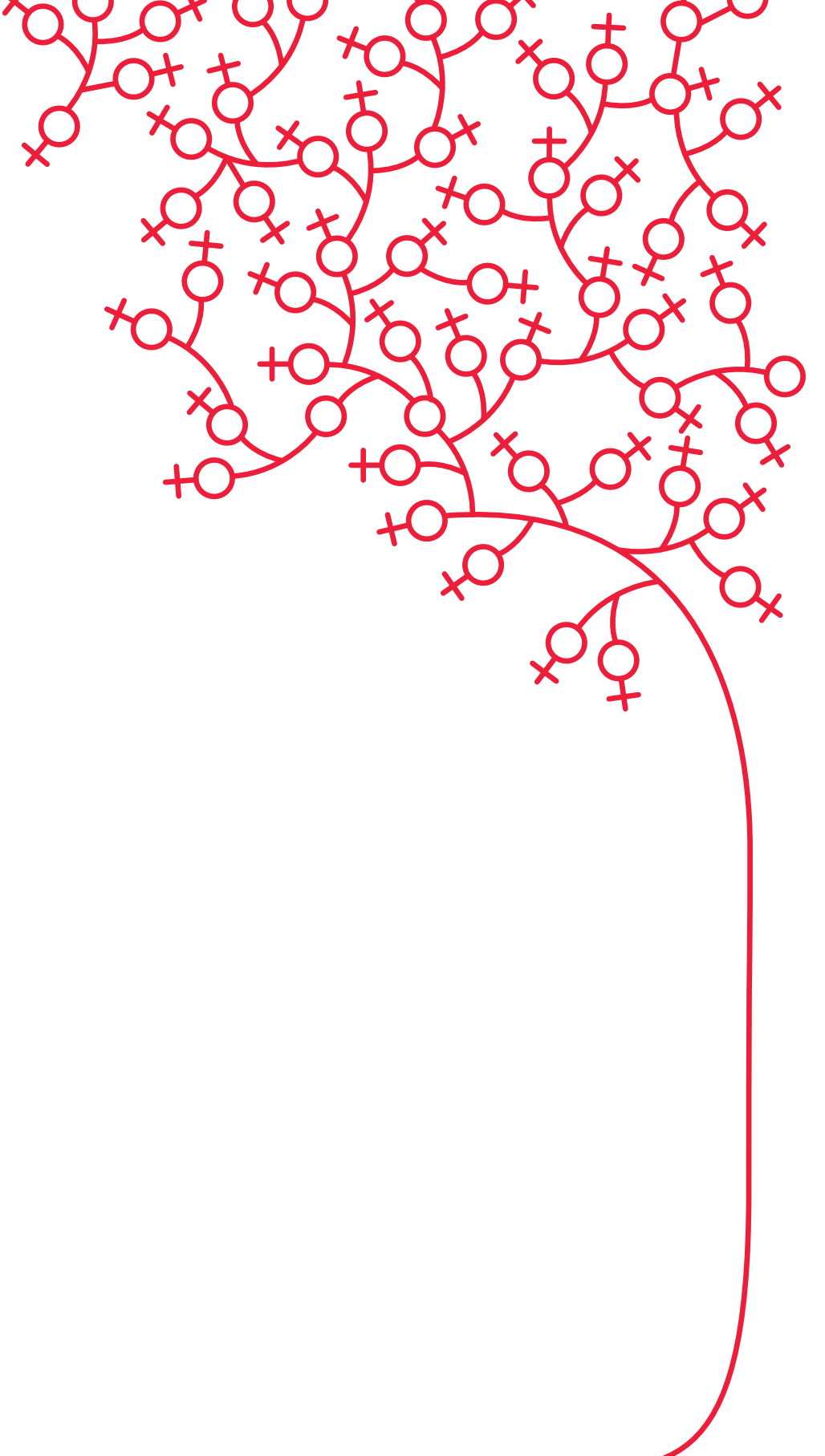
5. “Myoma”[tiab]: 3852 hits
6. “Myomas”[tiab]: 2140 hits
7. “Fibroid”[tiab]: 3124 hits
8. “Fibroids”[tiab]: 4122 hits
9. #3 OR #4 OR #5 OR #6 OR #7 OR #8: 19.247 hits
10. “High-Intensity Focused Ultrasound ablation”[Mesh]: 1679 hits
11. “High-Intensity Focused Ultrasound ablation”[tiab]: 242 hits
12. “High-Intensity Focused Ultrasound”[tiab]: 2542 hits
13. “focused ultrasound”[tiab]: 4552 hits
14. “Magnetic Resonance-Guided Focused Ultrasound”[tiab]:248 hits
15. “Magnetic Resonance-Guided High-Intensity Focused Ultrasound”[tiab]: 103 hits
16. #10 OR #11 OR #12 OR #13 OR #14 OR #15: 5020 hits
17. “Sonalleve”[tiab] OR “insightec”[tiab] OR “ExAblate 2000”[tiab]: 65 hits
18. “Magnetic Resonance Imaging”[Mesh]: 393422 hits
19. “Magnetic Resonance Imaging”[tiab]: 198173 hits
20. #18 OR #19: 464194 hits
21. #9 AND #16: 408 hits
22. #20 AND #21 AND ((“Treatment outcome”[MeSH Terms] OR “Follow-Up Studies”[MeSH Terms])): 87 hits
13. #20 AND #21: 202 hits

WHO International Clinical Trials Registry Platform (ICTRP)

1. “Leiomyoma”: 123 trials
2. “Myoma”: 103 trials
3. “Fibroid”: 112 trials
4. “Uterine Fibroid”: 60 trials
5. #1 OR #2 OR #3 OR #4: 298 trials
6. “HIFU”: 128 trials
7. “FUS”: 13 trials
8. “High Intensity Focused Ultrasound”: 143 trials
9. “Magnetic Resonance-Guided Focused Ultrasound”: 28 trials
10. “Magnetic Resonance-Guided High-Intensity Focused Ultrasound”: 19 trials
12. #5 AND (#6 OR #7 OR #8 OR #9 OR #10): 440 trials

Embase

Keywords contains:
1. ‘leiomyoma’/exp OR ‘leiomyoma’: 23.539 hits
2. ‘myoma’: 19.060 hits
3. ‘fibroid’: 5598 hits
4. ‘uterine fibroid’: 1658 hits
5. ‘uterine myoma’: 14.251 hits
6. #1 OR #2 OR #3 OR #4 or #5: 38.641 hits
7. ‘HIFU’: 3451 hits
8. ‘FUS’: 3948 hits
9. ‘High Intensity Focused Ultrasound’: 5341 hits
10. ‘Magnetic Resonance-Guided Focused Ultrasound’: 417 hits
11. ‘Magnetic Resonance-Guided High-Intensity Focused Ultrasound’: 146 hits
12. #6 AND (#7 OR #8 OR #9 OR #10 OR #11): 580 hits
13. #12 AND [English]/lim: 514 hits
14. ‘leiomyoma’/exp OR ‘leiomyoma’ AND (‘high intensity focused ultrasound’/exp OR ‘high intensity focused ultrasound’) AND [English]/lim: 79 hits
15. (‘leiomyoma’/exp OR ‘leiomyoma’) AND (‘high intensity focused ultrasound’/exp OR ‘high intensity focused ultrasound’ OR ‘magnetic resonance-guided high-intensity focused ultrasound’/exp OR ‘magnetic resonance-guided high-intensity focused ultrasound’ OR ‘magnetic resonance-guided focused ultrasound’/exp OR ‘magnetic resonance-guided focused ultrasound’) AND [English]/lim: 116 hits
Total screened hits: 568 hits



3

Comment on: Systematic review of pregnancy outcomes after fertility-preserving treatment of uterine fibroids

KJ Anneveldt, IM Nijholt, JR Dijkstra, JM Schutte, WJK Hehenkamp, MF Boomsma

Reproductive Medicine Online

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LETTER

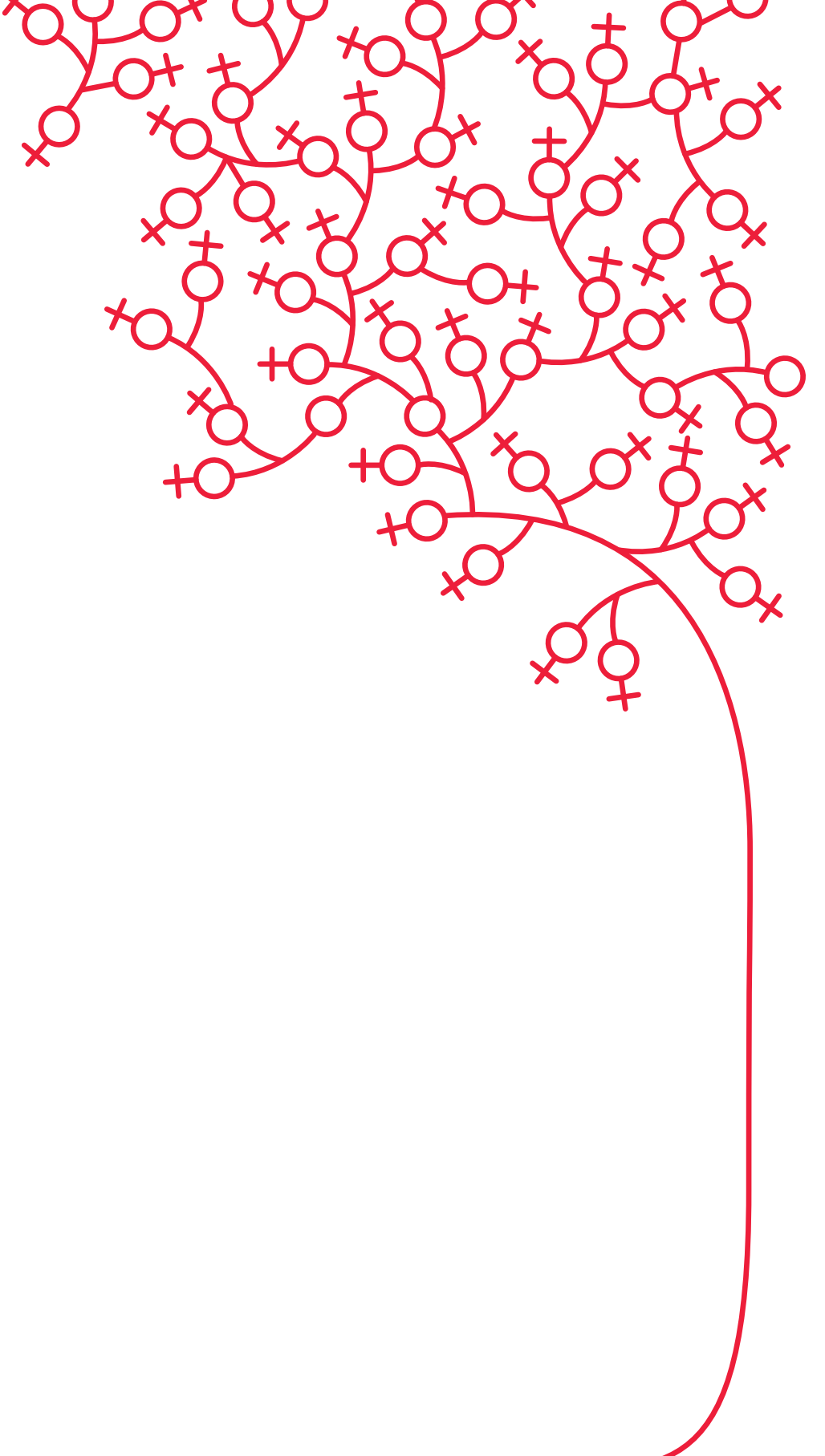
We read with great interest the systematic review by Khaw et al. (2020) in which they compared pregnancy outcomes after medical, surgical and radiological therapy for fibroids. From our experience with magnetic resonance-high intensity focused ultrasound (MR-HIFU) treatment of fibroids, we would like to comment on this review.

Ideally, relevant baseline parameters should be similar or corrected for when comparing different treatments. In this review no such correction was applied, most likely because these data were not available. Typically, fibroids are numerous with open myomectomy or uterine artery embolization and solitary with ablation or laparoscopic myomectomy. Age, which is maybe the most important predictor for pregnancy chances, was not mentioned. Data from retrospective, prospective and randomized studies were added together, as if the studies were of similar design.

Assuming that baseline parameters were comparable, we question the conclusion that myomectomy remains the treatment of choice. Although the percentage of live births was almost comparable between myomectomy and ablation, ablation was shown to have better outcomes with respect to miscarriage, preterm delivery, caesarian section, time to conceive and uterine rupture. Therefore, we feel that fibroid ablation may be an equally good option. Most importantly, it is not clear how many women in each group desired a pregnancy and achieved one. As long as these data remain unavailable, we should be careful in our statements because they influence the choices made. Direct comparison in randomized trials is needed to provide the answer as to which treatment should be offered to women with fibroids wishing to become pregnant.

REFERENCES

Khaw SC, Anderson RA, Lui M. Systematic review of pregnancy outcomes after fertility-preserving treatment of uterine fibroids. Reproductive BioMedicine Online 2020 Mar;40(3):429-444.



4

Systematic review of reproductive outcomes after High Intensity Focused Ultrasound treatment of uterine fibroids

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ABSTRACT

Purpose

Myomectomy is currently the gold standard for the treatment of uterine fibroids in women who desire pregnancy. However, this surgical fibroid removal has a long convalescence. Promising alternatives may be non-invasive High Intensity Focused Ultrasound (HIFU) under either MRI (MR-HIFU) or ultrasound guidance (USgHIFU). In this systematic review, an overview is provided of reproductive outcomes after these two relatively new ablation techniques.

Method

A systematic literature search was performed to identify studies reporting reproductive outcomes after HIFU treatment of fibroids. Only peer reviewed, full papers were included. Outcomes included pregnancy-, livebirth-, miscarriage and caesarian section rate, time to conceive, reported complications, and possible prognostic factors.

Results

In total 21 studies were included. Fourteen studies reported 124 pregnancies after MR-HIFU. Two placenta previas and no uterus ruptures were reported. Pregnancy rates were only retrospectively collected and ranged between 7% and 36%. Miscarriage rate in the oldest and largest prospective registry was 39%.

After USgHIFU 366 pregnancies were reported with one fetal intrauterine death, six placenta previas and no uterus ruptures. The only prospective study reported a pregnancy rate of 47% and a miscarriage rate of 11%. Possible prognostic factors like age were not available in most studies.

Conclusions

Based on the heterogeneous data currently available, reproductive outcomes after HIFU appear non-inferior to outcomes after the current standard of care. However, a (randomized) controlled trial comparing reproductive outcomes after HIFU and standard care is necessary to provide sufficient evidence on the preferred fibroid treatment for women with a pregnancy wish.

Keywords

Systematic review, Uterine fibroids, MR guided interventional procedures, US guided interventional procedures, High-intensity focused ultrasound ablation, Reproductive outcomes.

INTRODUCTION

Uterine fibroids are present in 70% of women during their fertile life, with a higher prevalence in later life (1). Fibroids cause symptoms in 25-50% of women, and these symptoms include heavy menstrual bleeding, abdominal pain, bulking problems and subfertility difficulties (1). Because women are having children at an increasingly advanced age, subfertility problems caused by a uterine fibroid are becoming a growing problem (2,3). Women seeking fertility assistance are diagnosed with uterine fibroids in 27% (3). Moreover, the presence of fibroids is correlated with a significantly lower live-birth rate and a significantly higher miscarriage rate (4). Several hypotheses are proposed to explain why fibroids cause fertility problems including alterations in blood flow, endometrial inflammation, altered hormonal environment, and interfered uterine contractility needed for sperm and ovum interaction and embryo migration (5). Subserosal fibroids do not seem to have an effect on fertility. The effect of intramural fibroids is unclear, although deformation of the uterine cavity might compromise fertility leading to a decrease of pregnancy rate of 19%. Submucosal fibroids reduce pregnancy and live-birth rate by 64% and 67% (3). First line treatment for submucosal fibroids <5 cm diameter is hysteroscopic resection (5). Abdominal myomectomy is the gold standard when hysteroscopic removal of a submucosal fibroid is not possible (3). Whether a myomectomy will improve pregnancy rate in women with uterine fibroids, has not been studied sufficiently (6). The possible advantages of fibroid resection for fertility reasons should be weighed against the risks of the treatment. Complications of myomectomy include major hemorrhage and intra-uterine and intra-abdominal adhesion formation (4). Additional limitations of abdominal myomectomy by laparoscopy or laparotomy are the four to eight weeks (7) convalescence and the general advice to extend any attempt to conceive for at least six months after treatment in order to facilitate proper wound healing of the uterus (8,9,10). The uterine incision is also associated with a higher risk of uterine rupture during pregnancy and an increased likelihood of caesarean section (CS) (4). Subfertility is usually not the main problem women with uterine fibroids report to their gynecologist. Symptom relieve provided by a myomectomy, should therefore be considered as well in the decision for treatment. In line with the current trend in healthcare, less invasive treatment options have come available (10,11). Uterine artery embolization (UAE), as an alternative minimal-invasive treatment option for women with a wish to conceive, is considered inferior to myomectomy. This may be explained by ovarian damage and impairment of myometrial and endometrial function (8,13). High Intensity Focused Ultrasound (HIFU) is a non-invasive, uterus-saving, treatment option with promising results (12). HIFU can be either magnetic resonance image guided (MR-HIFU) or ultrasound guided (USgHIFU). MR-HIFU allows planning of sonication based on MR images with fine anatomic detail and MR-thermometry provides a near real-time temperature map during sonication to

track the heating pattern (13). Temperature feedback is a key factor in hyperthermia applications, where high temperatures need to be maintained over a prolonged period of time to create the necessary high non-perfused volume percentage (NPV%) needed for an effective treatment (12,13). USgHIFU procedure allow real-time visualization of tissue ablation by an emerging echogenicity or increased grayscale intensity, but it does not provide precise information on achieved temperature or the thermal dose that is deposited in the target tissue (13,14,15). The guiding images obtained during ultrasound guided HIFU are inferior to those obtained during MRI guided HIFU (13,16), but this does not seem to result in a difference in safety or effectivity between the two HIFU treatment options (16,17). Initially, HIFU was primarily performed in women without a pregnancy wish because of the lack of obstetric outcomes. However, in the course of the years, more and more pregnancies were described and since 2010 pregnancy wish is no longer considered a contraindication (18). Today, reviews reporting reproductive outcomes are available, but often combine MRI and US guided HIFU or even include other types of fibroid ablation techniques like Radiofrequency Volumetric Thermal Ablation (RFTVA), resulting in insufficient data on the specific effect of the two HIFU treatment options (19). The aim of the current study was to systematically review current literature concerning reproductive outcomes after HIFU treatment, reporting the data of MR-HIFU and USgHIFU separately, and taking into account the study design, the primary outcome, in- and exclusion criteria, and possible prognostic factors such as age during treatment, reached NPV%, fibroid locations, and fibroid size.

METHODS

This review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines (20). After registration of the review at the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42020184078), the Cochrane Library, the PubMed/MEDLINE and EMBASE databases were thoroughly searched independently by two reviewers (KA and HO) on 28/09/2020. The search terms used are presented in Appendix A. Since reproductive outcomes were rarely mentioned in title and/or abstract, we included articles with all possible clinical outcomes after MR-HIFU or USgHIFU treatment for uterine fibroids and a follow-up of at least six months for full text screening. The following study designs were included when available: randomized controlled trials, prospective and retrospective cohort studies, case series and case reports published as full papers in peer-reviewed journals in English. References of the articles included were checked for additional publications. Furthermore, reviews on HIFU were scanned for additional primary data. Discrepancies on inclusion were resolved through consensus. Studies were excluded when reproductive

outcomes were not reported, full-text was not available or not in English, another type of ablation therapy was performed (not HIFU) or when adenomyosis, instead of uterine fibroids, was the treatment indication. When multiple publications from the same dataset were available, as much data as possible was extracted and combined. In case pregnancies had the same outcomes in a case report and a case series, we assumed that they referred to the same pregnancy and we only included the case series. Two authors (KA and HO) assessed level of evidence of all articles independently. The quality of case series was assessed by a 20-points criteria tool developed by The Institute of Health Economics through a Delphi technique (21). A score of 14-points or more indicated good quality. Discrepancies were identified and resolved through discussion. Of all included studies the following outcomes were extracted, if available, using a standardized form: study design, primary outcome, presence or absence of a control group, follow-up duration, whether pregnancy rate was an exclusion criteria during inclusion, age during treatment, inclusion of women with known in- or subfertility, number of pregnancies before HIFU, pregnancy rate, live-birth rate, elective abortion rate, miscarriage rate, ongoing pregnancy rate, time to conceive after HIFU treatment, gestational age during delivery, CS rate, birth weight, complications during pregnancy or labor, NPV% reached, fibroid location, and size of the treated fibroid. Meta analyses for a particular outcome were performed when ≥4 studies could be included using Open Meta-Analyst, Brown University, for Windows 10. We used the DerSimonian-Laird random effects model and considered an I2 value ≥50% indicative of substantial heterogeneity. No approval from an Ethical Review Board was needed since all data was extracted from published articles.

RESULTS

MR-HIFU

Fourteen articles reported on pregnancy outcomes after MR-HIFU treatment for uterine fibroids (Figure 1). Five additional articles met our inclusion criteria but reported pregnancy outcomes that were already reported in one of the fourteen included articles. Two studies collected data prospectively, two other studies retrospectively analyzed prospectively collected data (Table 1). Five case reports were included. Only one study reported on a control group of women treated by UAE (22). Seven of the fourteen studies had reproductive outcomes as their primary outcome. Two of the fourteen studies reported about pregnancies after MR-HIFU treatment while pregnancy wish was an exclusion criterion for their study (Table 1) (22,23). Two other studies altered their in- and exclusion criteria during data collection, i.e. pregnancy wish was no longer an exclusion criterion, and provided pregnancy outcomes after both protocols. These two studies were referred to as mixed studies (24,25).

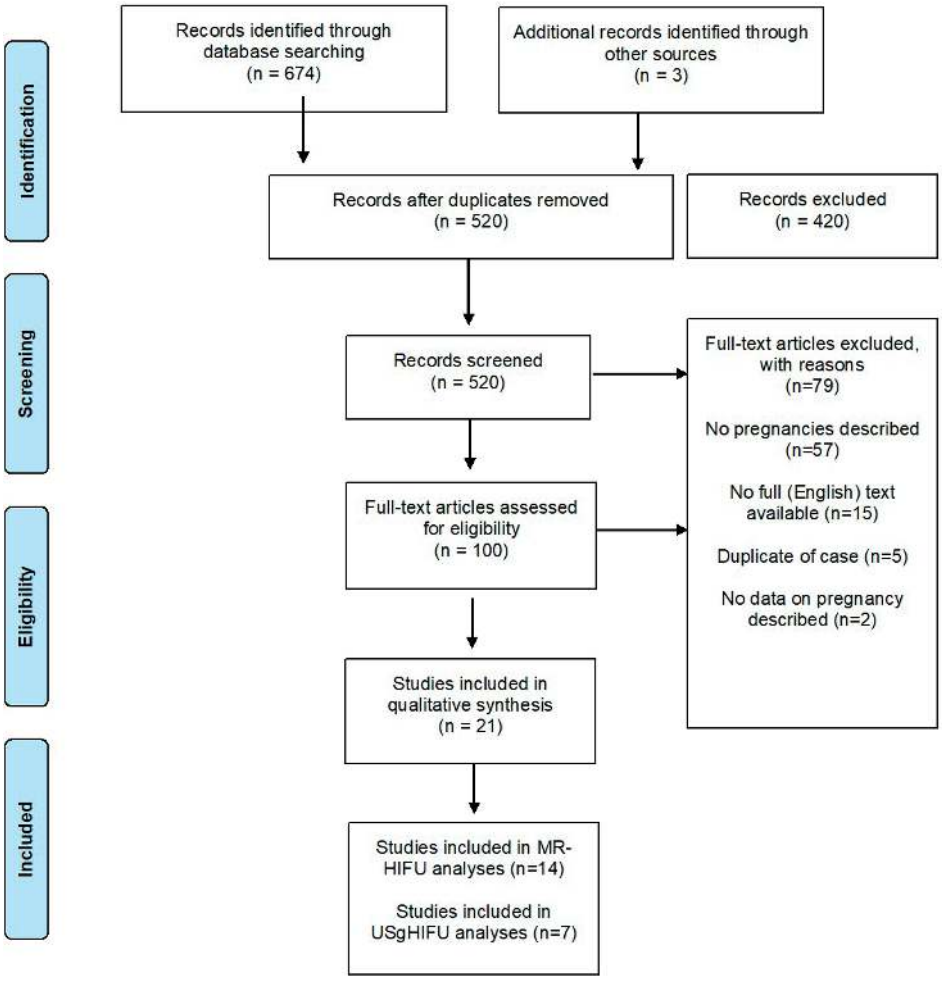

Figure 1: PRISMA flowchart of in- and excluded articles.

Pregnancy rate

Only three, retrospective, studies reported the number of women with a wish to conceive after MR-HIFU treatment (Table 2). In the study by Lozinski et al., all 276 included women suffered from infertility with other reasons for infertility, besides the existence of a fibroid, excluded (2). In 20 of the 276 women, 21 pregnancies occurred, resulting in a pregnancy rate of 7%. In the study by Mindjuk et al. and the mixed study by Verpalen et al., pregnancy rates of 15% (15/99) and 36% (4/11) were reported (24,26).

Table 1: Overview of characteristics of included articles performing MR-HIFU.

Study, year	Primary outcome	Control group	Quality	Follow-up duration in months	Number of women and pregnancies
Prospective					
Pregnancy no exclusion criterion					
Keserci, 2017 (40)	Other	No	15/20	6	3 and 3
Pregnancy partly exclusion criterion "mixed study"					
Rabinovici, 2010 (25)	Obstetric	No	8/20	LOD	51 and 54
Prospective and retrospective					
Pregnancy no exclusion criterion					
Funaki, 2009 (27)	Other	No	14/20	34 [range:6-54]	4 and 4
Pregnancy exclusion criterion					
Froeling, 2013 (22)	Other	Yes, uterine artery embolization	15/20	61	9 and 10
Retrospective					
Pregnancy no exclusion criterion					
Lozinski, 2019 (2)	Obstetric	No	12/20	LOD	20 and 21
Thiburce, 2015 (41)	Other	No	16/20	21 [range:6-59]	2 and 2
Mindjuk, 2014 (26)	Other	No	15/20	19 ±SD 8 [range:8-38]	15 and 15
Yoon, 2013 (42)	Other	No	14/20	12	1 and 1
Pregnancy partly exclusion criterion "mixed study"					
Verpalen, 2020 (24)	Other	No	14/20	64 ±SD 29	4 and 9
Case reports					
Zaher, 2011 (43)	Obstetric	n.a.	n.a.	LOD	1 and 1
Bouwsma, 2011 (44)	Obstetric	n.a.	n.a.	LOD	1 and 1
Zaher, 2010 (45)	Obstetric	n.a.	n.a.	LOD	1 and 1
Morita, 2007 (46)	Obstetric	n.a.	n.a.	LOD	1 and 1
Gavrilova, 2007 (23)	Obstetric	n.a.	n.a.	LOD	1 and 1

LOD: lack of data; n.a.: not applicable.

Live-birth and miscarriage rate

Of all 124 pregnancies reported after MR-HIFU treatment, 69 resulted in live-birth. Twenty pregnancies were still ongoing, seven ended in abortion and of three pregnancies, no outcome was reported, resulting in a live-birth rate of 73% (69/94). When mixed studies or studies with future pregnancy wish as exclusion criterion were excluded, 32 live-births were seen in 38 pregnancies resulting in a live-birth rate of 84% (95% CI; 73.7 – 94.5%, I2: 0%, Figure 2). In the largest and only prospective mixed registry by Rabinovici et al., a miscarriage rate of 39% (14/36) was observed (25). In the prospective and retrospective studies by Froeling et al. and Funaki et al, miscarriage percentage ranged between 30 and 50% and in the retrospective studies of Mindjuk et al., Lozinski et al., and Verpalen et al. between 8 and 22% (2,24,26).

Table 2: Overview of pregnancy outcomes after MR-HIFU treatment.

Study, year	Pregnancy before treatment	Infertile women included	Age in years	Location fibroid(s)	Size fibroid(s) in cm (diameter) or cm^3 (volume)	NPV%	Time to conceive in months	Pregnancy %
Prospective								
Pregnancy no exclusion criterion								
Keserci, 2017 (40)	LOD	LOD	LOD	LOD	LOD	LOD	<6	LOD
Pregnancy partly exclusion criterion								
Rabinovici, 2010 (25)	62%	Yes, 38%	37 ±SD 5 [range:28-49]	14/47 submucosal, 28/47 intramural, 9/47 subserosal, 3/47 transmural	Volume: 268 ±SD 203	40 [range:6-100]	8 ±SD 7 [range:0-30]	LOD
Prospective and retrospective								
Pregnancy no exclusion criterion								
Funaki, 2009 (27)	LOD	LOD	LOD	LOD	LOD	LOD	3-24	LOD
Pregnancy exclusion criterion								
Froeling, 2013 (22)	LOD	LOD	LOD	LOD	LOD	LOD	16 [range:9-24]	LOD
Retrospective								
Pregnancy no exclusion criterion								
Lozinski, 2019 (2)	20%	Yes	33 ±SD 4	LOD	Volume: 87	74 [range: 50-100]	LOD	7 (20/276)
Thiburce, 2015 (41)	LOD	LOD	LOD	LOD	LOD	LOD	LOD	LOD
Mindjuk, 2014 (26)	LOD	LOD	35 ±SD 3 [range:30-42]	LOD	LOD	LOD	20	15 (15/99)
Yoon, 2013 [(42)	LOD	LOD	LOD	LOD	LOD	LOD	4	LOD
Pregnancy partly exclusion criterion								
Verpalen, 2020 (24)	LOD	LOD	LOD	LOD	LOD	LOD	LOD	36 (4/11)
Case reports								
Zaher, 2011 (43)	100%	Yes	45	Intramural	Diameter: 9 x 6 x 7	90	10	n.a.

Table 2: Overview of pregnancy outcomes after MR-HIFU treatment. (*continued*)

Bouwsma, 2011 (44)	100%	Yes	37	Submucosal and intramural	Diameter: 5 x 5 x 4 and 4 x 3 x 3	68	3	n.a.
Zaher, 2010 (45)	100%	LOD	39	Submucosal and intramural	Diameter: 5 and 4	90	10	n.a.
Morita, 2007 (46)	0	LOD	29	Intramural	Volume: 215	52	3	n.a.
Gavrilova, 2007 (23)	0	LOD	38	LOD	Diameter: 10 x 9 x 10	LOD	18	n.a.
Study, year	**Live-birth %**	**Miscarriage %**	**Preterm %**	**Abortion %**	**Gestational age in weeks**	**Birth weight in kilogram**	**CS %**	
Prospective								
Pregnancy no exclusion criterion								
Keserci, 2017 (40)	LOD	LOD	LOD	LOD	LOD	LOD	LOD	
Pregnancy partly exclusion criterion								
Rabinovici, 2010 (25)	51 (22/43)	39 (14/36)	7 (1/15)	16 (7/43)	39 ±SD 2 [range:36-42]	3300 ±SD 40 [range:2660-3970]	36 (8/22)	
Prospective and retrospective								
Pregnancy no exclusion criterion								
Funaki, 2009 (27)	50 (2/4)	50 (2/4)	0	0	LOD	LOD	LOD	
Pregnancy exclusion criterion								
Froeling, 2013 (22)	70 (7/10)	30 (3/10)	LOD	0	LOD	LOD	LOD	
Retrospective								
Pregnancy no exclusion criterion								
Lozinski, 2019 (2)	79 (11/14)	21 (3/14)	0	0	39 [range:38-40]	3620 [range:3300-4260]	64 (7/11)	
Thiburce, 2015 (41)	100 (2/2)	0	0	0	LOD	LOD	0	
Mindjuk, 2014 (26)	92 (12/13)	8 (1/13)	LOD	0	LOD	LOD	LOD	
Yoon, 2013 (42)	100 (1/1)	0	0	0	LOD	LOD	0	
Pregnancy partly exclusion criterion								
Verpalen, 2020 (24)	78 (7/9)	22 (2/9)	14 (1/7)	0	LOD	LOD	60 (3/5)	

Table 2: Overview of pregnancy outcomes after MR-HIFU treatment. (*continued*)

Case reports							
Zaher, 2011 (43)	100 (1/1)	0	0	0	39	3050	100
Bouwsma, 2011 (44)	100 (1/1)	0	0	0	40	3450	0
Zaher, 2010 (45)	100 (1/1)	0	0	0	42	3580	0
Morita, 2007 (46)	100 (1/1)	0	0	0	39	3210	0
Gavrilova, 2007 (23)	100 (1/1)	0	0	0	LOD	LOD	0

LOD: lack of data; n.a.: not applicable.

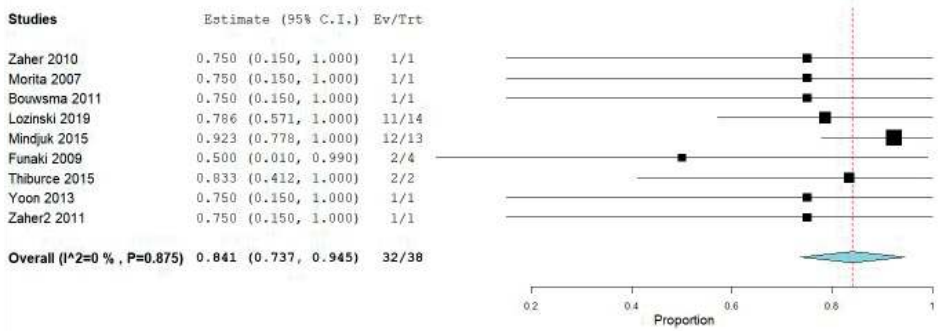

Figure 2: Forest plot of studies providing data on live-births after MR-HIFU treatment without future pregnancy wish as exclusion criterion or mixed studies during inclusion.

Time to conceive

In the prospective mixed registry by Rabinovici et al., conception after MR-HIFU treatment took on average eight months (25). All other studies combined, including the data of the case reports, showed that conception took zero to 36 months (Table 2).

Mode of delivery

Rabinovici et al. showed a CS rate of 36%, and a CS rate of 60% and 64% in the studies by Verpalen et al. and Lozinski et al. (2,24,25).

Complications during pregnancy and delivery

Different types of complications, possibly caused by the treatment, were reported during pregnancy and delivery. These included fibroid necrosis, placenta previa, and increase of fibroid volume (Table 3). Obstruction of labor caused by the fibroid was mentioned once. After delivery, a manual placenta removal was necessary once and post-partum hemorrhage occurred three times. In one case, severe maternal bleeding was seen, resulting in both disseminated intravascular coagulation and adult respiratory distress syndrome after an elective CS. No cases of intrauterine fetal demise were described, neither any uterine ruptures.

Possible prognostic factors: NPV%, age, fibroid size and fibroid location

Median NPV% directly post MR-HIFU treatment was only provided in two case series. In the registry by Rabinovici et al., a median NPV% of 40% was reached (range: 6-100%), in the study by Lozinski et al., a median of 74.% (range: 50-100%) (2,25). Age during treatment of women included in all fourteen studies ranged between 26 and 49 years. The mean age in the prospective registry was 37 ± SD 5 years (25). In that same study, most fibroids were intramurally located (28/47), followed by submucosal fibroids (14/47) and had an average volume of 268 ± SD 203 cm3. In all other studies, if location was known, fibroids were located submucosal or intramural and maximum diameter ranged between 4 and 10 cm and volume between 87 cm3 and 215 cm3 (Table 2).

Table 3: Overview of possible HIFU treatment related complications.

Study, year	Number of pregnancies	Number of deliveries	Possible HIFU related complication
Rabinovici, 2010 (25)	54	22	Abnormal vaginal bleeding: n=6 Placenta previa: n=2 Increase of fibroid volume: n=2 Manual placenta removal: n=1 DIC and ARDS: n=1
Verpalen, 2020 (24)	9	7	Fibroid necrosis: n=1 Obstruction of labor: n=1
Liu, 2018 (29)	88	74	Placenta previa and preterm: n=1 Obstruction of labor: n=1 Malpresentation: n=4 Post-partum hemorrhage: n=2
Li, 2017 (31)	133	93	Placenta previa: n=5 Placenta insufficiency and fetal intrauterine death: n=1 Post-partum hemorrhage: n=6 Abnormal bleeding during myomectomy: n=4
Qin, 2012 (28)	24	7	Abnormal vaginal bleeding: n=2

DIC: disseminated intravascular coagulation; ARDS: adult respiratory distress syndrome.

Comparison to other treatments

In the study by Froeling et al., a direct comparison was performed between 41 women undergoing UAE and 36 women undergoing MR-HIFU (22). No pregnancies were seen after UAE, nine women became pregnant after MR-HIFU. Study populations differed however. Women undergoing UAE were significantly older ($p < 0.001$) and their fibroid volume at baseline was significantly larger ($p = 0.005$) compared to MR-HIFU. Furthermore, future pregnancy wish was an exclusion criterion for participation in the study.

USgHIFU

Seven articles reported pregnancy outcomes after USgHIFU treatment of fibroids (Figure 1). None of these studies had future pregnancy wish as an exclusion criterion. However, one study published about the outcomes of unintended pregnancies (Table 4) (28). None of the studies performed a direct comparison to an alternative fibroid treatment option. One study had a prospective design; all other were retrospective studies. Four studies had reproductive outcomes as their primary outcome.

Pregnancy rate

The only prospective study described 88 pregnancies in 81 of the 174 women wishing to become pregnant, resulting in a pregnancy rate of 47% after a follow-up of 76 months (range:29-117, Table 5) (29). The pregnancy rates of three other, retrospective studies ranged between 10% (in Huang et al. after one-year follow-up) and 69% (in Li et al. after median follow-up of three years) (30,31). In the study by Zou et al., a pregnancy rate of 19% was seen during an unknown follow-up duration (32). When the data of these four studies were combined, the pregnancy rate in 838 women was 36% (95% CI; 10.8% - 61.8%, I2: 98.6%, Figure 3).

Table 4: Overview of characteristics of included articles performing USgHIFU.

Study, year	Primary outcome	Control group	Quality	Follow-up duration in months	Number of women and pregnancies
Prospective					
Liu, 2018 (29)	Obstetric	No	14/20	76 [range:29-117]	81 and 88
Retrospective					
He, 2018 (47)	Other	No	16/20	6	1 and 1
Zou, 2017 (32)	Obstetric	No	15/20	LOD	78 and 80
Huang, 2017 (30)	Other	No	14/20	12	7 and 7
Li, 2017 (31)	Obstetric	No	15/20	36 [range:12-60]	131 and 133
Lee, 2015 (48)	Other	No	13/20	12	3 and 3
Qin, 2012 (28)	Obstetric	No	14/20	12 ±SD 6 [range:5-24]	24 and 24

LOD: lack of data.

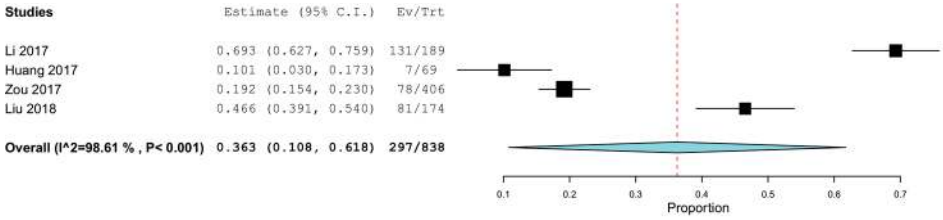

Figure 3: Forest plot of pregnancy rate after USgHIFU treatment.

Live-birth and miscarriage rate

The overall live-birth rate of all reported pregnancies was 91% (248/ 277; 95% CI; 85.0% - 96.2% I2: 52.5%, Figure 4). Liu et al. reported a miscarriage rate of 11% (9/83) and an abortion rate of 6% (5/88) (29). A much higher abortion rate of 71% (17/24) and no miscarriages were seen in the retrospective analyses by Qin et al., analyzing the outcomes of unintended pregnancies after USgHIFU (28). Li et al. and Zou et al. reported miscarriage rates of 15% (17/110) and 4% (3/74), Table 5) respectively (31,32).

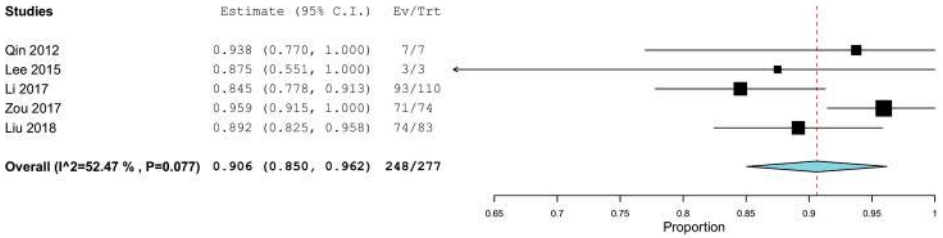

Figure 4: Forest plot of live-birth rate after USgHIFU treatment.

Table 5: Overview of pregnancy outcomes after USgHIFU treatment.

Study, year	Pregnancy before treatment	Infertile women included	Age in years	Location fibroid(s)	Size fibroid(s) in cm (diameter) or cm^3 (volume)	NPV%	Time to conceive in months	Pregnancy %
Prospective								
Liu, 2018 (29)	30%	Yes, 1/181	31 ±SD 4 [range:24-41]	15/81 submucosal56/81 intramural 10/81 subserosal	Volume: 90 ±SD 77	90 ±SD 0.1 [range: 39-100]	16 [range:1-66]	47 (81/174)
Retrospective								
He, 2018 (47)	LOD	LOD	27	LOD	Diameter: 14, 2 and 2	86, 92 and 100	3	n.a.
Zou, 2017 (32)	LOD	Yes, 9/78	35 ±SD 5 [range:25-53]	9% submucosal, 78% intramural, 4% submucosal and intramural, 9% subserosal	Diameter: 5 ±SD 3	84 ±SD 8	6 ±SD 3 [range:1-18]	19 (78/406)
Huang, 2017 (30)	LOD	LOD	LOD	Only intramural fibroids included	LOD	LOD	LOD	10 (7/69)
Li, 2017 (31)	LOD	Yes, 45/189	30 ±SD 4 [range:23-40]	5% submucosal, 81% intramural, 13% subserosal	Volume: 81 ±SD 82	LOD	*12 ±SD 10	69 (131/189)
Lee, 2015 (48)	0	LOD	LOD	LOD	LOD	LOD	LOD	LOD
Qin, 2012 (28)	21/24	Yes, 1/24	35 ±SD 5	LOD	Volume: 66 ±SD 59	84 ±10	**20 ±SD 9 **17 ±SD 10	LOD

Study, year	Live-birth %	Miscarriage %	Preterm %	Abortion %	Gestational age in weeks	Birth weight in kilograms	CS %
Prospective							
Liu, 2018 (29)	89 (74/83)	11 (9/83)	8 (7/74)	6 (5/88)	LOD	3300 ±SD 400	72 (53/74)
Retrospective							
He, 2018 (47)	LOD	LOD	0	LOD	LOD	LOD	0
Zou, 2017 (32)	96 (71/74)	4 (3/74)	4 (3/74)	1 (1/75)	38.1 ±SD 2	LOD	81 (56/71)
Huang, 2017 (30)	LOD	LOD	LOD	LOD	LOD	LOD	LOD
Li, 2017 (31)	85 (93/110)	15 (17/110)	6 (6/94)	3 (4/133)	LOD	3300 ±SD 40	72 (67/93)
Lee, 2015 (48)	100 (3/3)	0	LOD	0	LOD	LOD	33 (1/3)
Qin, 2012 (28)	100 (7/7)	0	LOD	71 (17/24)	39 [range:38-39]	3085 ±SD 459	100

LOD: lack of data; n.a.: not applicable, *all women were advised to wait for at least 3 months; ** reported in weeks and separated between time to pregnancy of women who did not continue their unplanned pregnancy and women who did continue their unplanned pregnancy.

Time to conceive

The median time to conceive in the prospective study by Liu et al. was 16 months (range:1-66 months, Table 5) (29). Other, retrospective, studies reported a mean of 16 and 20 weeks (Qin et al.), 12.3 months (± SD 9.9 Li et al.) and 5.6 months (± SD 2.7, Zou et al.) (28,31,32).

Mode of delivery

The three studies with most deliveries (238 in total) reported that between 72 and 80% of women delivered by CS (Table 5). According to Zou et al., 13% of these performed CS' were due to obstetric reasons (premature ruptures of membranes, fetal stress, breech position, cephalopelvic disproportion and amniotic fluid decrease) (32). In all other cases, CS was performed for social reasons. In the study by Li et al., 37% chose a CS for the fear of pain. In other pregnancies, an obstetric factor (21%) or the advice of the obstetrician (42%) was the reason for the performed CS (31). Finally, Liu et al. stated that 36 of 52 (69%) women requested a CS for social reasons, fifteen of them were worried about rupture of the uterus after the HIFU treatment and eleven were advised by their obstetrician to undergo a CS because of the HIFU treatment in the past (29). Five of 26 women (19%) failed trial of labor due to failure of progress and one time because of obstruction by the fibroid.

Complications during pregnancy and delivery

Three studies reported on complications during pregnancy or labor that might be related to the USgHIFU treatment (Table 3). These studies included 245 pregnancies and 171 deliveries. Placenta previa was seen six times and placenta insufficiency once, leading to intrauterine death at six months pregnancy (31). Abnormal vaginal bleeding during pregnancy occurred twice, post-partum hemorrhage eight times. An additional four times massive bleeding occurred during performing a myomectomy during CS. One preterm delivery was the result of a massive hemorrhage due to placenta previa at 30 weeks pregnancy (29). Obstruction of labor or malpresentation was reported five times (Table 3). No uterus ruptures were seen.

Possible prognostic factors: NPV%, age, fibroid size and fibroid location

In the prospective study by Liu et al., 81 treated fibroids reached a mean NPV% of 90 ± SD 0.1 (29). In the retrospective study by Zou et al., a mean NPV% of 84 ± SD 8 after treating 78 women was reported, and in the study by Qin et al. the mean NPV% of 24 fibroids was 84 ± SD 10 (28,32). In the study by Huang et al., only intramural located fibroids were included (30). In the studies by Li et al., Zou et al. and Liu et al., intramural fibroids were seen most frequently (Table 5). Mean pretreatment volume of the treated fibroids ranged between 66 ± SD 59cm3 and 90 ± SD 77cm3. Mean age ranged between

30 years ± SD 4 and 35 years ± SD 5 in the studies including more than one pregnancy, with a range with all studies combined between 23 and 53 years old (Table 5).

DISCUSSION

In this systematic review, we reported reproductive outcomes after both MRI and US guided HIFU treatment for uterine fibroids. A total of 124 pregnancies were reported in 114 women after MR-HIFU treatment. Only three cohort studies reported pregnancy rates (range between 7% and 36%). Live-birth rate of nine studies combined was 73%, but this was based on 94 pregnancies. Miscarriage rate data was very heterogeneous and ranged between zero and 50%. When combining all (mostly retrospective) studies after USgHIFU, 325 women became 336 times pregnant. The pregnancy and live-birth rates were 36% and 91% respectively. Miscarriage rates ranged between zero and 15%. The overall incidence of complications is encouragingly low for both techniques.

The current standard of care for women with symptomatic uterine fibroids and a pregnancy wish consists of myomectomy or a wait-and-see-policy. When comparing the reported reproductive outcomes after the two HIFU techniques with the outcomes of the current standard of care, it is important to keep in mind that NPV% after HIFU should be as high as possible, but at least 80% (26). The median NPV% after MR-HIFU was only reported twice and in both cases below 80% (40% and 74%). The reported NPV% after USgHIFU were all above 80%, but these concerned study averages. It is unclear whether institutional learning-curves of the HIFU technique had been completed when performing the treatments in the included studies and whether all fibroids present in the uterus were treated, or that some fibroids were left in place. Furthermore, ablated fibroids remain in the uterine wall after HIFU treatment and the impact of especially intramural located fibroids on implantation, placentation and uterine contractility during pregnancy, is still unknown (33).

The majority of the studies after both MR-HIFU and USgHIFU treatment were retrospective analyses that could have led to recall bias, and since most studies did not have reproductive outcomes as their primary outcome, often important data was missing, such as the number of women wishing to become pregnant. Moreover, the majority of the available pregnancy data was collected in studies in which, at least partially, a protocol was used that excluded women with a future pregnancy wish. To finalize, when comparing the effect of several uterine treatment options on reproductive outcomes, the age of participants should be more or less equal in each treatment group. Chance of pregnancy in the general population is 20% per cycle at age 30 according to the American Society of Reproductive medicine (34). When reaching 40 years, this drops to less than 5% per cycle. In this review, we found that

the age of women that became pregnant ranged from 23 to 53 years. Because of the small size of the included studies and missing data, no correction for possible prognostic factors, such as age and NPV% could be performed.

Pregnancy, live-birth and miscarriage rate

The available data on pregnancy rate after both HIFU techniques are lower compared to the pregnancy rate of 50 to 68% after myomectomy in infertile women, but higher compared to the 27% in women with untreated submucosal fibroids, both reported in the systematic review by Whynott et al. (3). The live-birth rate in our review was 73% after MR-HIFU and 91% after USgHIFU treatment. This is comparable to the 78% after myomectomy reported by Khaw et al., when ongoing pregnancies were excluded (19). The difference between MRI and US guided HIFU is most likely the result of the difference in NPV% between the two types of HIFU together with the pretreatment fibroid size. In the general population, the risk of miscarriage can be doubled to 14% because of fibroids (3). In our review, miscarriage rates ranged between zero and 50% after MR-HIFU and between zero and 15% after USgHIFU. Two more recent MR-HIFU treatment studies showed the lowest miscarriage numbers (7% and 21%), which is lower compared to the 24% miscarriage rate after removal of subserosal or intramural fibroids by myomectomy (3).

Time to conceive

The follow-up duration was not clearly described in some of the MR-HIFU treatment studies, and generally showed a large range. A short follow-up logically leads to lower chances to become pregnant and might explain low pregnancy rates. In general, women with fibroids need more time to get pregnant (35). Time to conceive after MR-HIFU took eight months in the largest and prospective registry after MR-HIFU and sixteen months in the largest prospective study after USgHIFU. The short time to pregnancy after MR-HIFU is beneficial, especially for older women already struggling with lower pregnancy chances. Women are often advised to wait to become pregnant for at least six months after a myomectomy, to allow adequate postsurgical healing (9). A latency period between HIFU and conception for safety reasons does not seem to be necessary (36).

Complications and mode of delivery

No stillbirths were reported after MR-HIFU, one case after USgHIFU, and no uterus ruptures after both therapies. These results are encouraging, although the number of evaluated pregnancies is low. The risk of a uterus rupture after myomectomy is found to be 0.9% (9). Because of this risk, most women are advised to deliver by CS to prevent a possible rupture (37). CS rate is in general increased in the fibroid population (48.8%) compared to women without fibroids (13.3%) and can be influenced by social

determinants besides medical necessity (2,37). The CS rate after myomectomy of 60% is comparable to our findings after both MR-HIFU and USgHIFU (19). However, the women treated with USgHIFU were mostly treated in China during the one child policy. Lower CS rates are expected when those cultural factors would not interfere. In the 124 pregnancies after MR-HIFU treatment, two cases of placenta previa were described. Six cases were reported after 266 pregnancies after USgHIFU. Since the quality of imaging during treatment is lower during USgHIFU compared to MR-HIFU, it is possible that this leads to more damage to normal endometrium tissue. More data is however necessary to confirm this possibility (16).

Strengths and limitations

We deliberately decided to report reproductive outcomes after MR-HIFU and USgHIFU separately. MRI and US guided HIFU techniques differ and combining these two different types of treatment may lead to inconclusive results (38). Furthermore, we did not include data after other, more-invasive ablation techniques either, since we believe that the non-invasive nature of HIFU treatment might be the advantage of the technique compared to other ablation techniques. The ablation technique RFVTA for example, involves intraperitoneal access when performed laparoscopically and entering the abdomen with electrodes through the serosa may induce injury of healthy muscular layers. This treatment is therefore considered a more invasive procedure (33,39). Moreover, the number of reported pregnancies after RFVTA is very small (19,33). Another strength of this study is that we took into account possible prognostic factors like age, size of the fibroid and reached NPV %. Furthermore, we collected relevant data systematically. The most important limitation of this review is the lack of (large) prospective comparative trials including randomized controlled trials with pregnancy outcome as the primary outcome. Therefore, not enough data is available to provide more certainty on the effect of HIFU for women with uterine fibroids and a desire for pregnancy. Furthermore, the sample size of the included studies was rather small and most of the included studies did not provide data on possible prognostic factors for reproductive outcomes. When evaluating reproductive outcomes it is important to take possible confounders such as age into account (35). Finally, unfortunately no data is currently available to distinguish between the effect of HIFU treatment on reproductive outcome in women with subfertility as their main uterine fibroid symptom, and women with other uterine fibroid symptoms as their main symptoms and a pregnancy wish.

CONCLUSION

In spite of the heterogeneous character of the currently available data on reproductive outcomes after HIFU techniques, pregnancy rate, live-birth rate, miscarriage rate and time to conceive appear to be non-inferior to the current standard of care. Because of the non-invasive character of HIFU and the low number of registered complications, we consider HIFU a promising treatment option for women with symptomatic uterine fibroids and a wish to conceive. Our results underline however the need to perform a randomized controlled trial, comparing reproductive outcomes as primary outcome after HIFU to standard treatment in women with symptomatic fibroids, while applying the latest insights in the HIFU technique where full ablation is a prerequisite for an adequate treatment. Only then, sufficient evidence can be gathered on the preferred treatment in women with (symptomatic) fibroids and a wish to conceive.

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APPENDIX A

Literature search

Cochrane library

Title, abstract, keywords contains:
1 [Leiomyoma] MeSH term: 687 items found
2 [Pregnancy Outcome] MeSH term: 3,604 items found
3 [High-Intensity Focused Ultrasound Ablation] MeSH term: 70 items found
4 #1 AND #2 AND #3: 0 items found
5 #1 AND #3: **11 items found**
Eleven articles screened on title and abstract
Nine articles excluded on title and abstract
Two articles included for full text screening
Zero articles included for final inclusion

Medline/PubMed

Keywords contains:
1 “Leiomyoma” [Mesh]: 21,001 items found
2 Myomas: 7,291 items found
3 “Reproductive Physiological Phenomena” [Mesh]: 1,387,972 items found
4 “Reproductive Health” [Mesh]: 3,449 items found
5 “High-Intensity Focused Ultrasound Ablation” [Mesh]: 2,151 items found
6 “Ablation Techniques”[Mesh]: 115,743 items found
7 ”Focused ultrasound surgery”: 313 items found
8 “Focused ultrasound”: 6,380 items found
9 #1 AND #3 AND #5: 19 items found
10 #1 AND #5: 195 items found
11 #1 AND #7: 88 items found
12 #1 AND #8: 350 items found
13 #1 OR #2 AND #5 OR #8: 6,380 items found
14 #1 OR #2 AND #8: **370 items found**
370 articles available screened on title and abstract
Nine duplicates 361 articles screened on title and abstract
285 articles excluded on title and abstract
76 articles included for full text screening
21 articles included for final inclusion

Embase

Keywords contains:
1 ‘Leiomyoma’/exp → 26,379 items found
2 Myomas → 3,708 items found
3 ‘Reproductive Physiological Phenomena’/exp → 1,294,670 items found
4 ‘Reproductive Health’/exp → 17,660 items found
5 ‘High-Intensity Focused Ultrasound ablation’/exp → 5,604 items found
6 ‘Ablation Techniques’/exp → 50,425 items found
7 “Focused Ultrasound Surgery” → 449 items found
8 “Focused Ultrasound” → 10,379 items found
9 #1 AND #3 AND #5 → 16 items found
10 #1 AND #5 → 126 items found
11 #1 AND #7 → 52 items found
12 #1 AND #8 → 229 items found
13 #1 OR #2 AND #5 OR #8 → 293 items found

14 #1 OR #2 AND #8 → 293 items found
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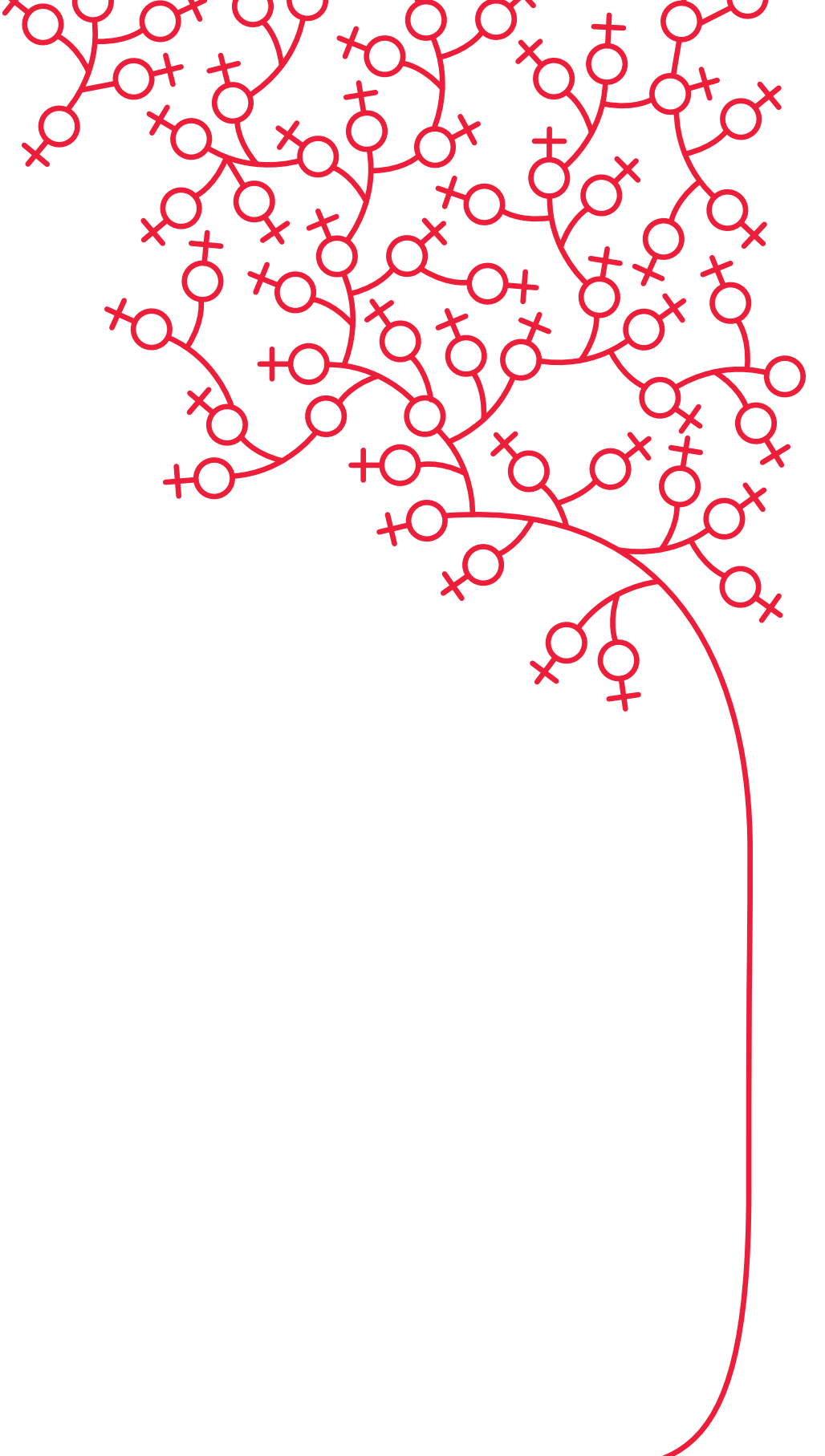
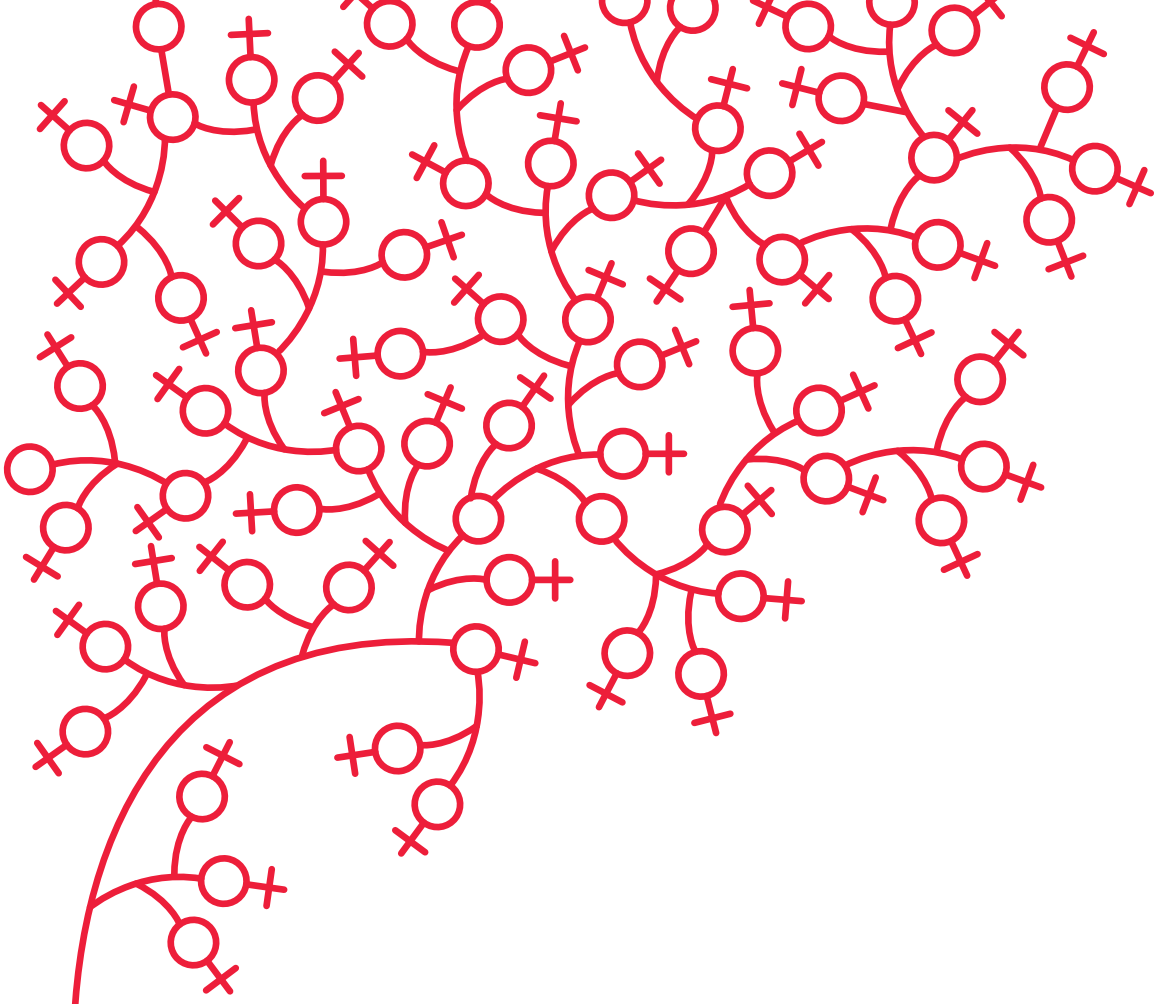
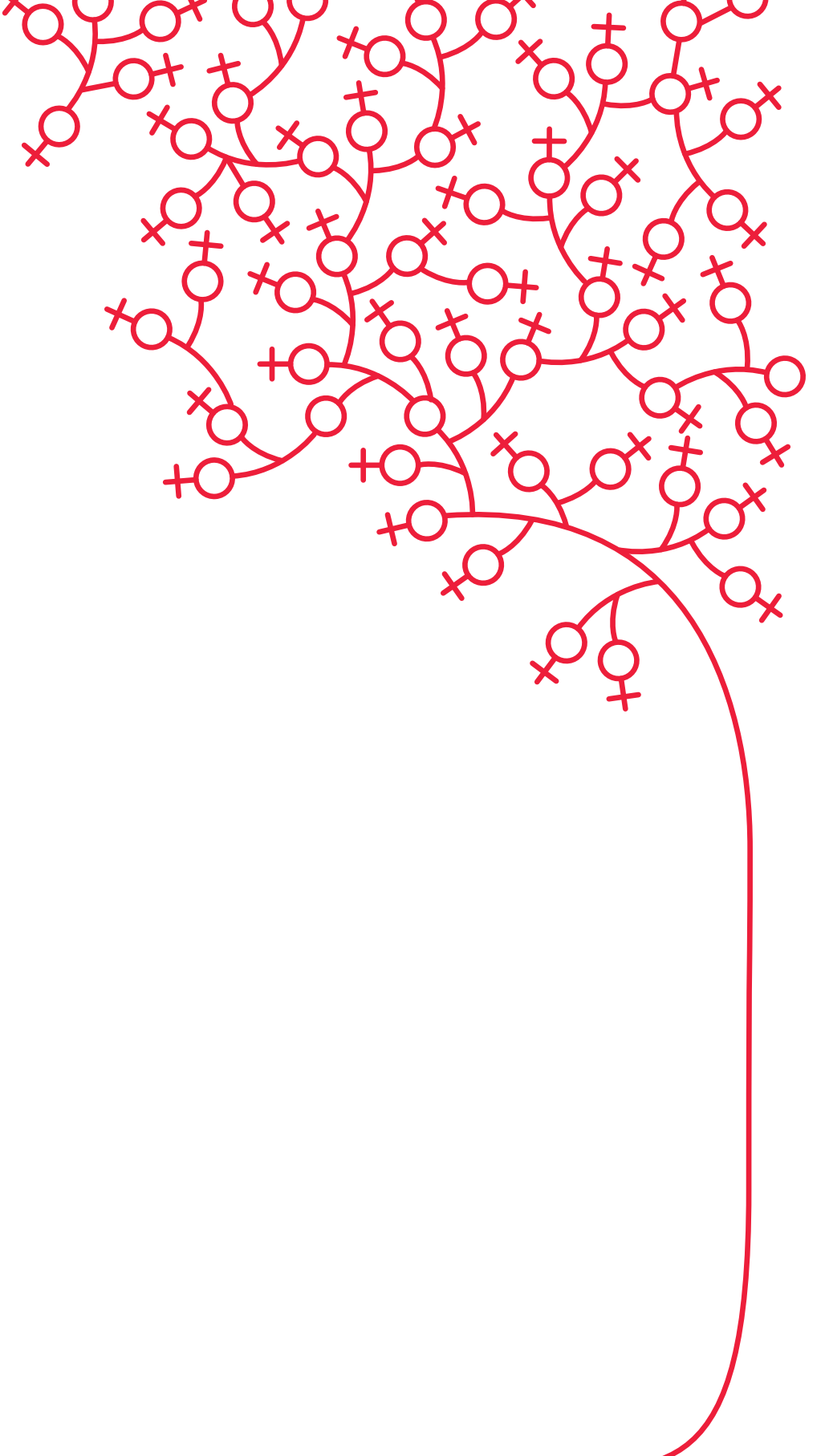
126 articles excluded on title and abstract
19 articles included for full text screening
Zero articles included for final inclusion





PART 2

MEASURES TO IMPROVE EFFECTIVITY



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Lessons learned during implementation of Magnetic Resonance image guided High Intensity Focused ultrasound treatment of uterine fibroids to facilitate future adoption

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ABSTRACT

Background

Although promising results have been reported for Magnetic Resonance image-guided High-Intensity Focused Ultrasound (MR-HIFU) treatment of uterine fibroids, this treatment is not yet widely implemented in clinical practice. During the implementation of a new technology, lessons are learned and an institutional learning-curve often has to be completed. The primary aim of our prospective cohort study was to characterize our learning-curve based on our clinical outcomes. Secondary aims included identifying our lessons learned during implementation of MR-HIFU on a technical, patient selection, patient counseling, medical specialists and organizational level.

Results

Our first seventy patients showed significant symptom reduction and improvement of quality of life at 3, 6 and 12 months after MR-HIFU treatment compared to baseline. After the first 25 cases, a clear plateau phase was reached in terms of failed treatments. The median non-perfused volume percentage of these first 25 treatments was 44.6% (range: 0–99.7), compared to a median of 74.7% (range: 0–120.6) for the subsequent treatments.

Conclusions

Our findings describe the learning-curve during the implementation of MR-HIFU and include straightforward suggestions to shorten learning-curves for future users. Moreover, the lessons we learned on technique, patient selection, patient counseling, medical specialists and organization, together with the provided supplements, may be of benefit to other institutions aiming to implement MR-HIFU treatment of uterine fibroids.

Keywords

Magnetic resonance imaging, Minimally invasive surgery, Uterine fibroids, Learning-curve, MR-HIFU.

BACKGROUND

Uterine fibroids are benign tumors and clinically apparent in 25% of women during their reproductive age. They cause symptoms such as heavy menstrual bleeding, abdominal pain or pressure and subfertility (1). In recent years, new (innovative) therapies for the treatment of uterine fibroids became available. These include hormonal medical therapy such as GnRH analogs or oral contraceptives and non-hormonal medical therapy such as tranexamic acid or non-steroidal anti-inflammatory drugs. Less invasive, non-medical treatment options consist of hysteroscopic removal of submucosal fibroids, endometrial ablation and uterine artery embolization (2). However, despite promising clinical outcomes, implementation in daily practice is challenging (3). One non-invasive treatment that has become available is Magnetic Resonance image-guided High-Intensity Focused Ultrasound (MR-HIFU). This technique can be used for a wide range of benign and malignant diseases including uterine fibroids (4). Complication rate is low and recovery fast (5). Furthermore, because of the uterus-saving character of this treatment, women with a wish to conceive can be treated by MR-HIFU (6). Therapeutic success of MR-HIFU is often measured by the percentage of non-perfused volume (NPV%) compared to the total volume of the fibroid pre-treatment. A high NPV% is closely related to treatment results and, in particular, clinical effectiveness (5). To achieve a high NPV%, proper screening of eligible patients is essential but remains a challenging task that needs to be further improved (7).

Clinical and technical aspects of the MR-HIFU treatment have already been reported in detail (5,8,9). Learning-curves of the MR-HIFU treatment for fibroids and suggestions on how to implement MR-HIFU treatment have also been described , however, were not the primary goal of these studies (8,10,11). In the present study, we assessed the learning-curve during the implementation of the MR-HIFU treatment of uterine fibroids in our center as our primary objective. Our secondary objective was to inventory all hurdles we needed to overcome and the lessons we learned during the implementation process. In this way, we aimed to facilitate future implementation of this new innovative technique.

METHODS

Study design and protocol

We designed a single-arm prospective cohort study (the Myoma Screening Study; MaSS; registry ID ISRCTN14634593). This study consisted of two parts; both parts were approved by our medical ethical board and participants needed to sign informed consent

before participating. The implementation of the MR-HIFU treatment described in this article concerns participants of the second part, the MaSSII study.

MaSSI

In the first part (MaSSI; protocol ID NL53499.075.15) we aimed to get an overview of the uterine fibroid tissue type distribution using multiparametric magnetic resonance imaging (MRI) parameters (sagittal and axial T2-weighted turbo spin echo, T1-weighted contrast enhanced 3D fast field echo, short-TE and long-TE DWI series and T2-mapping, Additional file 1) on a 1.5-T Achieva MRI scanner (Philips Healthcare, Best, The Netherlands) (7). All women consecutively visiting our gynecology department between December 2015 and January 2019 because of symptomatic uterine fibroids, as confirmed by vaginal ultrasound, were offered an MRI scan after counseling and signing informed consent, independent of their eligibility for the MR-HIFU treatment.

MaSSII

The primary aim of the second part (MaSSII; protocol ID NL56182.075.16) was to explore whether biomarkers found by the multiparametric MaSSI MRI scan could predict MR-HIFU treatment outcome. Women participating in the MaSSI study between June 2016 and January 2019 and eligible for MR-HIFU, were offered the MR-HIFU treatment option. Inclusion criteria were women with uterine fibroid-related symptoms, aged between 18 and 59 years and pre- or perimenopausal status. Women were excluded when post-menopausal, pregnant, not willing or able to sign informed consent, had a wish to conceive, a BMI > 40 kg/m2, had a previous embolization or contraindications to undergo an MRI scan. Based on the MaSSI MRI scan women were eligible in case of a subcutaneous fat layer < 4 cm, a fibroid diameter between 1 and 10 cm, one or two dominant fibroid(s) likely to cause the clinical symptoms and no calcified fibroids. The Funaki classification, which classifies fibroids into Funaki type 1, 2 or 3 fibroids based on signal intensity on T2-weighted MRI images, was also used as a screening tool (Figure 1) (7,12). Fibroids classified as a Funaki type 1 or 2 fibroid were considered eligible for the MR-HIFU treatment. Relative contra-indications of MR-HIFU included Funaki type 3 fibroids, interposed bowel loops or ovaries and a retroverted uterus. MaSSI participants who also participated in the MaSSII study were again counseled and signed a second informed consent form. After signing this informed consent, women were asked to fill out the Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire (UFS-QoL) (13).

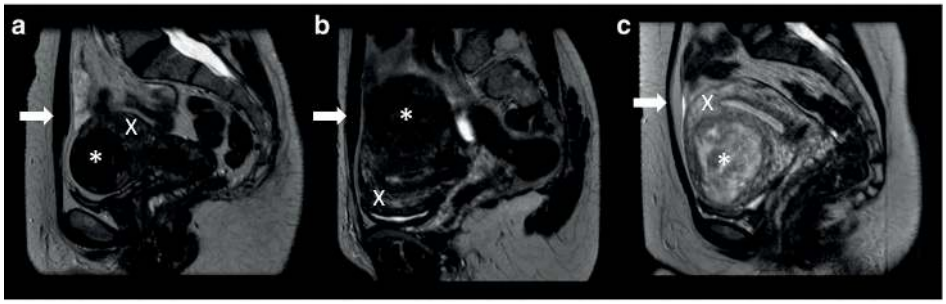

Figure 1: Funaki classification. a Funaki I fibroid (signal intensity lower than myometrium and muscle); b Funaki II fibroid (signal intensity lower than myometrium, but higher than muscle); c Funaki III fibroid (signal intensity higher than muscle and myometrium). Asterisks (*) are located in the uterine fibroid. Arrows point at abdominal muscle. Cross (X) is located in myometrium tissue.

MR-HIFU treatment

Pre-treatment

When women were considered eligible for MR-HIFU treatment and willing to participate, they were screened at the anesthesiology department and received information about the conscious sedation during the MR-HIFU procedure. The evening before the treatment, women had to shave their lower abdomen and had to fast overnight. In the morning at admission to day care, women received a bladder catheter, an enema, an intravenous line and pre-medication (Additional file 1). Women were placed in prone position in the MRI scanner, and a pretreatment MRI scan was performed for a final fibroid position check. The MR-HIFU treatment was performed on the Sonalleve V1 (Profound Medical Inc., Mississauga, Canada), integrated into a 1.5-T Achieva MRI scanner (Philips Healthcare, Best, The Netherlands). Our sedation protocol included continuous propofol 20 mg/ml infusion between a 1 ml/hour and 12 ml/hour rate and administration of fentanyl bolus of 25 µg/0.5 ml or 50 µg/1.0 ml (Additional file 1) depending on experienced pain.

Treatment

MR-HIFU fibroid ablation combines high-intensity focused ultrasound with real-time MRI. A focused ultrasound beam targets uterine fibroid tissue and induces coagulative necrosis (14). Safety is provided by MR thermometry that measures almost real-time heating of the targeted tissue and critical surrounding structures (15). We aimed for complete ablation of the fibroid (16), and our therapy strategy was to ablate the complete posterior part of the fibroid first, followed by the middle and anterior part of the fibroid (17).

During the treatment, both the patient and the attending radiologist could press an emergency button if necessary, which would result in an immediate stop of the current sonication. After the last sonication, a contrast agent (gadoteric acid—gadoterate meglumine, 0.1 mmol/kg) was administered to assess the NPV%.

Post-treatment

After the procedure, patients stayed at day care for a few hours. Before discharge, the radiologist visited the patient to check for vital parameters, adverse events like (radiating) pain and possible signs of skin burn of the abdomen. If no irregularities were found, patients could leave the hospital the same day. Follow-up by the gynecologist was planned one week after treatment, and 3 and 6 months post-treatment at the outpatient clinic (Additional file 1). Recovery, possible adverse events and the decrease in symptoms were discussed with the patient during these follow-up appointments.

Data collection

Data concerning the treatment (e.g., treatment time, reached NPV%) were collected in a standardized form, and an MRI report was added to the electronic patient file (Additional file 1). In case more than one fibroid was treated, NPV% of all fibroids was collected. When complete ablation was not achieved, the most likely reason for this was recorded after internal discussion within the treatment team. Six months after treatment, a follow-up MRI scan was performed to measure the fibroid's size and the remaining NPV%. Fibroid volume and NPV%, collected from the screening MRI scan, the MRI scan immediately after treatment and the 6-month follow-up MRI scan, were measured by K.A. and I.V., both two years of experience with uterine fibroid MR-HIFU, using IntelliSpace Portal (ISP) software (Philips Healthcare) by semiautomatic segmentation in the tumor tracking function with review and manual correction of the segmentation (7). In case more than one fibroid was treated, volume (changes) and NPV% (changes) were measured for all treated fibroids. Adverse events during recovery were recorded in the electronic patient file and classified according to the classification of surgical complications, ranging between grade I (any deviation from the normal postoperative course) and grade V (death of a patient) (18).

Patients received the UFS-QoL questionnaire at 3-, 6- and 12-month follow-up. Differences by 10 points between baseline and follow-up on the 0–100 scale were considered clinically relevant (5). In February 2020, after an MaSSII protocol addendum was approved (dated 07-11-2019) by our medical ethical board, manually electronic patient file search was performed to screen for possible reinterventions and pregnancy outcomes of all included patients. Second MR-HIFU treatments for different fibroids were not considered as reinterventions, nor were (re)start of medication or an intra-uterine device. Women were requested not to fill out the follow-up UFS-QoL questionnaire after a reintervention.

Assessment of the learning-curve

During MaSSII inclusions, all failed treatments were logged and analyses to determine the most probable cause of failure took place immediately by the involved treatment team. When solutions were available, they were directly implemented in upcoming treatments

and date of implementation was recorded. After finishing MaSSII inclusions, all causes of treatment failure were categorized and their occurrence in time, revealed an expected learning-curve per type of failure. We then evaluated our expected learning-curve by comparing reached NPV%, symptom and QoL improvement and reintervention rates between those women treated during and those women treated after completing our learning-curve.

Evaluation of implementation process

While implementing MR-HIFU in our hospital, different process steps were taken (Table 1) (19). The implementation process was coordinated by an MR-HIFU radiologist who was appointed as principal investigator. A dedicated multidisciplinary team was installed, including two gynecologists, four (intervention) radiologists, a medical clinical physicist and an anesthesiologist. This multidisciplinary team defined the implementation goals together with additional stakeholders in our institution after an inventory of current uterine fibroid healthcare in our hospital was executed. Stakeholders included other physicians, hospital board members, administration staff, financial experts, epidemiologists, technicians and nursing staff of the gynecology, radiology and anesthesiology department. A PhD candidate was responsible for the documentation of all steps in the implementation process, and communication between gynecology, radiology and anesthesiology departments. When facing implementation hurdles or treatment failures, consultation between members of the study team led to the development and selection of improvement suggestions. The formulated lessons learned as a result of these consultations, were categorized on a technical, patient screening, patient counseling, medical specialist or organizational level. Alterations on these levels were documented in the relevant protocols, presented to the involved parties and carried through during the MaSSII study.

Table 1: Different steps used during implementation process.

	Description of step
Step 1	Development proposal of change
Step 2	Analysis of actual care, defining implementation goals
Step 3	Problem analysis, target group and setting
Step 4	Development and selection of interventions
Step 5	Develop, test and execute implementation plan
Step 6	Integration into daily practice
Step 7	Evaluation: reflection on outcome measures

Statistics

Statistical analyses were performed using IBM SPSS version 26. Categorical data were presented as numbers and percentages. Continuous variables were presented as mean

(SD ±) in case of normal distribution or median (range) in case of skewed distribution. Distribution was assessed by the Shapiro–Wilk test and complemented by plots. Differences between symptom severity (transformed Symptom Severity Score; tSSS), QoL (transformed Health-Related Quality of Life score; tHRQL), NPV% and fibroid volume at baseline/directly post-treatment and follow-up were tested by means of the Wilcoxon signed rank test. Differences between age, BMI, fibroid diameter, tSSS, tHRQL, NPV% and fibroid volume of women that were treated during the learning-curve phase and women that were treated after this phase were assessed by the Mann–Whitney U test. A p value of < 0.05 was considered significant. Multiple testing correction was performed using the Holm–Bonferroni method. To estimate confounding by loss-to-follow-up, we compared NPV% between patients who completed the questionnaires during follow-up and patients who were lost to follow-up.

RESULTS

In total 168 women were included in the MaSSI study. Seventy women (41.7%) with 102 fibroids were treated as part of the MaSSII study. Demographic characteristics and fibroid characteristics are described in Table 2. Four of seventy women were treated twice as a result of a failed procedure at the first attempt, and two other women were treated twice for different fibroids. Thus, a total of 76 treatments (64 women with one treatment and six women with two treatments) could be analyzed in more detail.

The median of the NPV% after treatment was 66.5% (range: 0–120.6; Table 3). In seventeen out of seventy women, a grade 1 adverse event was reported on treatment day (18). This included mostly pain or nausea. One woman experienced strength loss in one leg, which was self-limiting. Another woman had a third-degree skin burn (grade 3b adverse event) which needed additional recovery surgery. During follow-up, one woman suffered from pain in her lower arm as a result of nerve compression due to the prone position during MR-HIFU, which resolved without sequelae. Two women experienced a urinary tract infection and were treated with antibiotics. At 12 months, 36 patients were lost to follow-up for the UFS-QoL questionnaires since they did not fill in the questionnaire, even after being reminded both digitally and by phone, or they had undergone a reintervention. There was no statistically significant difference in NPV% between women who completed all questionnaires and those who did not ($p = 0.13$). tSSS was significantly reduced at all follow-up points when compared to baseline, tHRQL score was significantly increased compared to baseline (Table 4). The clinically relevant 10-point difference was reached as well.

Table 2: Demographic and clinical characteristics of 70 women who underwent MR-HIFU treatments.

Characteristics of all 70 women		**Characteristics of first 22 women**		**Characteristics of remaining 48 women**	
Age (years) median [range] 46.0 [26-57]		Age (years) median [range] 47.0 [41-57]		Age (years) median[range] 45.0 [26-54]*	
BMI (kg/m^2) median [range] 24.3 [17.5-35.5]		BMI (kg/m^2) median [range] 24.0 [20.4-31.9]		BMI (kg/m^2) median [range] 24.6 [17.5-35.5]	
Characteristics of all 76 treatments		**Characteristics of first 25 treatments**		**Characteristics of remaining 51 treatments**	
Amount of fibroids treated N(%)		Amount of fibroids treated N(%)		Amount of fibroids treated N(%)	
1	61 (80.3%)	*1*	24 (96.0%)	*1*	37 (72.5%)
2	6 (7.9%)	*2*	1 (4.0%)	*2*	5 (9.8%)
3	6 (7.9%)	*3*	0	*3*	6 (11.8%)
4	2 (2.6%)	*4*	0	*4*	2 (3.9%)
5	1 (1.3%)	*5*	0	*5*	1 (2.0%)
Characteristics of all 102 fibroids		**Characteristics of first 21 fibroids**		**Characteristics of remaining 81 fibroids**	
Location N (%)		Location N (%)		Location N (%)	
Submucosal	27 (26.5%)	Submucosal	6 (28.6%)	Submucosal	21 (25.9%)
Intramural	26 (25.5%)	Intramural	3 (14.3%)	Intramural	23 (28.4%)
Subserosal	33 (32.4%)	Subserosal	9 (42.9%)	Subserosal	24 (29.6%)
Hybrid	16 (15.7%)	Hybrid	3 (14.3%)	Hybrid	13 (16.0%)
Funaki type	N (%)	Funaki type	N (%)	Funaki type	N (%)
1	10 (9.8%)	1	1 (4.8%)	1	9 (11.1%)
2	83 (81.4%)	2	19 (90.5%)	2	64 (79.0%)
3	9 (8.8%)	3	1 (4.8%)	3	8 (9.9%)
Diameter (cm) median [range] 4.8 [1.4-18.1]		Diameter (cm) median [range] 6.0 [1.7-10.3]		Diameter (cm) median [range] 4.6 [1.4-18.1]	

The 22 women treated in the first 25 treatments (second column) were compared to the 48 women treated in the remaining 51 MR-HIFU treatments (third column). * p=<0.05 between the first 22 and second 48 women treated.

Table 3: Treatment results and follow-up data.

Treatment outcomes	N (%), median[range]
NPV% directly after treatment	66.5% [0-120.6]
First 25 treatments: 21 fibroids	44.6% [0-99.7]*
Remaining treatments: 81 fibroids	74.7% [0-120.6]**
Adverse events per woman	
Grade 1 adverse event on treatment day	17/70 (24.2%) pain/nausea
Grade 3b adverse event on treatment day	1/70 (1.4%) 3th degree skin burn
Grade 1 adverse event follow-up	22/70 (31.4%) pain/ bleeding
Grade 2 adverse event follow-up	2/70 (2.9%) urinary tract infection
Adverse events needing treatment	3/70 (4.3%) antibiotics/operation
Volume decrease of fibroids with an available MRI scan at 6 months follow-up	42.4% [-173.2-100]
First 25 treatments: 14 fibroids	31.7% [7.1-62.2]
Remaining treatments: 70 fibroids	48.3% [-173.2-100]
Reintervention rate per woman	19/70 (27.1%)
Hysterectomy	10/19 (52.6%)
Myosure	2/19 (10.5%)
UAE	4/19 (21.1%)
MR-HIFU	4/19 (21.1%)
First 22 women	10/22 (45.5%)
Second 48 women	9/48 (18.8%)
Moment of reintervention	8 months [1-27]
Follow-up duration	24 months [14-44]
Failure of treatment	19/76 (25.0%)
First 25 treatments	12/25 (48.0%)
Second 48 treatments	7/51 (13.7%)
Kind of failures	
Treatment	13/19 (68.4%)
Heating	6/19 (31.6%)

* p=<0.05 between the first 25 and second 51 treatments. ** An NPV% of >100% could be found when the measured NPV volume exceeded the measured volume of the fibroid at screening MRI scan. This could be caused by either fibroid growth, measurement accuracies or increase of the fibroid directly after treatment due to treatment effect.

Table 4: UFS-QoL questionnaire scores at baseline, 3, 6 and 12 months follow-up.

All women	Baseline N=70	3m N=61	6m N=55	12m N=37
tSSS	50.4 ±SD15.9	36.0 ±SD16.9 Δ-14.4*	31.2 [range:0-78.1] Δ-19.2*	32.6 ±SD18.1 Δ-17.8*
tHRQL	57.4 ±SD19.0	70.0 [range:13-100] Δ12.6*	80.0 [range:10-100] Δ22.6*	73.5 ±SD19.3 Δ16.1*
First 22 women	**baseline**	**3m N=17**	**6m N=17**	**12m N=13**
tSSS	48.6 ±SD14.8	33.6 ±SD15.3 Δ-15*	32.0 ±SD23.9 Δ-16.6*	30.5 ±SD18.1 Δ-18.1*
tHRQL	63.5 ±SD17.9	72.5 ±SD15.3 Δ9	83.0 [range:10-98] Δ19.5	78.0 ±SD17.0 Δ14.5*
Second 48 women	**baseline**	**3m N=44**	**6m N=38**	**12m N=24**
tSSS	51.3 ±1SD6.5	37.0 ±SD17.5 Δ-14.3*	33.5 ±SD18.9 Δ-17.8*	33.8 ±SD18.4 Δ-17.5*
tHRQL	54.6 ±SD19.0	70.1 ±SD19.5 Δ15.5*	79.5 [range:21-100] Δ24.9*	71.0 ±SD20.4 Δ16.4*
P-value	p=0.33 and p=0.06	p=0.56 and p=0.78	p=0.69 and p=1.00	p=0.53 and p=0.37

Showing all women and divided in the first 22 and second 48 women treated. Δ shows the absolute difference with baseline and *shows a significant difference (p=<0.05) compared to baseline. The bottom row of the table shows p-values of the difference between the first 22 and second 48 women treated for tSSS or tHRQL at that particular time point, tested by Mann-Whitney U test. **Multiple testing correction was performed using the Holm-Bonferroni method.

Median follow-up time for the assessment of reinterventions was 24 months (range: 14–44). A total of nineteen women (27.1%) needed a reintervention. One woman needed two reinterventions. The median NPV% post-treatment of women that underwent a reintervention was 4.5% (range: 0–98.3). Fifteen of twenty reinterventions (75%) took place in the first 12 months and nineteen of twenty reinterventions (95%) in the first 24 months after the initial MR-HIFU treatment.

Learning-curve

A total of 25% (19/76) of the treatments could be classified as treatment failures due to different reasons (Table 5).

During thirteen treatments, bowels, ovaries or an abdominal scar obstructed the sonication beam pathway to such an extent that a too small part of the fibroid was accessible for sufficient sonications or treatments failed due to patients experiencing too much pain leading to preliminary abortion of sonications. The remaining six treatment failures were all due to inadequate heating of the fibroid tissue.

Table 5: Overview of failed treatments, reason of failure and possible solution.

Treatment number	Patient number	Category failure	Kind of failure	Possible solution
1	1	Treatment	Interposition of bowel	New manipulation protocol
2	2	Treatment	Abdominal scar in pathway	New manipulation protocol
3	2	Treatment	Abdominal scar in pathway	New manipulation protocol
4	3	Treatment	Interposition of bowel	New manipulation protocol
5	3	Treatment	Interposition of bowel	New manipulation protocol
6	4	Treatment	Interposition of bowel	New manipulation protocol
7	5	Treatment	Interposition of bowel, part unreachable because of distance and abdominal scar	New manipulation protocol
8	6	Treatment	Interposition of bowel and small fibroid	New manipulation protocol and breath hold instructions
9	7	Treatment	Pain, interposition of bowel	New manipulation protocol and alterations in sedation protocol
10	8	Heating	Pain, no adequate heating and part unreachable	Alterations in sedation protocol and adequate screening of patients
11	9	Treatment	Pain during treatment	Alterations in sedation protocol
12	10	Heating	No adequate heating	Adequate screening of patients
13	11	Heating	No adequate heating	Adequate screening of patients
14	12	Heating	No adequate heating	Adequate screening of patients
15	13	Treatment	Interposition of bowel	New manipulation protocol
16	14	Heating	No adequate heating	Adequate screening of patients
17	15	Heating	No adequate heating	Adequate screening of patients
18	16	Treatment	Interposition of bowel	New manipulation protocol
19	17	Treatment	Interposition of bowel	New manipulation protocol

The occurrence in time of the nineteen treatment failures was analyzed. Of these failures, twelve occurred within the first 25 treatments, resulting in a failure rate of 48% (12/25, Figure 2). The remaining treatment failures occurred after the 25 treatments, resulting in a failure rate of 14% (7/51). This means that not all failures occurred during our learning-curve. However, the cause of the failures during and after the learning-curve differed. Eleven of the twelve failures during first 25 treatments, could be attributed to inexperience and solved by alterations in the treatment protocol. Six out of seven failures, after completing the learning-curve, did not seem to be the result of inexperience, but rather the result of the extension of the inclusion criteria and as a result including more challenging cases with a higher risk on failure. We therefore considered the first 25 treatments our learning-curve. This learning-curve included 22 women, since three women were treated twice within these first 25 treatments (Table 2). Women treated during the learning-curve were significantly older (p = 0.005), and the NPV% immediately post-treatment was significantly lower (44.6% range: 0–99.7 versus 74.7% range 0–120.6; p = 0.011). The percentage of women with a reintervention after the first 25 treatments was 45.5%, compared to 18.8% after the remaining treatments (Table 3). The degree of symptom reduction and QoL improvement after the first 25 and the subsequent treatments also differed, albeit not statistical significantly (Table 4).

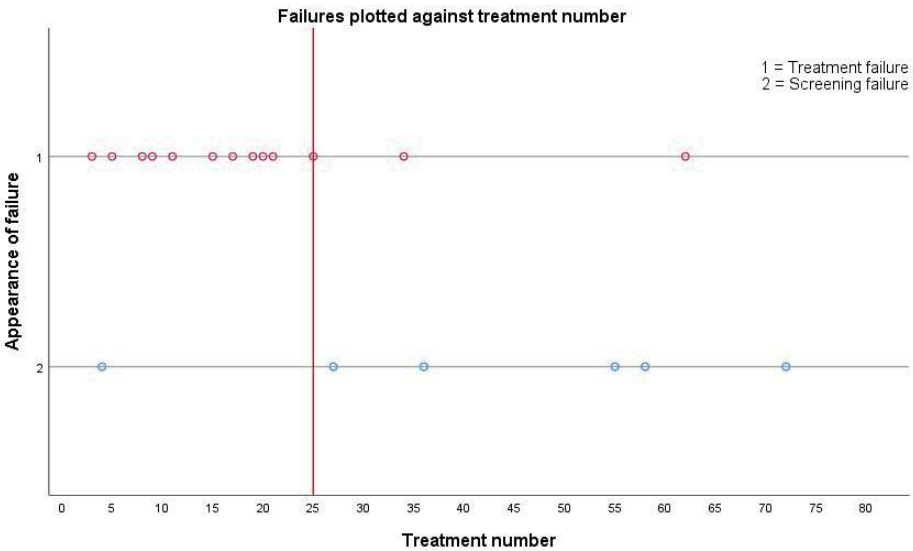

Figure 2: Appearance of treatment failure when plotted against the number of treatments. Blue dots represent treatment failures; pink dots represent screening failures.

Table 6: Different identified barriers and lessons learned on technical, patient selection, patient counseling, medical specialist and organizational level.

Level	Barriers	Lessons learned
Technique	1. Malfunction of device 2. Treatment failures resulting in low NPV% • Bowel/ovaries in sonication beam pathway • Abdominal scar in sonication beam pathway • Abortion of sonication as a result of experienced pain • Motion artefacts in case of small fibroids	1. Ensure well-trained technical medical staff 2. Facilitate site visitation by proctor before start 3. Train team after every update of device 4. Ensure the possibility of remote consultation of device manufacturer 5. Optimize manipulation protocol 6. Ensure continuous feedback from patient during treatment 7. Be able to perform alterations in treatment strategy: longer intermissions between sonications, wider distribution of sonication, altered wattage of sonication 8. Use a light or moderate sedation protocol with the possibility to perform patient specific alterations 9. Use breath holding instructions in case of small (<3cm diameter) fibroids
Patient selection	1. Low eligibility number 2. Heating failures resulting in no or low NPV% 3. High number of adverse events 4. Misinterpretation of retention bladder 5. Low NPV% resulting in high reintervention rate 6. No uniformity in collected MRI data leading to difficulties in assessing eligibility 7. No uniformity in collected MRI data of treatment effect in follow-up	1. Expend inclusion criteria based on recent literature and gained experience 2. Keep in mind that multiple inclusion criteria combined can lead to unsuitable patients 3. Use the latest equipment version including an integrated cooling system 4. Keep in mind that a uterine fibroid on a bladder ultrasound, performed after removal of a catheter, can be mistaken for urinary retention and therefore lead to unnecessary interventions 5. Manipulation and sedation protocol optimization can contribute to a high NPV% 6. Develop MRI scan review templates, either for screening, treatment or follow-up leads to uniform data collection
Patient counseling	1. Inadequate counseling 2. To high expectations of treatment effect	1. Facilitate additional counseling performed by a direct involved member of the treatment team 2. Emphasize on realistic expectations of MR-HIFU treatment and timespan of treatment effect
Medical specialists	1. Fear for loss of income at gynecology department 2. Responsibility for patient on treatment day	1. Collect referral data 2. Perform substitution analysis 3. Appoint a responsible medical specialist for screening, treatment day and follow-up

Table 6: Different identified barriers and lessons learned on technical, patient selection, patient counseling, medical specialist and organizational level. (*continued*)

Level	Barriers	Lessons learned
Organization	1. Unfamiliar with implementation of new treatment option 2. Lack of research department in non-academic hospital 3. Lack of nursing ward in radiology department and unfamiliarity with MR-HIFU treatment on nursing ward. 4. Sparse MRI scanner time and time consuming preparations	1. Invest in infrastructure (e.g. a research unit) to smoothen the implementation process 2. Involve all responsible parties (e.g. medical specialists) from the start to feel jointly responsible for success of implementation 3. Train nurses and develop a standardized nursing protocol 4. Develop a Standardized Operating Procedure (SOP) besides a nursing protocol to save sparse MRI scanner time and improve both efficiency and safety 5. Add administration of carbetocin during treatment to improve sonication efficiency

DISCUSSION

In this paper we defined our learning-curve and described the implementation process of MR-HIFU treatment of uterine fibroids in our non-academic teaching hospital. Overall, we observed a significant symptom reduction and increased QoL at three, six and twelve months of follow-up and reached a median NPV of 66.5% directly after MR-HIFU treatment. It became clear that most treatment failures occurred during the first 25 treatments, resulting in both increase in NPV% and decrease in reintervention rate when we compared the first 25 treatments to the remaining 51 treatments. We therefore considered the first 25 treatments our learning-curve. During implementation of MR-HIFU and evaluation of our clinical results, we identified various hurdles that needed to be overcome and lessons that needed to be learned. We ordered those lessons on the level of technique, patient selection, patient counseling, medical specialists and organization (Table 6) and comment on most of these in this section.

Technical level

On top of the 76 described treatments in the result section, three additional treatments were planned, but treatment could not take place. Twice this was due to malfunction of the device and once due to a power cut at the radiology department. No solution could be found during the treatment, even after consulting the technical team of our hospital and the experts of the vendor. During two other treatments, that were included in the result section, malfunction of the device occurred as well, leading to a delay of treatment and/or the decision to stop the treatment prematurely because of lack of time. We therefore

believe that manufacturers should continue to focus on prevention of these malfunctions and these problems emphasize the importance of well-trained technical staff that can be consulted when needed.

The advantages we experienced by using a manipulation protocol, and the advantages of the protocol we used, were described before (5,20,21) and included the

following three steps: (1) the BRB (bladder filling, rectal filling, bladder emptying) maneuver with adjusted rectal filling by adding psyllium fibers to the solution; (2) Trendelenburg position combined with bowel massage; (3) the manual uterine manipulation (MUM) method for uterine repositioning. Verpalen et al. showed the eligibility improvement of our patient population after implementing this manipulation protocol in detail before (21).

Women with an abdominal scar in the beam pathway could be treated by repositioning the patient to avoid skin burns and without using a scar pad (8). As described before by Mindjuk et al., in case heating through the scar is unavoidable, special attention to near field heating close to the skin, combined with the patients' feedback experiencing pain, is required and results in more safe treatments. Furthermore, longer intermissions between sonications, wider distribution of the sonications in the fibroid or use of a lower wattage are advised (5).

To reduce failures as a result of experienced pain by the patient, our sedation protocol was optimized. Procedural Sedation and Analgesia (PSA) is increasingly used during uncomfortable radiological interventions and is also suitable for the MR-HIFU treatment of fibroids (22,23). Sedation is performed to prevent the patient from deep visceral pain, hot sensations on the skin and motion artifacts. Light to moderate sedation results in regular breathing patterns and quick recovery, whereas deep sedation can lead to irregular breathing patterns and involuntary motions. These instable breathing patterns and involuntary motions can complicate the procedure and communication of patients about pain or discomfort during the procedure, which could lead to adverse events like skin burns (23). Initially we used only light sedation, but after 25 patients we liberated our protocol and left more room for an increased administration of both sedatives and analgesics to a moderate sedation level (Additional file 1).

The six remaining failures during treatment, in which the fibroid could not be adequately heated, occurred when we extended our inclusion criteria. In retrospect, manage the previous described treatment failures, and started including fibroid types not suitable for MR-HIFU treatment.

When analyzing all failures in time, it became clear that most treatment failures occurred within the first 25 treatments and therefore we considered this our learning-curve. Earlier studies reported the existence of a learning-curve during implementation of the MR-HIFU treatment of uterine fibroids (24,25). Okada et al. observed a significant increase in NPV% and decrease in reinterventions when comparing the first 144 treatments performed in four different clinics (not equally distributed) to the second 143 performed treatments (11).

Mindjuk et al. also mentioned an increase in NPV% due to learning-curve effect and in a previous publication of the same group, the improvement of technique was appointed to be a main reason for this clinical treatment improvement (5,26) This is in line with our study showing that the NPV% achieved immediately post-treatment increased significantly after the first 25 treatments from 44.6 to 74.7%. An NPV of 74.7% is similar to other studies using a full-ablation protocol, reporting NPV percentages between 45.4 and 97.7%. Furthermore, our mean decrease in fibroid volume of 42.4% at 6-month follow-up, is comparable with previous literature as well, with a median fibroid volume decrease of 36.6% after 6 months in the systematic review by Verpalen et al. (16). After overcoming our learning-curve, we had a reintervention rate of 18.8%, with a median follow-up of 24 months, which is comparable to UAE (20% in Volkers et al.), but higher compared to the previous publication by Mindjuk et al. (12.7%, mean NPV 88.7%) with a comparable mean follow-up of 19.4 months (5,27). This is most likely the result of our lower NPV%. As Mindjuk et al. emphasize in their paper, reintervention rate is closely related to NPV% and an NPV% above 80% leads to clinical success rate in 81%, compared to 51% in case of an NPV below 80% (5).

Patient selection

When our initial inclusion and exclusion criteria were applied to the women participating in our MaSSI study, 47.6% (80/168) of women would have been eligible for MR-HIFU treatment. We found that the risk on failure was particularly high in case of deep sonications (10–12 cm from skin to fibroid) and/or a thick abdominal fat layer (3–4 cm) in combination with high signal intensity on the T2-weighted MRI scan (Funaki 2 or 3). When this combination of factors is present, restraints should be exercised in the decision to treat this patient.

As we gained experience, we adjusted our inclusion and exclusion criteria to increase eligibility, particularly fibroids classified as Funaki 3 fibroids. We experienced that several Funaki 3 fibroids could successfully be treated, although including high signal intensity fibroids also led to treatment failures. Therefore at this point, we are reluctant to include Funaki 3 fibroids.

Initially, we intended to treat only women with one fibroid. However, if more than one but less than five fibroids seemed to cause symptoms, more fibroids were treated from June 2017 (after 22 treatments) onward. In October 2017 (after 26 treatments) we implemented our new manipulation protocol (21), and from November 2017 (after 29 treatments) onward, future pregnancy wish was no reason for exclusion anymore. These changes also led to increased eligibility of patients. After extending our inclusion criteria, we retrospectively analyzed that our eligibility rate would have been 69.6% (117/168) when applied on all MaSSI participants. This percentage is much higher than reported in other, older, studies where the eligibility ranged between 23 and 27% (17,28).

In 26% (18/70) of patients, an adverse event on treatment day occurred (Table 3) and in 4.3% (3/70) an event needed additional treatment. The use of a dated version

of the device without an integrated cooling system might have caused a higher risk for health-related adverse events (1.4% of all complications) (16, 29). In the latest version of the Sonalleve (V2 tabletop), an integrated cooling system cools down the skin temperature after every sonication. Use of the V2 might have prevented skin burns in our case.

Patient counseling

Counseling of patients about the different fibroid treatment options, including MR-HIFU, was performed by the gynecologist. However, since MR-HIFU is performed by radiologists, additional counseling by radiologists is recommended for those patients who opt for MR-HIFU. At the beginning of our study, we experienced very high expectations of the effect of MR-HIFU, particularly concerning the time women could expect improvement. Later, more emphasis was put on realistic expectations and the timeline.

Differences in perspective from the involved medical specialists

In order to successfully implement MR-HIFU treatment of uterine fibroids, collaboration between radiologists and gynecologists is essential (8). Since MR-HIFU is performed at the radiology department, the gynecology department initially feared loss of revenues due to a decrease in fibroid-related surgeries after MR-HIFU implementation. However, the implementation of the MR-HIFU treatment led to a higher referral rate from other institutions so that the total number of patients in need for surgical treatment options did not decrease.

In order to manage expectations of all stakeholder, we advise to register patients' referral patterns and costs of alterations in these patterns for both radiology and gynecology departments. This registration can be used as input for a budget impact substitution analysis

to predict potential negative financial consequences for both the gynecology and radiology department by loss of revenues and increased costs, respectively.

Since the MR-HIFU treatment was performed by the radiologist and the follow-up was handled by the gynecologist, clear agreements needed to be made on who had which responsibilities at what stage with regard to the patient. We decided in our institution that the radiologist was responsible during treatment and the following 24 h, the gynecologist was responsible from 24 h after treatment onward.

Organization level

Implementation of a new treatment can be challenging, and publications on process evaluation or implementation strategy are scarce in general (30). We appointed a full-time PhD candidate to support the MR-HIFU team with implementation, setting up the workflow and clinical protocols. For successfully introducing the MR-HIFU technology, we acknowledged that a multidisciplinary treatment concerning different medical specialties, requires close collaboration between departments to be successful. We therefore updated all stakeholders during the entire implementation process, which is highly recommended to ensure shared responsibility to make implementation successful.

Before we started with the implementation of MR-HIFU, we could not find formats such as template reports of screening MRI scans, multidisciplinary meetings and Standard Operating Procedure (SOP's). We expected that these documents would reduce logistic barriers, would improve efficiency and effectiveness and would facilitate implementation. Since the radiology department did not have a nursing ward, nurses needed to be trained to take care of our MR-HIFU patients at the gynecology department. A standardized nursing protocol was implemented in June 2017. Additionally, we implemented preparations at the gynecology ward, such as the blather catheter, premedication and IV-line to increase efficiency and save valuable MRI time. All these procedures were described in an SOP that included counseling, screening, treatment and follow-up to improve the efficiency of all different stages of the MR-HIFU treatment (Additional file 1). All MR-HIFU radiologists reviewed screening MRI scans for eligibility. The development of a template MRI report for the screening MRI scan helped them collecting all the data needed to assess eligibility (Additional file 1). Similar templates were designed to ensure that uniform reports were prepared of the MRI scan immediately after MR-HIFU treatment and at 6-month follow-up.

Furthermore to improve treatment efficiency, from January 2018 we implemented the administration of a uterus stimulant in our treatment protocol at the start of sonications when no contra-indications were known (Table 6). Previous studies indicate that the use

of a uterus stimulant has a beneficial effect on treatment effectivity, but its (cost)effectivity needs to be proven in future studies (31,32).

The last remaining hurdle to take is at a societal level. Due to the lack of randomized controlled trials in which the long-term follow-up outcomes of the MR-HIFU treatment are compared with standard care, the MR-HIFU treatment is not included in Dutch national guidelines and there is no reimbursement by the health insurance companies. We strongly recommend close collaboration with the most important stakeholders (e.g., the national societies of obstetrics and gynecology, insurance companies and the hospital board) from the start of implementation of this new technique, in order to facilitate dissemination and further adoption after proven (cost)effectiveness (33).

Strengths and limitations

MR-HIFU itself and the implementation of this multidisciplinary uterine fibroid treatment are complex, especially with the current lack of standard guidelines, and this might discourage new sites to start offering this noninvasive treatment option. In this article we reported all lessons learned, while we implemented the MR-HIFU treatment of uterine fibroids in our hospital and we provided straightforward ready-to-use protocols on how to perform sedation, suggestions for MRI examination and SOPs on logistics in our supplements. On different levels of implementation, Table 6 can be used as an inspiration for possible hurdles that need to be overcome, although these can be rather site specific and are not inexhaustible.

We believe the most important strength of this article is that by doing so, we provide other centers an overview of what is necessary to start implementing MR-HIFU for uterine fibroid treatment. Furthermore, we identified a learning-curve of 25 treatments and we believe this information is helpful for the expectation management of all involved parties of when to expect successful treatment. Finally, we addressed frequent types of MR-HIFU treatment failures and reported possible solutions that will result in higher eligibility rates and might even shorten the learning-curve.

The primary goal of our MaSS study, and this article, was not to evaluate all clinical outcomes in detail. Therefore, multiple limitations can be reported concerning the clinical outcome data collection. A high lost-to-follow-up number was seen, partly due to reinterventions, which might have led to an overestimation of clinical symptom and QoL improvement, although outcomes are in line with current literature. Baseline characteristics of our first 25 patients differed from the remaining patients, probably leading to favorable and unfavorable situations, and the follow-up duration varies between the first 25 and the subsequent group, although follow-up was at least one year and most reinterventions of the learning-curve took

place within the first year. Moreover, the use of oral contraceptives or intra-uterine devices after MRHIFU treatment could have interfered with symptom improvement. Nevertheless, we believe this does not curtail the usefulness of our lessons learned.

Since the improvement of our counseling, screening and treatment protocols took place continuously during inclusion, identifying which of them contributed to the change in clinical outcome is challenging. The cutoff point used for the analysis of our clinical outcomes was somewhat arbitrary. However, despite we broadened eligibility and included more complicated cases, after completing our learning-curve, failure rate decreased and relevant outcomes like NPV% and reintervention rate improved.

We used an adjusted process evaluation model when retrospectively evaluating our implementation process. For future analyses we recommend to prospectively evaluate the implementation processes, since this ease the process and can be used for quality improvements (34).

Future perspectives

Some hurdles still have to be overcome in order to reach complete adoption of the MR-HIFU treatment of uterine fibroids. When it comes to clinical outcomes, improvement can be reached by further optimizing screening. On a technical level, tools to sonicate fibroids with high signal intensity and techniques to measure NPV% during treatment are necessary to further increase eligibility and shorten treatment time. Randomized controlled trials comparing long-term (cost)effectiveness of MR-HIFU with standard fibroid care, from both clinical and societal perspective, are needed.

CONCLUSION

In this article we identified our learning-curve by analyzing our clinical results, and we presented the implementation of uterine fibroid MR-HIFU treatment in our non-academic teaching hospital. Our lessons learned on a technical, patient selection, patient counseling, medical specialists and organizational level, are described in detail, and the provided supplements are likely to be of benefit to other hospitals willing to commence with offering MR-HIFU as novel treatment option to women with symptomatic uterine fibroids.

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SUPPLEMENT 1

Standard Operating Procedure (SOP)

Preparation

Action	Person in charge
Diagnosing patient with uterus myomatosus and screening for MR-HIFU treatment eligibility	Gynecologist
Counseling patient. Signing informed consent	Gynecologist
Ordering screening MRI scan	Gynecologist
Reviewing screening MRI scan and ordering multidisciplinary meeting	Radiologist
Attending multidisciplinary meeting	Gynecologist Radiologist PhD candidate
Recording results of multidisciplinary meeting in patient file	Gynecologist
Giving feedback of meeting to patient, ordering MR-HIFU treatment	Gynecologist
Planning MR-HIFU treatment including appointment at the anesthesia department and short stay	Secretary
Counseling sedation protocol including use of carbetocin during treatment	Anesthetist
Preparing patient for hospital admission	Secretary

Pre-procedural

Action	Person in charge
Prescribing pre-medication on day of treatment	Radiologist
Performing rounds before treatment at general nursing ward	Radiologist
Preparing patients as described in nursing protocol	Nurse
Performing time-out procedure before start treatment at MRI scanner	Radiologist
Positioning of patient on MRI scanner	MRI technicians

Peri-procedural

Action	Person in charge
Executing MR-HIFU treatment	Radiologist

Post-procedural

Action	Person in charge
Inspection of abdominal skin at MRI scanner	Radiologist
Performing rounds after treatment at general nursing ward	Radiologist
Documenting treatment in patient file, sending discharge letter to general practitioner	Radiologist
Ordering follow-up appointments	Radiologist

SUPPLEMENT 2

Sedation protocol

Preparation

All patients are screened for eligibility for Procedural Sedation and Analgesia (PSA) and use of carbetocin during a physical consultation at the anesthesiology department. Patients need to arrive sober on treatment day (for at least 6 hours). At the general nursing ward, oral pre-medication will be administered. This includes 100mg diclofenac, 1000mg paracetamol and 5mg oxycodone. At the nursing ward, an intravenous cannula will be applied for continuous infusion of 0.9% saline.

Necessities at the MRI scanner

Sedation trolley including MRI compatible CO2 and O2 monitoring materials, suction materials, perfusion materials, cage of Faraday and sedation (emergency) medication including:

- atropine
- ephedrine
- phenylephrine
- fentanyl
- granisetron
- propofol
- NaCl 0.9%
- carbetocin 100µg/ml

Work plan during MR-HIFU treatment

A sedation professional continuously monitors patients' vital signs with a three-lead electrocardiogram (ECG), pulse oximetry (SpO2), non-invasive blood pressure (NIBP) measurement, measured at 5-minute intervals or more frequently when needed, and continuous capnography. All patients receive supplemental oxygen (2 L/min) by nasal cannula.

Propofol, 20mg/mL is administered by a continuous infusion pump on a rate between 1mL/hour and 12mL/hour. In case necessary, propofol can be increased with 0.5ml/h or 1ml/h or a bolus of 10mg/1mL. When pre-medication effects decreases, fentanyl bolus can be administered (25µg/0.5mL or 50µg/1mL). During treatment the sedation professional communicates with the patient on a regular basis between sonications.

After first successful sonication, one ampoule of 100µg/ml carbetocin is slowly intravenously administered.

Recovery

When treatment is finished, recovery will take place on the general nursing ward. Patient' vital signs will be measured according nursing protocol and more frequent when necessary.

SUPPLEMENT 3

Screening MRI protocol

	T2w axial	T2w sagittal	T2-mapping	DWI	DWI long TE	CE-T1w
Scan type	TSE multishot TSE factor 18	TSE multishot TSE factor 17	GRASE multishot TSE factor 12 EPI factor 5	Single shot SE-EPI EPI factor 51	Single shot SE-EPI EPI factor 51	3D FFE TFE multishot TFE factor 44
T_E (ms)	110	125	*n* x 20	64	140	2.6
T_R (ms)	3656	6219	2438	2673	6715	5.4
Flip angle (˚)	90	90	90	90	90	10
Slice thickness (mm)	3.5	3.0	7.0	7.0	7.0	3.0
ACQ Matrix	356x198	356x187	112x82	112x80	112x80	168x157
FOV (mm)	250x180	250x180	250x188	250x188	250x188	250x250
ACQ Voxel size (mm)	0.7x0.88	0.7x0.94	2.23x2.23	2.23x2.26	2.23x2.26	1.5x1.49
Scan%	77.3	73.0	98.2	95.6	95.6	94
NSA	2	3	2	4	4	3
Half scan	No	No	No	Yes	Yes	No
Fat supression	No	No	SPIR	SPAIR	SPAIR	SPAIR
Scan duration (min:s)	2:48.2	3:31.5	2:55.5	6:51.6	4:35.3	2:31.2

DWI: Diffusion Weighted Imaging; TE: echo time; TSE: Turbo Spin Echo; GRASE: gradient and spin echo; EPI: Echo Planar Imaging; SE: Spin Echo; FFE: Fast Field Echo; TFE: Turbo Field Echo; TR: repetition time; ACQ: acquired; FOV: Field of View; Scan%: Scan percentage; NSA: Number of Signal Averages; SPIR: spectral presaturation inversion recovery; SPAIR; Spectral Selection Attenuated Inversion Recovery

Screening MRI report

Indication

Symptomatic uterus myomatosus, eligible for MR-HIFU treatment?

Medical history

…

Report

MRI female genitals including contrast
Used sequences: T2-weighted, T1-weighted before and after contrast, T2 mapping (GRASE) and diffusion weighted MRI. No vaginal or rectal contrast infusion.
Position uterus: anteflexion/interposition/retroflexion
Bowel interposition: yes/no
Subcutaneous fat layer: …cm

Fibroid
Type: submucosal/intramural/subserosal and FIGO classification (0-7)
Location: anterior/posterior/in fundo and/or left/right dorsal/ventral located
Diameter of fibroid: …cm
Distance center fibroid to sacral plexus: …cm
Distance fibroid to subcutaneous fat layer: …cm
Funaki classification: 1/2/3
Contrast enhancement: homogeneous/heterogeneous/no enhancement

Other fibroids
…

Incidental findings
…

Conclusion
...

MR-HIFU treatment report

Indication
Symptomatic uterus myomatosus

Report of treatment
Counseling performed and recorded in patient file
Informed consent collected and stored in patient file
Pre medication provided: diclofenac 100mg, paracetamol 1000mg and oxycodone 10mg
Preparation on nursing ward without irregularities: enema, catheter, intravenous line.
Time of arrival at MRI: …h
Time Out Procedure performed.
Start of positioning: …h
Scout images show: uterus in anteflexion/interposition/retroflexion.
Interposition of bowels: yes/no
Manipulation provided: yes/no
Type of manipulation: BRB with/without metamucil and/or bowel massage and/or uterus manipulation
Start of treatment: …h
A MR-HIFU treatment is performed.
The treatment was successful: yes/no
Heating of fibroid was with/without notifications
Number of sonications: …
Time of signification: …h
Particularities: …
End of treatment: …h
After contrast administration: …% NPV and …cm3
Particularities: …
The % NPV was expected: yes/no
MRI room available for next patient: …h

Conclusion
MR-HIFU treatment with bad/moderate/good technical result and a NPV of …%

Six months follow-up MRI report

Medical indication
Symptomatic uterus myomatosus

Research question
Six month follow-up MRI scan after MR-HIFU treatment

Report
MRI female genitals including contrast
Used sequences: T2-weighted, T1-weighted before and after contrast, T2 mapping (GRASE) and diffusion weighted MRI. No vaginal or rectal contrast infusion.

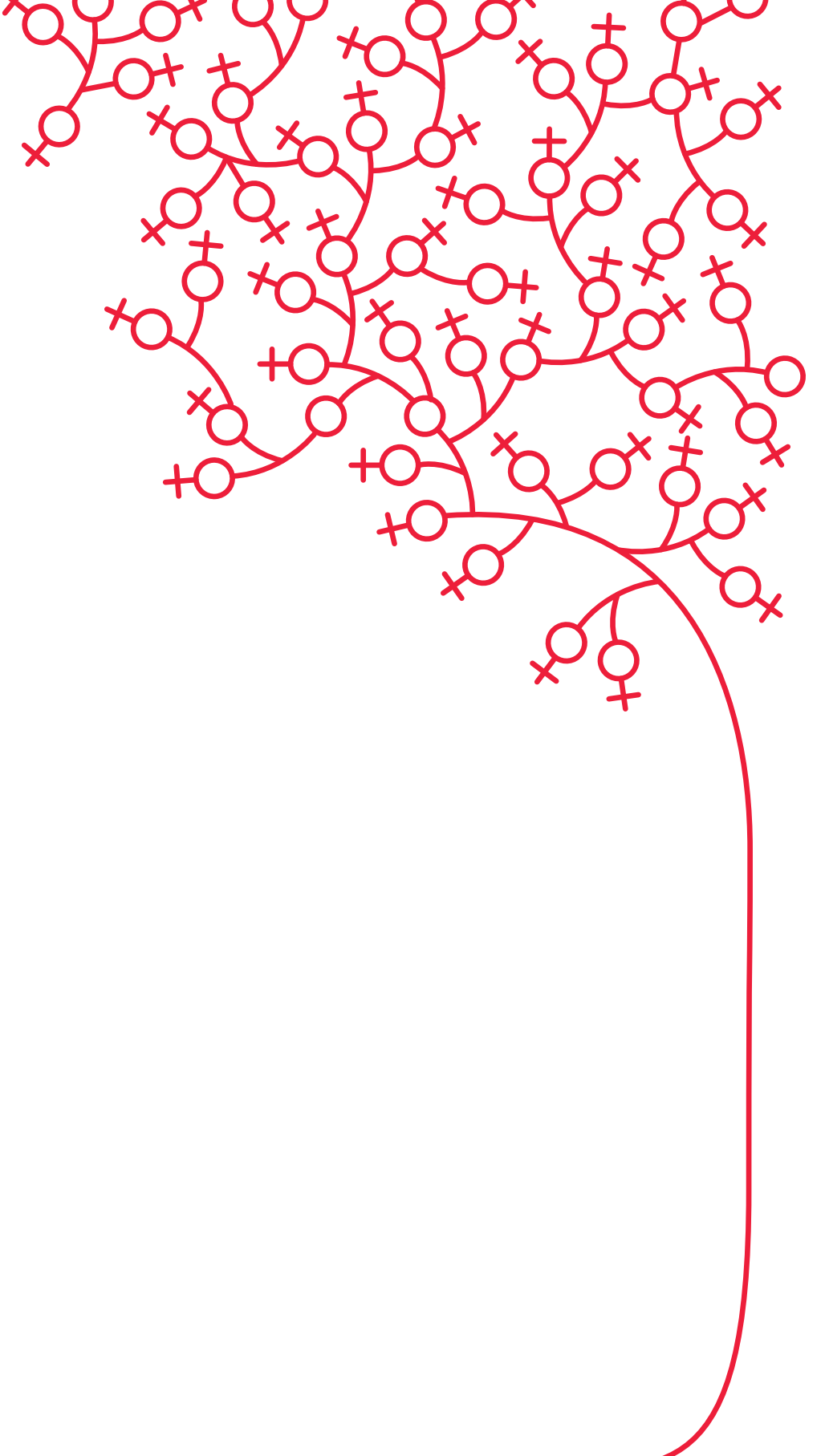
NPV
NPV post MR-HIFU treatment was …cm3 and is …cm3 at this point.
Further decrease is expected: yes/no.

Dimensions treated fibroid
Fibroid measured …x… cm and is …x…cm at this point. Therefore, decrease/increase of the fibroid is measured.

Other fibroids
…

Incidental findings
…

Conclusion
Volume reduction of the treated fibroid is achieved: yes/no
More decrease in size is expected: yes/no.



6

Increased MR-guided High Intensity Focused Ultrasound (MR-HIFU) sonication efficiency of uterine fibroids after carbetocin administration

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ABSTRACT

Purpose

We investigated whether administration of the long-acting uterus stimulant carbetocin increased intrasubject sonication efficiency during Magnetic Resonance image guided High Intensity Focused Ultrasound (MR-HIFU) treatment of uterine fibroids.

Method

In this prospective cohort study, thirty women with symptomatic uterine fibroids undergoing MR-HIFU treatment were included between January 2018 and January 2019. Treatment started with three sonications on one side of the uterine fibroid. Subsequently, one ampoule of 1 mL carbetocin (100 μg/mL) was administered intravenously and treatment continued with three sonications on the other side of the uterine fibroid. We compared the intra-subject sonication efficiency, in terms of Energy Efficiency Factor (EEF), thermal dose volume and sonication time to ablate one cm3 of fibroid tissue, before and after carbetocin administration. Adverse events that occurred within 30 min after carbetocin administration were recorded.

Results

Sonication efficiency improved after carbetocin administration as indicated by a significant decrease in EEF and sonication time ($p = 0.006$ and $p = 0.001$ respectively), and a significant increase in thermal dose volume reached ($p = <0.001$). Five women (16.7%) experienced temporary tachycardia, one women in combination with headache, within 30 min after carbetocin administration.

Conclusion

Administration of the long-acting uterus stimulant carbetocin improved the MR-HIFU treatment intra-subject sonication efficiency in women with symptomatic uterine fibroids.

Keywords

MR guided interventional procedures; High-intensity focused ultrasound ablation; Uterine fibroids; Myoma; Uterus stimulant; Efficiency

INTRODUCTION

For women suffering from symptomatic uterine fibroids, Magnetic Resonance image guided High Intensity Focused Ultrasound (MR-HIFU) is currently the only non-invasive treatment option when medication is not effective and/or undesirable. MR-HIFU has several advantages over (minimally) invasive treatments like hysterectomy or uterine artery embolization, including a low number of complications, short recovery time and no need for general or epidural anesthesia (1). During MR-HIFU thermal ablation, an ultrasound transducer produces a focused beam of high-intensity ultrasound waves. Inside the focal area, the targeted tissue absorbs the acoustic energy leading to a temperature rise, which causes coagulative necrosis (1). Thermal ablation is performed by multiple sonications of which the number and duration depend on the size and tissue characteristics of the fibroid. Directly post MR-HIFU, a contrast enhanced T1 weighted imaging (T1w-CE) MRI-scan is used to visualize the ablated tissue, which can be observed on such scans as a non-perfused volume (NPV). A high NPV to total fibroid volume (NPV%) is a technical predictor for good clinical outcomes and low re-intervention rates (2).

Not all women suffering from symptomatic uterine fibroids are eligible for MR-HIFU treatment, either due to patient characteristics, e.g. too high BMI, or fibroids characteristics such as high tissue perfusion (3,4). Patient eligibility is based on a screening MRI-scan classification. The Funaki classification and Scaled Signal Intensity (SSI) score are the two most commonly used classifications and roughly distinguish fibroids that are expected to be easily ablated and those that will likely result in inefficient sonications (5,6). Besides limited patient eligibility, another hurdle for clinical implementation of MR-HIFU is the treatment duration. Complete ablation takes on average two to three hours of costly MRI-scanner time per patient and light sedation is necessary during treatment for patient comfort (1). This urges the need for a more efficient treatment, i.e. reaching a high NPV% in a shorter period of time without jeopardizing treatment safety. Broadening eligibility and reducing treatment time are essential factors for faster adoption of MR-HIFU treatment for uterine fibroids in clinical practice (7).

Previous studies showed that the use of the short-acting uterus stimulant oxytocin during ultrasound- or MR-guided HIFU treatment positively influences clinical outcomes on a treatment level (4,8). Since oxytocin receptors could not be detected in the myometrium, it was initially believed that uterotonics did not have an effect on the non-pregnant uterus (9). However, oxytocin infusion during myomectomy decreases blood loss (10). Due to the contracting effect of the uterus stimulant, less blood flow in the uterine fibroid tissue is expected. This lower blood flow will result in less blood volume that needs to be heated and this is expected to result to more effective heating of fibroid tissue during MR-HIFU

treatment, and less of the so called “cooling effect” (4,9). Carbetocin is a synthetic octapeptide analogue of oxytocin with agonist properties at the oxytocin receptor (11–13). Due to molecular changes, carbetocin is more stable and has a gradual breakdown, resulting in an up to ten times longer half-life time of carbetocin compared to oxytocin (11). It was hypothesized before that sonication efficiency would benefit more from the use of the long-acting uterus stimulant carbetocin, instead of the short-acting oxytocin, because the MR-HIFU treatment can take up to three hours (14). In previous studies, the effect of uterus stimulant administration on MR-HIFU treatment outcomes was determined on a treatment level by comparing women who had or had not received a uterus stimulant during the MR-HIFU treatment (9,14). It could, however, not be excluded that several inter-subject differences like tissue characteristics, location of fibroid or radiologist’s treatment experience also influenced treatment outcome. To circumvent the influence of inter-subject differences on the effect of uterus stimulants on sonication efficiency, we performed an intra-subject analysis in which we compared technical outcomes on a sonication level before and after uterus stimulant administration. The primary objective of this study was to investigate whether sonication efficiency in terms of the Energy Efficiency Factor (EEF), thermal dose volume and sonication time to ablate one cm3 of fibroid tissue, would improve after administration of uterus stimulant carbetocin during MR-HIFU treatment.

MATERIAL AND METHODS

Study design

We included women who took part in a prospective cohort study performed in our hospital (the Myoma Screening Study; MaSS registry ID ISRCTN14634593). Eligibility for MR-HIFU treatment was determined by a screening MRI-scan (performed on a 1.5 T MRI-scanner, Achieva, Philips Healthcare, Eindhoven, The Netherlands). All women who underwent the MR-HIFU treatment between January 2018 and January 2019, received carbetocin during treatment, unless a contraindication for the use of a uterotonic was known. Women receiving a second MR-HIFU treatment for the same fibroid were excluded from our intra-subject analyses, as were the data of cases with technical and treatment failures (Figure 1). When adequate heating could not be achieved, or when bowels were located within the beam pathway and could not be manipulated out of it, cases were considered as treatment failures.

MR-HIFU treatment

Each MR-HIFU treatment was performed by one of our radiologists trained on the Sonalleve V1 device (Profound Medical Inc. Mississauga, Canada), integrated into a 1.5 T MRI-scanner (Achieva, Philips Healthcare, Eindhoven, The Netherlands). Four

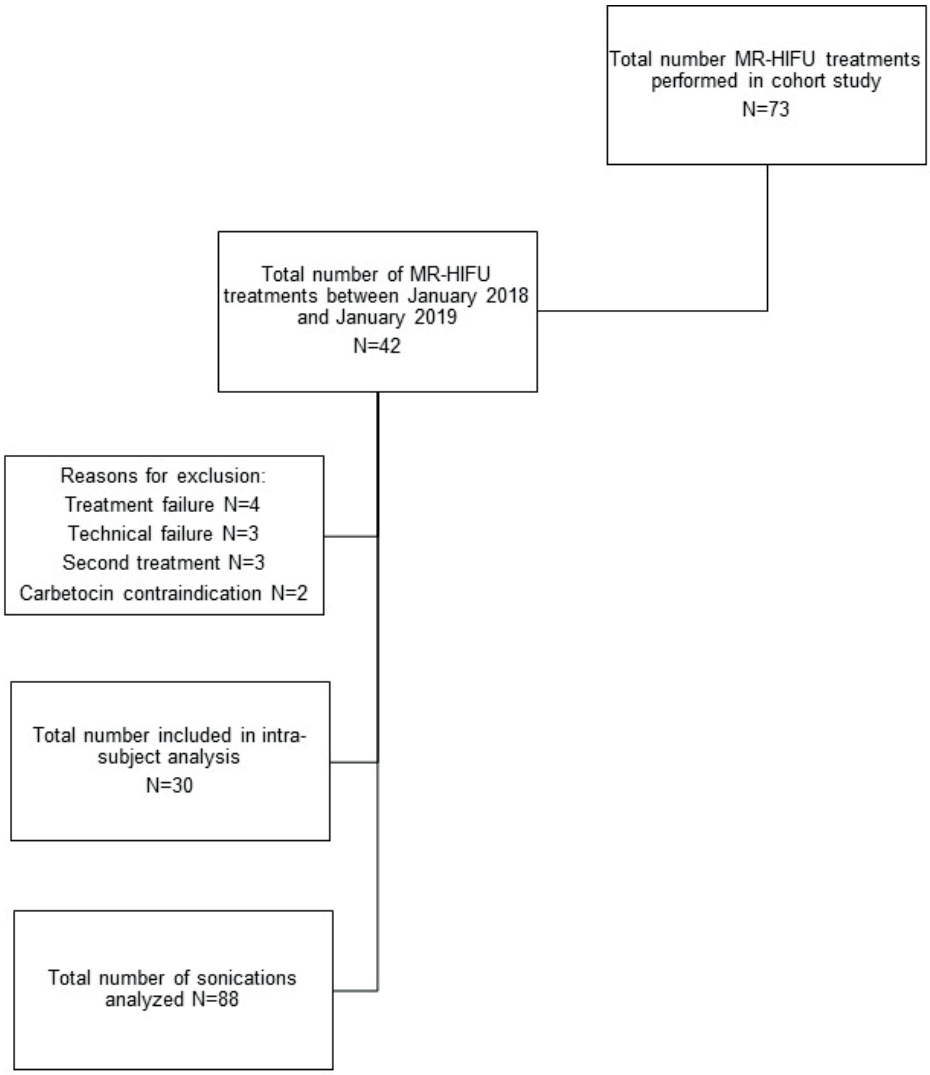

Figure 1: Flow diagram of women included in the intra-subject analysis.

differently sized ellipsoidal treatment cells of 4, 8, 12 or 16 mm in the axial dimension with volumes of 0.08, 0.67, 2.26 and 5.36 mL respectively, were available for volumetric ablation on the V1 device (7) and for every sonication the level of acoustic power (80–200 W) was determined based on the results of an initial test sonication using low power (40–60 W). Each treatment started with one or two test sonications and continued with at least three sonications on one side of the uterine fibroid (Figure 2). Next, one ampoule of 1 mL carbetocin (100 µg/mL) was administered intravenously. Five minutes after the carbetocin administration was completed, treatment continued with at least three sonications on the other side of the same uterine fibroid. These sonications were

part of the same treatment cell cluster, i.e. the distance between the transducer and the sonication target was comparable. After each sonication, the advised cooling time of the HIFU device was adhered to. During treatment, patients received light sedation including propofol infusion and administration of fentanyl bolus. A sedation professional continuously monitored patients' vital signs with a three-lead electrocardiogram, pulse oximetry, non-invasive blood pressure measurement, and continuous capnography. After collecting all necessary data of the six sonications to be analyzed, the treatment continued as usual (15). Immediately after completion of the MR-HIFU treatment, the NPV% was determined on a T1w-CE MRI-scan (DOTAREM®, 0.2 mL/kg; Gadoterate Meglumine, 0.1 mmol/kg; Guerbet, France). Fibroid and NPV volume were measured using IntelliSpace Portal software (Philips Healthcare) by semiautomatic segmentation in the tumor tracking function with review and manual correction of the segmentation (16).

Data collection

Three sonications before and three sonications after completion of carbetocin admission, were selected for analyses by IV and the performing radiologist (EB, RH or MV) during treatment. These sonications had to meet the following criteria: no technically failed sonication (due to either abortion by patient or software), sonication within the same treatment cluster (i.e. comparable distance from abdominal wall), optimal heating pattern (e.g. not gradually increasing, not reaching the plateau phase, prolonged time to reach the plateau phase or irregular temperature upslope) and comparable appearance on the T2 weighted imaging (T2w) MRI planning images, without visible heterogeneity of the fibroid tissue. When these criteria were not met, data of that sonication was excluded and the subsequent sonication that complied was included. Since uterine fibroids are not perfectly oval shaped, it was not always possible to obtain treatment cells of the same size within the same treatment cluster. In those cases, we needed to select a smaller or larger sized treatment cell. When selecting the sonications for post carbetocin administration analyses, overlap with previously treated cells was avoided to prevent treatment of preheated tissue. In exceptional cases, almost none of the performed sonications could be finished successfully. In these cases, IV and the performing radiologist chose sonications that were comparable in size and visually comparable in signal intensity (SI) or heating pattern until abortion. Analyses were performed by KA, HO and IN, who did not take part in these treatments. Data on the size, location and number of fibroids per patient were retrieved from the screening T2w MRI-scans. These scans were also used to determine the Funaki classification and SSI score (16). Possible adverse events occurring within 30 min after carbetocin administration were collected by the performing radiologist.

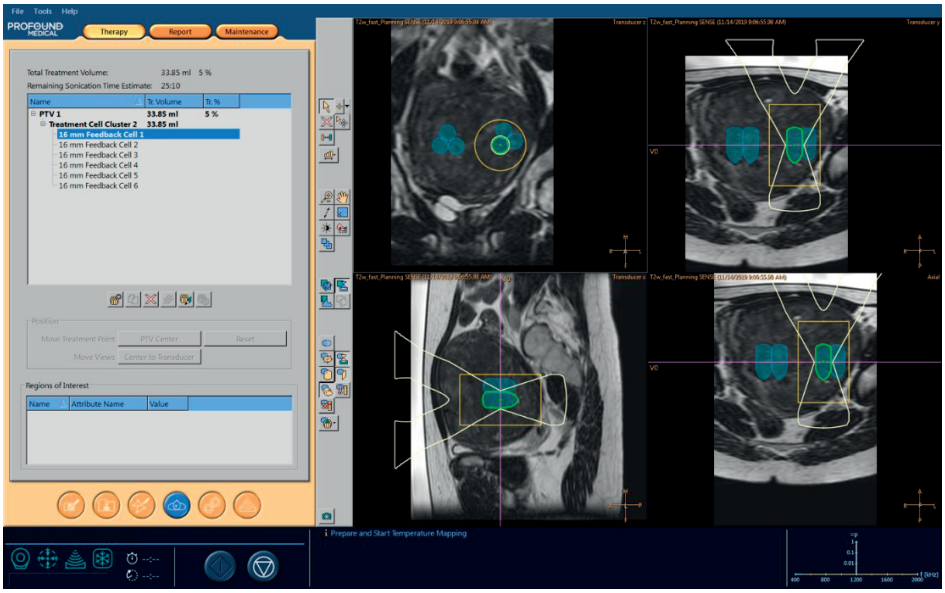

Figure 2: Screenshot of the Sonalleve MR-HIFU therapy application-planning screen with sonications planned on T2w MRI-scan images. description: During treatment preparation, the uterine fibroid is displayed in three directions; top left coronal direction, top and bottom right axial direction and bottom left sagittal direction. The three sonications (blue shaped, sized 16 mm) before carbetocin administration are marked with white asterisks and placed on one side of the uterine fibroid. The three sonications (blue shaped, sized 16 mm) after carbetocin administration are marked with white crosses and placed on the other side of the uterine fibroid. The selected sonication is illuminating in green and the borders of the ultrasound beam are displayed in yellow in all three directions.

Sonication efficiency

Sonication efficiency was determined in terms of EEF, thermal dose volume and time needed to ablate one cm3 of fibroid tissue on a sonication level. The EEF is the energy required to ablate one mm3 of fibroid tissue (7,17). To calculate the EEF the following formulas were used (17):

$$Energy\ (J) = Power\ (W) \times Heating\ duration\ (s)$$
$$EEF\ (J/mm3) = Energy\ (J)/Thermal\ dose\ volume\ (mm3)$$

The thermal dose is a measure of the effect of heating of tissue for a certain amount of time (7,18). Whether this dose is lethal, depends on the biological characteristics of the heated tissue. A commonly accepted thermal dose threshold for cell death to occur is 240 equivalent minutes (EM) at 43 ˚C (18). The HIFU device automatically calculated thermal dose maps with a unit of EM at 43 ˚C, and displayed the volume where a thermal dose > 240 EM at 43 ˚C was reached (7). We refer to this volume as the thermal dose volume. Time needed to ablate one cm3 of fibroid tissue is referred to as the sonication time/cm3 and was calculated as follows (17):

$$Sonication\ time/cm3\ (s/cm3) = Heating\ duration\ (s)/Thermal\ dose\ volume\ (cm3)$$

The selected acoustic power (W) transmitted by the transducer, the heating duration (s), the reached temperature (˚C) and thermal dose volume (volume (cm3) of 240 EM at 43 ˚C reached) of all three sonications before and after carbetocin administration were collected from the HIFU device report. In case multiple fibroids were treated, only the efficiency data of the first treated fibroid was collected.

Statistics

Statistical analyses were performed using IBM SPSS version 26 and STATA version 15. Categorical data were presented as n (%), continuous variables were presented as mean (± SD) in case of a normal distribution, or median (range) in case of a skewed distribution. Distribution was assessed by normal probability plots and eyeball testing. We tested for differences between efficiency determinants before and after carbetocin administration on a sonication level using linear multilevel analysis with correction for potential individual differences. For this, a two-level structure was used; efficiency determinants before and after carbetocin were clustered per patient. We analyzed the difference between efficiency determinants pre and post administration with and without addition of the possible confounder treatment cell size, classified as a categorical variable. Furthermore, a sensitivity analyses was performed, excluding the cases with a difference in treatment cell size before and after administration.

RESULTS

Study population

Median age of the 30 included women was 43.5 years (range 26–54, Table 1) and most fibroids were classified as Funaki 2 fibroids (86.7%).

Sonication efficiency

The overall mean selected treatment cells size (mm) pre and post carbetocin administration differed. In 18 of 30 cases (60.0%), treatment cell size (mm) before and after carbetocin administration was the same, in 10 cases the treatment cell size was larger pre carbetocin administration, in the remaining two cases, the cell size was larger post carbetocin administration. In two cases, the uterine fibroid was too small to collect data of three sonications without overlap with three previous sonications. In these two cases, only two sonications before and after carbetocin administration were selected for analysis. Before and after correction for treatment cell size, the selected acoustic power (W) was significantly higher (respectively $p < 0.001$ and $p = 0.001$) after carbetocin administration (Table 2). The transmitted energy (J) and the heating duration (s) did both not differ significantly (Table 2). The thermal dose volume (cm3) of the three

Table 1: Patient characteristics.

Patient characteristics	N=30. Mean ± SD or median [range]
Age (years)	43.5 [26-54]
BMI (kg/m^2)	25.1 ± 3.0
Number of fibroids:	
1	14 (46.7%)
2	5 (16.7%)
3	4 (13.3%)
4	1 (3.3%)
5	3 (10.0%)
>5	3 (10.0%)
Location of fibroids*	
Submucosal	12 (40.0%)
Intramural	6 (20.0%)
Subserosal	6 (20.0%)
Hybrid	6 (20.0%)
Fibroid diameter (cm)*	5.6 [1.6-16.9]
Fibroid volume (mL)*	66.3 [2.7-1094.5]
Funaki type:*	
1	2 (6.7%)
2	26 (86.7%)
3	2 (6.7%)
SSI score*	9.3 [-3.0-90.0]

*Only measured on largest fibroid in case of multiple fibroids. SSI: Scaled Signal Intensity.

sonications after carbetocin administration, and after treatment cell size correction, was significantly higher ($p < 0.001$) than the three sonications before carbetocin administration (Table 2). The EEF (J/mm3) and sonication time to ablate one cm3 (s/cm3) decreased significantly after carbetocin administration ($p = 0.006$ and $p = 0.001$ respectively, Table 2). Comparable results were seen when performing sensitivity analysis, as shown in the supplement. There were relatively large inter-subject differences between the mean of the sonication efficiency parameters of the three sonications before and after carbetocin administration (Figure 3). After all sonications were performed, a median NPV of 91.9% [14.5–100] was reached.

Adverse events

Tachycardia within 30 min after administration of carbetocin occurred in 16.7% of patients (5/30). One patient reported a headache in combination with the tachycardia. All of these side effects were temporary and resolved spontaneously.

Table 2. Intra-subject analyses technical parameters pre- and post carbetocin administration.

Variable N=30	Pre-carbetocin Mean ± SD	Post-carbetocin Mean ± SD	Mean difference [CI]	P-value	Mean difference [CI] with TCS as covariate	P-value with TCS as covariate
Temperature reached (°C)	66.9 ± 4.0	67.9 ± 4.8	1.0 [-0.1 – 2.1]	0.069	0.7 [-0.4 – 1.8]	0.188
Power (W)	133.0 ± 27.6	140.6 ± 28.1	7.6 [4.0 – 11.2]	<0.001*	5.9 [2.4– 9.5]	0.001*
Heating duration (s)	41.1 ± 14.6	38.7 ± 12.5	-2.4 [-5 – 0.2]	0.073	0.9 [-1.5 – 3.2]	0.468
Energy (J)	5347.7 ± 1837.4	5371.6 ± 1799.5	23.8 [-302.9 – 350.6]	0.886	338.8 [29.5 – 648.0]	0.032*
Thermal dose volume (cm^3)	2.0 ± 1.6	2.5 ± 1.8	0.5 [0.2 – 0.8]	<0.001*	0.7 [0.4 – 1.0]	<0.001*
EEF (J/mm^3)	4.8 ± 10.7	2.8 ± 3.4	-2.1 [-3.9 – (- 0.4)]	0.018*	-2.6 [-4.5 – (-0.8)]	0.006*
Sonication time (s/cm^3)	46.0 ± 79.2	25.9 ± 26.0	-20.1 [-33.5 – (- 6.7)]	0.003*	-23.0 [-38.1 – (-9.9)]	0.001*

*Significant difference between pre- and post-carbetocin administration. CI: Confidence interval; TCS: Treatment cell size; EEF: Energy Efficiency Factor

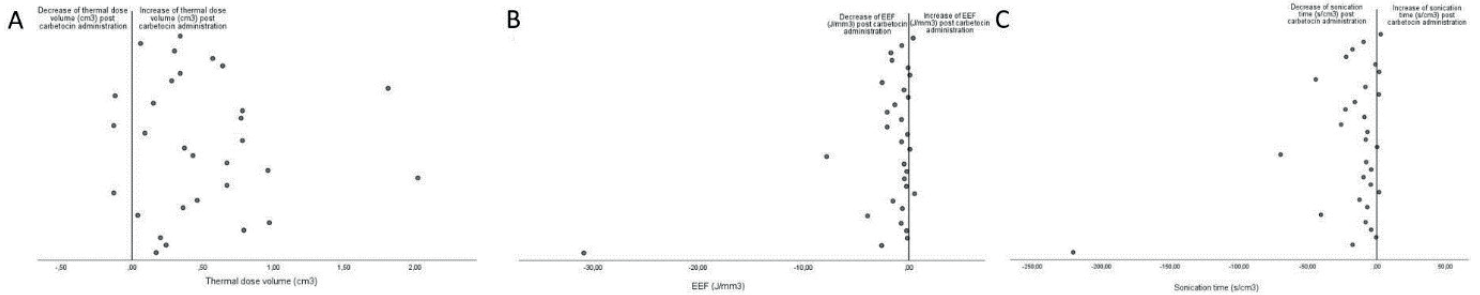

Figure 3: Scatter plots of the difference of efficiency parameters pre and post carbetocin administration. Plots showing the difference in thermal dose volume (A), Energy Efficiency Factor (EEF) (B) and sonication time to ablate one cm3 of fibroid tissue (C) between post and pre carbetocin administration for each individual patient. Each patient is represented by a dot.

DISCUSSION

In this study, we showed on a sonication level that the administration of the long-acting uterus stimulant carbetocin led to a significant decrease in EEF and sonication time needed to ablate one cm3 of fibroid tissue, and a significant increase in thermal dose volume. An increase in thermal dose after carbetocin administration reduces the time needed to sonicate one cm3 of fibroid tissue whereas it does not affect the duration of a sonication i.e. heating duration. Thus, the same duration of a sonication can be applied to heat a larger volume of fibroid tissue, leading to more efficient MR-HIFU sonications. It is expected that the use of carbetocine during a complete MR-HIFU treatment, will result in a more efficient overall uterine fibroid treatment as well.

Our findings are a quantitative analysis of the effect of a uterus stimulant on fibroid tissue during a sonication, and are line with the previously described significant reduction in sonication power and treatment time needed on a treatment level as reported by Jeong et al. They compared women treated with carbetocin during MR-HIFU, to women in a control group who did not receive carbetocin (14). Zhang et al. analyzed EEF and time needed to ablate one cm3 of adenomyose tissue after administration of oxytocin during ultrasound guided HIFU (17). In their study, a significant decrease in EEF on a treatment level was seen in women who had received oxytocin compared to women who had received normal saline. Furthermore, a significant decrease in sonication time on a treatment level was seen in the oxytocin group. It is important to note that external factors as intermediate cooling time, planning difficulties or patient check-ups can prolong the total procedure time. Therefore, total procedure time might not be an appropriate measure to analyze the effect of a uterus stimulant on MR-HIFU treatment efficiency.

A related problem occurs when comparing NPV% reached after the treatment with and without uterus stimulant administration. The studies of Zhang et al., Jeong et al. and Lozinski et al., all reported a significant improvement in NPV% on treatment level, as a result of introducing oxytocin or carbetocin administration in their treatment protocol (9,14,17). NPV% is an important predictor of clinical symptom improvement, and a high NPV% should be aimed for (1,19). Final NPV% reached is, however, dependent on external factors as well. These include possible technical difficulties, impossibilities in manipulation, treatment site or radiologist learning-curve stage and treatment time left. Our study design allowed for an intra-subject analysis, which was independent of these external factors and therefore added valuable information on the effect of carbetocin. The more effective heating of the fibroid tissue on a sonication level in our study might, on a treatment level, have led to more sonications within the same time frame. This more effective heating may also have

contributed to our post treatment average NPV% of 91%, which can be considered a very good result (1).

The sonication efficiency improvement of carbetocin is expected to be the result of uterus contractions reducing blood flow in fibroid tissue (9,20). A high blood flow carries away the local heat generated and therefore the tissue around the blood vessel is not sufficiently heated and ultimately not completely ablated (20). This is referred to as the “cooling” or “heat-sink” effect (9,20). A study by Otonkoski et al., showed that oxytocin administration resulted in a strong decrease in blood flow of the fibroid tissue, while having minor or no effect on the blood flow of normal myometrium. Therefore, not the increased contractility of the uterus, but the fibroid itself or the supplying circulation might be related to this effect (21). Furthermore, they stated that routine use of oxytocin during HIFU treatment might make the treatment suitable to a larger group of women.

At this point, not all women are suitable for MR-HIFU treatment. Funaki classifies fibroids in fibroids with a higher SI compared to myometrium (Funaki type 3) or lower SI compared to myometrium (Funaki type 1 and 2) and in general, ablating Funaki type 3 fibroids leads to a low NPV% (5). This is due to the fact that Funaki 3 fibroids are more heterogeneous, resulting in less effective heating due to scattering of ultrasound waves, and contain higher blood flow and vascularization, making it difficult to obtain adequate temperature elevation (due to heat-sink effect) (20). Park et al. developed the SSI score as an alternative for the Funaki classification. Fibroids reaching an SSI score above 16, on a 0–100 scale, often result in a NPV of 45% or below (6]) Funaki type 3 fibroids or fibroids with a high SSI score may particularly benefit from the reduced blood flow through the fibroid by the administration of a uterus stimulant. Maybe a blood flow cutoff point should be identified as eligibility tool, as was suggested by Otonkoski et al. (21). Because most fibroids of the patients in our study were classified as Funaki 2, we could not analyze the effect of carbetocin administration per Funaki subtype.

As far as we know, no data is at this point available on the effect of heating of carbetocin. However, no effects are expected due to the limited dosage and no adverse events reported in previous studies om the use of uterus stimulants during HIFU treatment (14,17). In our study, we observed possible carbetocin administration related adverse events in five of 30 women, but all adverse events were temporary, relieved spontaneously and are known side effects of carbetocin. Furthermore, Holleboom et al. suggested that the administration of a single injection of carbetocin is more convenient compared to continuous bolus injections of oxytocin, which requires preparation of a dosing pump and is therefore more prone to dosing errors (13).

Limitations

Ideally, we would have performed three sonications with the same size before and after carbetocin administration and compared their efficiency parameters. However, in reality, additional sonications needed to be performed since they did not meet the selection criteria and additional sonications were performed while the effect of carbetocin was awaited, to minimize wasting valuable treatment time. Sonications were selected based on visually comparable heating patterns. Not optimal heating patterns are often seen during MR-HIFU treatment, and by excluding this data, both before and after carbetocin administration, risk of eliminating effect of carbetocin on the heating pattern is not expected. Since fibroid tissue is heterogeneous, another limitation of our method is the possibility that the SI of the pre carbetocin sonication location differed from the post-carbetocine location. Fibroid tissue with a low SI on T2w MRI-scans is easier to heat compared to high SI fibroid tissue, and selection of different tissue before and after carbetocin administration, could therefore lead to incorrect assumptions. Furthermore, it might be possible that post carbetocin locations were preheated by pre carbetocin sonications due to thermal conductivity, resulting in beneficial results for the post-carbetocin sonications (22). However, we believe this impact is negligible since we awaited the advised cooling time. To minimize selection bias, analyses were performed by KA, HO and IN, who were not involved in the treatment procedure and therefore sonication selection. However, they were not blinded for the fact if a sonication was performed before or after carbetocin administration.

By analyzing different sized treatment cells before and after carbetocin, another bias could have been introduced. Therefore, treatment cell size was included as possible confounder in the intra-subject analyses and a separate sensitivity analyses was performed as well, excluding all unequal treatment cells (Supplementary).

Despite the long-acting activity of carbetocin in comparison to the short-acting oxytocin, the effect of this long-acting uterus stimulant might still decline over time. Little is known about the effect of carbetocin on fibroid tissue after half time has passed. Since the half time of carbetocin' is 40 min, and average treatment time between 120 and 180 min, a second dosage might be necessary to achieve an optimal effect of carbetocin during the complete procedure.

Future perspectives

Our intra-subject analysis showed that carbetocin has a beneficial effect on the sonication efficiency on a sonication level and is therefore implemented in our clinical practice. However, not enough is known about the effect of carbetocin on fibroids with different SI's and on the most important outcome from a patient perspective, the improvement

of symptoms and quality of life. Future studies should therefore include a larger study population with a better distribution over the Funaki classification and/or SSI scores and perform preplanning of the three sonications on each side, in order to determine whether carbetocin administration is especially beneficial for the treatment of more fluid rich fibroids. This would aid prognostic models that can predict MR-HIFU treatment outcome. The optimal way to assess the effect of carbetocin on clinical outcomes may be by performing a large double blind randomized placebo-controlled trial.

Conclusion

Administration of carbetocin during MR-HIFU treatment of uterine fibroids leads to more efficient sonications when analyzed on an intra-subject level.

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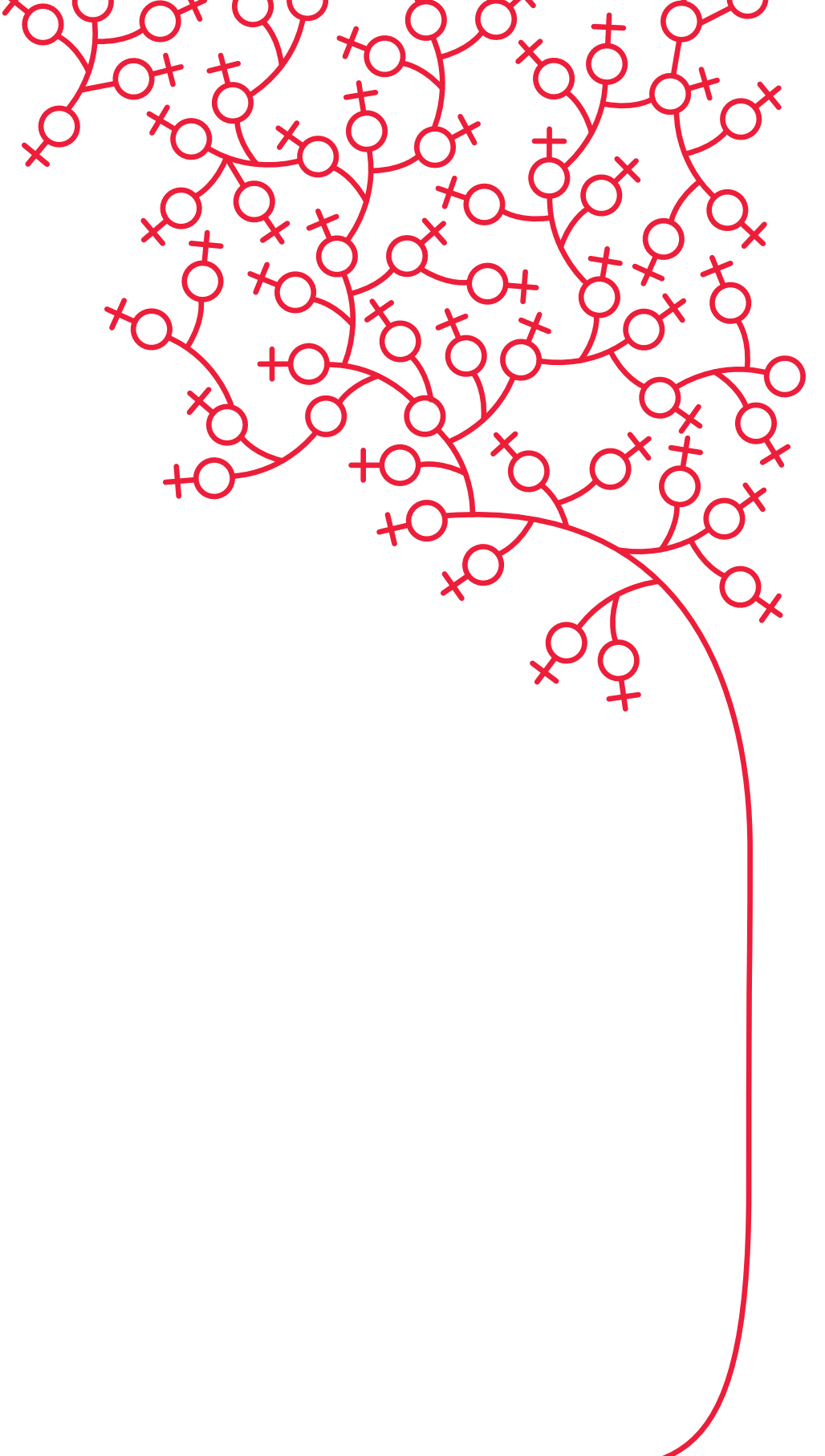
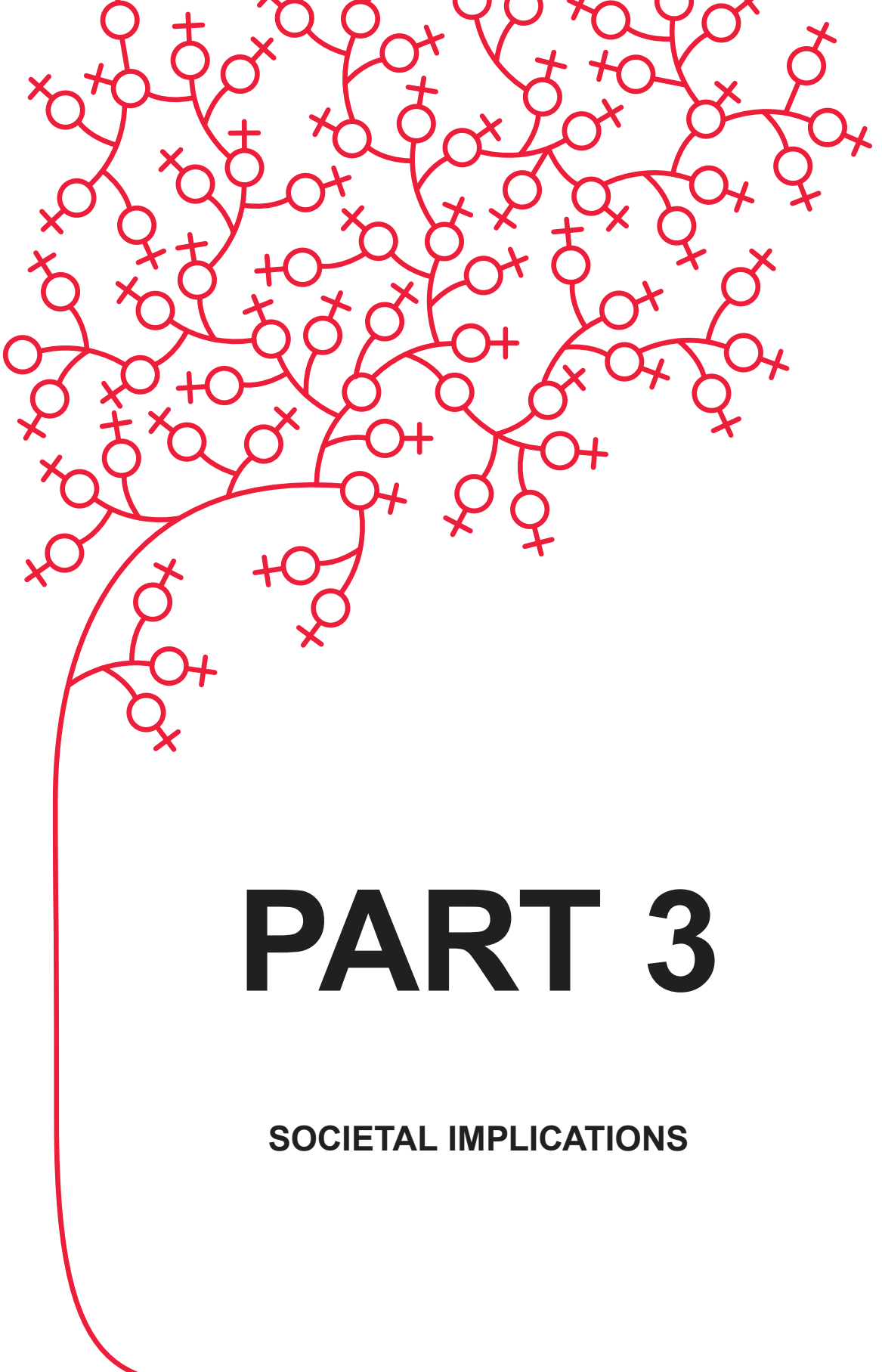
APPENDIX A. SUPPORTING INFORMATION

Intra-subject analyses technical parameters pre- and post carbetocin administration; sensitivity analysis

Variable N=18	Pre-carbetocin Mean ± SD	Post-carbetocin Mean ± SD	Mean difference [CI]	P-value
Temperature reached (°C)	67.1 ± 3.9	67.4 ± 5.3	0.3 [-0.1 – 1.5]	0.695
Power (W)	137.9 ± 28.7	143.2 ± 28.7	5.3 [1.2 – 9.4]	0.012*
Heating duration (s)	38.4 ± 11.8	38.8 ± 13.2	0.4 [-2.2 – 3.1]	0.753
Energy (J)	5168.9 ± 1510.7	5475.2 ± 1918.5	306.3 [-61.2 –673.9]	0.102
Thermal dose volume (cm^3)	2.0 ± 1.8	2.4 ± 1.9	0.6 [0.2 – 0.9]	0.001*
EEF (J/mm^3)	6.0 ± 13.6	3.1 ± 4.1	-2.9 [-5.7 – (0.0)]	0.053
Sonication time (s/cm^3)	52.1 ± 98.6	28.4 ± 30.3	-23.7 [-45.3 – (- 2.2)]	0.031*

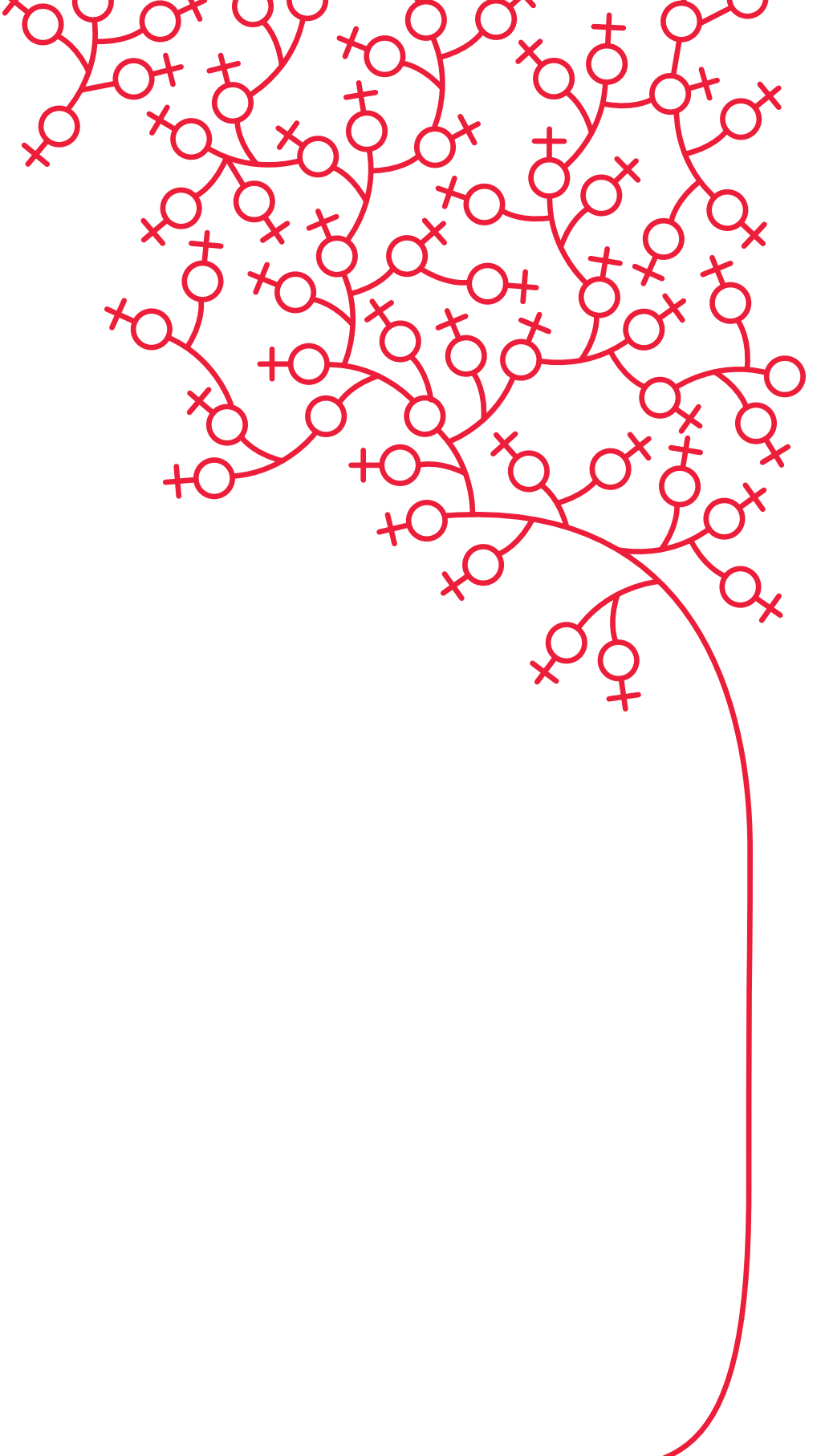
*Significant difference between pre- and post-carbetocin administration. CI: Confidence interval; EEF: Energy Efficiency Factor.





PART 3

SOCIETAL IMPLICATIONS



7

Comparison of (Cost-)Effectiveness of Magnetic Resonance Image–Guided High-Intensity–Focused Ultrasound With Standard (Minimally) Invasive Fibroid Treatments: Protocol for a Multicenter Randomized Controlled Trial (MYCHOICE)

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JMIR research protocols

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ABSTRACT

Background

Magnetic resonance image–guided high-intensity–focused ultrasound (MR-HIFU) is a rather new, noninvasive option for the treatment of uterine fibroids. It is safe, effective, and has a very short recovery time. However, a lack of prospectively collected data on long-term (cost-)effectiveness of the MR-HIFU treatment compared with standard uterine fibroid care prevents the MR-HIFU treatment from being reimbursed for this indication. Therefore, at this point, when conservative treatment for uterine fibroid symptoms has failed or is not accepted by patients, standard care includes the more invasive treatments hysterectomy, myomectomy, and uterine artery embolization (UAE). Primary outcomes of currently available data on MR-HIFU treatment often consist of technical outcomes, instead of patient-centered outcomes such as quality of life (QoL), and do not include the use of the latest equipment or most up-to-date treatment strategies. Moreover, data on cost-effectiveness are rare and seldom include data on a societal level such as productivity loss or use of painkillers. Because of the lack of reimbursement, broad clinical implementation has not taken place, nor is the proper role of MR-HIFU in uterine fibroid care sufficiently clear.

Objective

The objective of our study is to determine the long-term (cost-)effectiveness of MR-HIFU compared with standard (minimally) invasive fibroid treatments.

Methods

The MYCHOICE study is a national, multicenter, open randomized controlled trial with randomization in a 2:1 ratio to MR-HIFU or standard care including hysterectomy, myomectomy, and UAE. The sample size is 240 patients in total. Women are included when they are 18 years or older, in premenopausal stage, diagnosed with symptomatic uterine fibroids, conservative treatment has failed or is not accepted, and eligible for MR-HIFU. Primary outcomes of the study are QoL 24 months after treatment and costs of treatment including direct health care costs, loss of productivity, and patient costs.

Results

Inclusion for the MYCHOICE study started in November 2020 and enrollment will continue until 2024. Data collection is expected to be completed in 2026.

Conclusions

By collecting data on the long-term (cost-)effectiveness of the MR-HIFU treatment in comparison to current standard fibroid care, we provide currently unavailable evidence

about the proper place of MR-HIFU in the fibroid treatment spectrum. This will also facilitate reimbursement and inclusion of MR-HIFU in (inter)national uterine fibroid care guidelines.

Keywords

High-intensity–focused ultrasound ablation; magnetic resonance imaging, interventional; leiomyoma; randomized controlled trial; cost-effectiveness analysis; clinical trial protocol.

INTRODUCTION

Fibroids are the most common benign gynecological tumors in women of reproductive age, occurring in up to 70% of the population. Approximately 25% of the uterine fibroids are symptomatic (1). Symptoms include abdominal pain, menstrual disorders, lower urinary tract or bowel symptoms, and fertility disorders (2). On a global level, fibroids represent an enormous economic burden to the health care system and costs can reach as much as US $5.9-34.4 billion each year in the United States (3). Conservative treatment of fibroids fails in 50% of patients, many of whom subsequently opt for surgical procedures (4). Hysterectomy is currently the most common treatment for symptomatic uterine fibroids, with millions of procedures performed annually around the world (5). However, hysterectomies and myomectomies have a high risk of complications, long recovery, and might compromise future pregnancies (6), with the latter mainly due to peritoneal and intrauterine adhesions, a high rate of abnormal placentation, and fragility of myometrium as a result of myomectomy (7). Furthermore, even a hysterectomy does not guarantee an intervention-free life, mostly because of complications caused by the operation itself (8). This has led to a strong desire for less invasive treatments (4).

Currently, uterine artery embolization (UAE) is the only reimbursed minimally invasive treatment available in the Netherlands. The general treatment results after UAE are 60% fibroid volume reduction and on average 80%-90% patient satisfaction (9). Complications after UAE include non-target embolization, infection/septicemia and ovarian failure due to impairment of ovarian blood flow, and infection leading to fallopian tube damage with subsequent infertility (9,10).

Magnetic resonance image–guided high-intensity–focused ultrasound (MR-HIFU) is a thermal ablation technique, which enables noninvasive treatment of symptomatic uterine fibroids by selective tissue heating (11). The ultrasound transducer produces convergent high-intensity ultrasound waves. The targeted tissue absorbs the acoustic energy leading to a temperature rise, which causes coagulative necrosis (12). Magnetic resonance imaging (MRI) facilitates treatment planning and real-time monitoring by temperature mapping (13). Directly after MR-HIFU, a contrast-enhanced MRI scan can visualize the ablated tissue, referred to as the non-perfused volume (NPV). NPV% (NPV divided by the initial fibroid volume) is one of the commonly used parameters to indicate technical treatment success (11).

When the MR-HIFU therapy of uterine fibroids was first introduced in clinical practice, it was allowed to ablate only 33%, and later on 50%, of the uterine fibroid. However, it soon became clear that clinical outcomes are closely related to high NPV percentages.

Therefore, nowadays full ablation protocols are used (12,14). In addition, better results and less adverse events were seen when using the latest generation of treatment devices (11). Not all patients with symptomatic uterine fibroid are eligible for MR-HIFU treatment due to either patient or fibroid tissue characteristics, such as the number of fibroids or the extent of vascularization of a fibroid and the possibility to heat the tissue (15). A wish to conceive is not a contraindication, although data on pregnancy outcomes remain sparse (16,17). Careful screening is in all cases recommended (18). Hitherto, only 5 studies were published on the cost-effectiveness of the MR-HIFU uterine fibroid treatment (19-23). All used outdated, less effective MR-HIFU treatment protocols and costs of sanitary products, over-the-counter remedies, and alternative and complementary therapies were typically not taken into account. Nevertheless, these cost-effectiveness studies still concluded that MR-HIFU can be cost-effective at commonly accepted willingness-to-pay thresholds (11).

At this point, phase 1, 2a, and 2b studies according to the Idea, Development, Exploration, Assessment and Long-term study (IDEAL) framework have been completed in numerous sites all over the world (24), confirming safety and short- to middle-term technical and clinical outcomes. Conversely, no (non)randomized controlled trials are available in which MR-HIFU is directly compared with the current standard of care, and in which the full ablation protocol or the latest version of the MR-HIFU equipment was used. For example, in a comprehensive cohort trial comparing MR-HIFU with UAE, lower reintervention rates and greater improvement in symptoms were observed after UAE (25). However, these results could be explained by impairment of ovarian reserve at follow-up in the UAE group and the use of outdated MR-HIFU equipment, which resulted in a rather low average NPV of 42.9% after treatment. With regard to follow-up, only 2 single-arm studies (26,27) with a follow-up of more than 12 months and using a full ablation protocol have been performed until now (11).

Because of the lack of randomized controlled trials (RCTs) that established long-term treatment outcomes and cost-effectiveness of MR-HIFU using an unrestricted, full ablation protocol and the latest equipment, we are now embarking on phase 3 of the IDEAL framework and will perform a randomized controlled (cost-)effectiveness study with a long-term follow-up.

The primary aim of this MYCHOICE study is to compare quality of life (QoL) at 24 months after MR-HIFU with QoL 24 months after standard fibroid care, which consists of hysterectomy, myomectomy, and UAE. Furthermore, we aim to determine the long-term cost-effectiveness of MR-HIFU compared with standard (minimally) invasive fibroid care. We expect that QoL after MR-HIFU is non-inferior to QoL after standard care and that MR-HIFU is cost-effective compared with standard care.

METHODS

This protocol was developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement (28).

Study Design and Setting

The MYCHOICE study (MYoma treatment Comparison study: High-intensity image–guided fOcused ultrasound versus standard [minimally] Invasive fibroid care—a (Cost-) Effectiveness analysis; Netherlands Trial Register NL8863) is designed as an open, national, multicenter, RCT. By including both academic and nonacademic centers as participating hospitals in the MYCHOICE study, high volume and expertise are warranted. Participating hospitals provide a representative geographic spread across the country. All participating hospitals are specialized uterine fibroid centers and perform standard (minimally) invasive fibroid care. The MR-HIFU treatment will, however, be performed in the only 2 hospitals in the Netherlands that offer MR-HIFU treatment (Isala Zwolle and University Medical Center Utrecht) in addition to standard uterine fibroid care.

Study Population and Eligibility

Overview

Our study population consists of women in the premenopausal phase visiting the gynecological outpatient clinic with symptoms caused by uterine fibroids. Symptoms of fibroids may comprise heavy menstrual bleeding and bulk symptoms such as pelvic pressure, micturition/defecation problems, or pain symptoms. A combination of several symptoms or a single symptom will be equally qualified as “symptomatic.” To optimize external validity of our study results, the inclusion and exclusion criteria defined in this study (Textbox 1) are similar to the inclusion and exclusion criteria applied for MR-HIFU in clinical practice. However, 2 exceptions are made. Women need to be motivated to undergo 1 of the 3 treatments in the control group, in case of being randomized to the control group, before participating in the MYCHOICE study. Furthermore, a wish to conceive within 1 year after inclusion is a reason to be not eligible for participating, because there is not yet a consensus about the standard of care for these women. Women without an active child wish but for whom a pregnancy in the future is not ruled out can be included in the study.

The MYCHOICE study procedure consists of several steps (Figure 1). The eligibility procedure for this study consists of 2 screening phases. Only women that are considered eligible for participating in the study based on these 2 screening phases will be randomized.

Textbox 1: Inclusion criteria for participation in the MYCHOICE (MYoma treatment Comparison study: High-intensity image–guided fOcused ultrasound versus standard (minimally) Invasive fibroid care—a (Cost-)Effectiveness analysis) study.

Inclusion criteria

- Symptomatic fibroids warranting (minimally) invasive treatment, that is, either hysterectomy, myomectomy, or uterine artery embolization
- Conservative treatment failed or not accepted
- Premenopausal
- Age ≥18 years
- Eligible for magnetic resonance image–guided high-intensity focused ultrasound (MR-HIFU) treatment.

Exclusion criteria

- Asymptomatic fibroids
- Postmenopausal
- BMI of ≥35 kg/m2 or abdominal subcutis ≥4 cm or both
- More than 5 uterine fibroids unless 1 or 2 fibroids causing the symptoms can be clearly identified
- Magnetic resonance imaging contraindications or contrast allergy
- Current pregnancy
- A wish to conceive within 1 year after inclusion
- Suspicion of malignancy
- Dominant adenomyosis, defined as more volume of adenomyosis rather than fibroids
- Not willing to accept pretreatment with leuprorelin before MR-HIFU in case of a uterine fibroid with a diameter >10 cm or classified as Funaki 3
- Not willing to remove an interfering intrauterine contraception device prior to MR-HIFU
- Not eligible for MR-HIFU as determined by the multidisciplinary MR-HIFU team in Isala based on a screening magnetic resonance imaging:
  - Uterine fibroid(s) either submucosal or subserosal stalked or with a diameter <2 cm
  - Fibroids suitable for hysteroscopical removal
  - Distance of abdominal wall to the dorsal side of uterine fibroids expected to be >12 cm even after the use of manipulation techniques
  - Calcified uterine fibroids or fibroids without contrast enhancement **Inclusion criteria**

Phase 1 of the Screening Procedure

Patients presenting with uterine fibroid–related symptoms at the Department of Gynecology of the participating centers will undergo standard consultation, physical examination, and vaginal ultrasonography. The patient is briefly informed about the study when she appears to be eligible for participation in the study based on the physical examination and the vaginal ultrasonography (step 1 in Figure 1). In case the patient is interested in participating in the study, an appointment with a member of the research team or local research nurse will be made and the patient will receive more detailed study information to read at home (step 2 in Figure 1). In case a patient does not want to participate, the gynecologist asks the patient if she is willing to disclose the reason for not participating. During the appointment with a member of the research team or local research nurse, additional counseling will take place.

Phase 2 of the Screening Procedure

Once the patient has signed the informed consent form, a screening MRI scan according to a predefined protocol will be planned in the local hospital (step 3 in Figure 1).

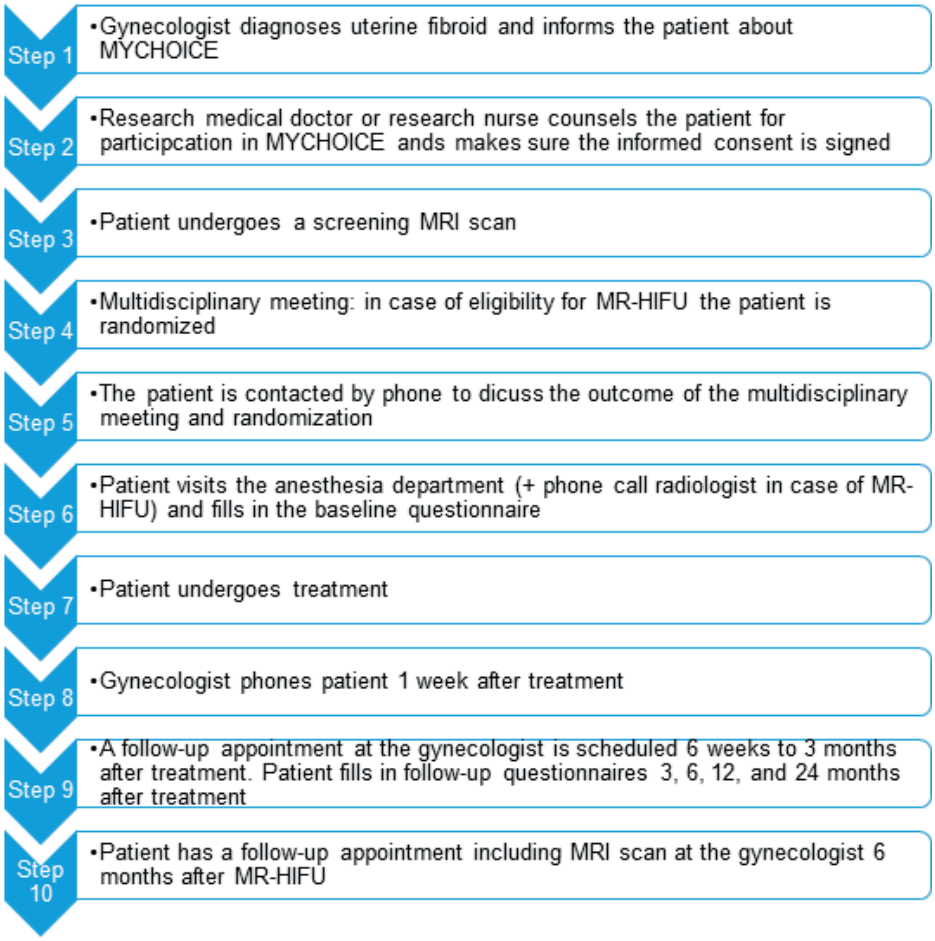

Figure 1: Flow diagram of the MYCHOICE procedure. MR-HIFU: magnetic resonance image–guided high-intensity focused ultrasound; MRI: magnetic resonance imaging; MYCHOICE: MYoma treatment Comparison study: High-intensity image–guided fOcused ultrasound versus standard (minimally) Invasive fibroid care—a (Cost-)Effectiveness analysis.

Final eligibility of the patients of all participating centers will be determined by the multidisciplinary MR-HIFU team in the coordinating center based on the screening MRI scan and the inclusion and exclusion criteria (step 4 in Figure 1). These meetings will be accessible to members of the other participating hospitals. By performing central screening, a bias caused by differences per site is minimized and eligibility for MR-HIFU is secured.

Intervention

Pretreatment

The participant's gynecologist and general practitioner are informed about the outcome of the eligibility assessment and, if the patient is considered eligible, the randomization outcome (step 5 in Figure 1). Subsequently, the gynecologist will inform the patient about the outcome and baseline data will be collected by a member of the research team or the local research nurse and entered into the electronic case report form (Research Manager). In case a patient is randomized to the MR-HIFU treatment arm, she will be referred to an MR-HIFU performing hospital if her hospital is not 1 of the 2 hospitals in which the MR-HIFU treatment is performed. In case she is randomized to the standard care treatment arm, she can be treated in her own hospital.

MR-HIFU

MR-HIFU will be performed by well-trained and experienced radiologists using the latest version of the CE-marked Sonalleve MR-HIFU platform (Profound Medical Inc.) integrated into a 1.5-T MR-scanner (Achieva; Philips Healthcare) using a full ablation protocol. A uniform treatment protocol will be used in accordance with the manufacturer's guidelines on the use of the device and the latest insights in the field of MR-HIFU treatment of uterine fibroids. Six months after treatment, a follow-up MRI scan will be performed before the follow-up appointment at the gynecologist (step 10 in Figure 1).

Control Group

The care as usual group will be offered surgery or UAE. Surgery will be either hysterectomy or myomectomy. Both hysterectomies and myomectomies can be performed by laparoscopy or laparotomy depending on the size and location of the fibroids. Participants allocated to the control group can decide together with their gynecologist which of the (minimally) invasive treatments they wish to undergo. All of the usual care treatments are performed extensively at the participating centers and will be performed according to national guidelines and local protocols. Surgery is preceded by a preoperative screening for anesthetic risk assessment. Depending on the modus of the hysterectomy or myomectomy, patients will be hospitalized for a minimum of 1-3 nights. UAE will be performed by well-trained and experienced radiologists. UAE can be either unilateral or bilateral. The patient usually has to stay in the hospital for 1-3 nights for careful pain

monitoring after the procedure. Six weeks after all usual care treatments, a follow-up appointment at the gynecology department will be scheduled.

Use of Co-interventions

All included treatments aim for complete symptom reduction; however, clinical practice shows that additional treatment can be necessary during, for example, menstruation. Women can choose to use additional over-the-counter pain medication or prescribed medication such as oral contraception pills or antifibrinolytic drugs. These pills can influence symptom severity (both bleeding and pain). Therefore, data on the use of this medication are collected at both baseline and follow-up as part of the patient characteristics and medical consumption questionnaires.

Data Collection

Data collection will take place before treatment, and at 3, 6, 12, and 24 months after treatment by questionnaires. Furthermore, baseline data of patient and treatment costs will be collected before treatment and after data lock-in (Table 1).

Table 1: Timeline of data collection.

Data	Baseline	Treatment	3 months	6 months	12 months	24 months	Data lock-in
Informed consent	X						
Patient characteristics[a]	X						
Pregnancy outcomes[b]	X					X	
UFS-QoL[b,c]	X		X	X	X	X	
EQ-5D-5L[b,d]	X		X	X	X	X	
Onset of menopause[b]						X	
(Time to) reintervention[a]			X	X	X	X	X
PREM[b,e]	X	X	X	X	X	X	
Recovery time[a]		X	X	X			
Medical Consumption Questionnaire[b,f]	X		X	X	X	X	
Productivity Costs Questionnaire[b,f]	X		X	X	X	X	
Costs of treatment[a]							X
Reason for not participating[a,g]	X						

[a]Retrieved from questionnaires and medical record, [b]Retrieved from questionnaires solely, [c]UFS-QoL: Uterine Fibroid Symptom and Quality of Life questionnaire, [d]EQ-5D-5L: 5-level version of the EuroQoL Questionnaire, [e]PREM: patient-reported experience measurement, [f]Used for the cost-effectiveness analysis, [g]Data collected by the gynecologist in case of not willing to participate.

Outcomes

Primary Outcomes

In the MYCHOICE study, primary outcomes include [1] QoL at the follow-up time point of 24 months after treatment and [2] cost-effectiveness of MR-HIFU.

QoL is commonly measured with the validated Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QoL) (29).This questionnaire consists of 2 parts: 8 symptom questions and 29 questions concerning health-related QoL with 6 subscales. The 8 symptom severity questions concern duration, frequency and severity of menstruation, urination pattern, tightness or pressure in the pelvic area, and fatigue. The 6 subscales of the HR QoL part of the questionnaire are concern, activities, energy/mood, control, self-consciousness, and sexual function. All items are scored on a 5-point Likert scale. Both internal consistency reliability (subscale Cronbach α =.83-.95, overall health-related QoL score α =.97) and test–retest reliability (intraclass correlation coefficients 0.76–0.93) of this questionnaire were shown to be adequate. Moreover, the UFS-QoL has an excellent construct and discriminative validity (29). From the symptom-specific part of the questionnaire, a symptom severity score (SSS; range 0-100, with higher scores indicating more [severe] symptoms) can be calculated. Because symptom reduction is the main aim of all uterine fibroid treatments, we define QoL at the follow-up time point of 24 months as a change in reported symptom severity compared with baseline.

The cost-effectiveness analysis will be performed from a societal perspective. Cost-effectiveness will be reported as incremental cost-effectiveness ratio, that is, the ratio between the expected difference in cost and the expected difference in effect (clinical effect or utility [quality-adjusted life year] and net [monetary] benefit). Cost-effectiveness acceptability curves will be presented to summarize the impact of uncertainty on the result of the economic evaluation.

The Dutch value set will be applied to the 5-level version of the EuroQoL questionnaire (EQ-5D-5L) to produce quality-adjusted life year values (30).

We consider 4 cost categories: [1] direct medical in-hospital costs (eg, preprocedural costs, in-hospital costs related to the intervention, any additional in-hospital medical costs during follow-up); [2] direct medical out-of-hospital costs (e.g. unscheduled general practitioner visits and use of medication out of hospital); [3] direct nonmedical costs (patient expenses such as travel costs and sanitary measures); and [4] indirect costs (productivity-related costs due to absence from work) (31).

The unit costs of direct medical in-hospital cost volumes will be based on Dutch guidelines for economic evaluations. The cost volumes of MR-HIFU, UAE, myomectomy, and hysterectomy are based on detailed micro costing by using data recorded in the case record forms and patient records in all participating hospitals. The cost volumes related to complications will be recorded prospectively in the case record form (eg, type of complication, unscheduled outpatient visit, subsequent diagnostic and therapeutic measures). All interventions include 1 follow-up by phone (at 1 week after primary intervention; Figure 1). In case of an UAE, myomectomy, and hysterectomy, 1 follow-up visit at the outpatient gynecology department will be planned at 6 weeks after the primary intervention; in case of MR-HIFU at 3 and 6 months, a follow-up appointment at the gynecology department will take place, at 6 months combined with an MRI scan. This will be considered standard care, and will therefore be included in our cost analysis. Any further follow-up visits conducted for study purposes will be excluded from our analysis unless these are unscheduled follow-up visits for medical problems related to the primary intervention.

The unit costs of direct medical out-of-hospital costs, direct nonmedical costs, and indirect costs will also be based on Dutch guidelines for cost calculations in health care. The following altered patient questionnaires will be used: iMTA Productivity Cost Questionnaire (iPCQ) and iMTA Medical Consumption Questionnaire (iMCQ). The iPCQ questionnaire is a short generic measurement instrument on the impact of disease on the ability of a person to perform work. It also contains questions about absence from unpaid labor. This questionnaire is a generic instrument for measuring medical costs, including questions related to frequently occurring contacts with health care providers. All questionnaires will be sent by email or post according to the preference of the participant at baseline and at 3, 6, 12, and 24 months after treatment (Table 1). Patients will receive an automatic reminder by email. Indirect costs due to absence from work will be estimated as the actual working time lost (hours) multiplied by the average net income according to the friction cost method.

A decision analytic model with lifetime horizon will be developed by combining costs and effects. Complete uncertainty analyses (deterministic and probabilistic sensitivity analyses) will be performed.

In addition, a budget impact model will be constructed, taking the (gradual) implementation of MR-HIFU over time, the initial investments, and the savings into account that were shown to be realistic in the trial. The model will use different perspectives:

[1] The net Dutch Budgetary Framework for Healthcare (Budgettair Kader Zorg) perspective; and [2] health insurance/third-party payer perspective.

Table 2. Secondary outcomes of the MYCHOICEa study, including measurement tool and statistical analyses.

Outcome	Description	Measurement	Statistical analyses
QoL parameters	QoL is expected to be negatively correlated with symptom severity. When symptoms decrease, the QoL is expected to improve.	UFS-QoL[b] questionnaire and EQ-5D-5L[c] questionnaire	The time course of the change in health-related quality of life after treatment will be analyzed using longitudinal covariance analysis similar to the analysis of the change in SSS[d].
Adverse events and complications	The nature of adverse events and complications of the 2 treatment arms are expected to differ.	Adverse events will be classified according to the classification of surgical complications [25].	Adverse events are analyzed using descriptive statistics. Adverse events per treatment group and treatment will be presented with their occurrence rate.
Length of hospital stay	Reduced hospital stay is beneficial in terms of health care costs but is also considered as a great advantage by patients.	Length of hospital stay will be collected from the patient hospital file.	The average length of the hospital stay will be reported as mean (SD) or median (interquartile range).
Periprocedural and postprocedural pain	Pain perception may influence treatment experience and therefore satisfaction with the treatment.	Periprocedural and postprocedural pain will be measured on a numerical rating scale from 0 to 10 in the 3 months' follow-up questionnaire. Pain complaints at 3, 6, 12, and 24 months after treatment will be registered by the amount and duration of pain killers used.	The numerical rating score is considered to be a semicontinuous measure (range 0-10: higher score represents more pain). Pain experienced will be reported as mean (SD) or median interquartile range.
Patient-reported satisfaction with treatment and treatment preference (PREM[e])	Because a randomized controlled trial will be performed, satisfaction with treatment might be effected by not being allocated to preferred treatment. Furthermore, we expect women declining participating because of the randomization aspect of the trial.	The PREM consists of a concise set of statements about the experience of the patients with the treatment and whether they would recommend the treatment to a friend. In addition, the preference will be registered for a particular treatment of potential participants before randomization. Women who decline participation in the study will also be asked if they are willing to disclose their reasons for declining.	The PREM score is scored on a 5-point Likert scale: higher score represents better experience. Whether there is a difference in PREM outcome between the 2 treatment arms is determined using linear regression analysis.

Table 2. Secondary outcomes of the MYCHOICEa study, including measurement tool and statistical analyses. (*continued*)

Outcome	Description	Measurement	Statistical analyses
(Co)medication	Women (still) experiencing symptoms after treatment may take or may start to take medication to relieve these symptoms. Medication might also be used as contraceptive and to mask possible fibroid-related symptoms at the same time.	Data on any prescribed or over-the-counter medication taken to reduce fibroid symptoms as reported by the patient will be collected via the questionnaires at baseline, 3, 6, 12, and 24 months after treatment.	The number of women taking medication to suppress fibroid-related symptoms is measured at baseline and 3, 6, 12, and 24 months after treatment. The absolute numbers and percentage of women taking comedication per group per time point will be presented.
Reintervention rate and time to reintervention	A reintervention is defined as an additional intervention due to persisting or recurring symptoms of the treated fibroid or due to complications of the initial fibroid treatment.	Occurrence and type of reintervention are collected via both electronic patient file and questionnaires at 3-, 6-, 12-, and 24-month follow-up.	The reintervention rate at the follow-up time point of 24 months after MR-HIFU[f] is presented as percentage reinterventions with its 95% CI. Reintervention rate will be presented per treatment arm but also per treatment. To investigate whether the time to reintervention differs between the 2 treatment arms, Cox proportional hazards analysis will be used.
Onset of menopause after uterus-saving treatments	Uterine fibroid symptoms diminish after menopause along with fibroid-related symptoms. Because this may affect symptom reduction, QoL, and the possible need for a reintervention, the menopausal state of the participants will be determined.	Onset of menopause is defined as 1 year without menstrual bleeding and measured by a questionnaire at the 24-month follow-up.	The absolute numbers and percentage of postmenopausal women per group and treatment will be presented.
Reproductive outcomes after uterus-saving treatments	Only women with an active wish to conceive within 1 year after treatment will be excluded from this study. Thus, some women may get pregnant after the uterus-saving treatment.	Reproductive outcomes will be collected of all women that underwent a uterus-saving treatment by a questionnaire at 24-month follow-up.	Reproductive outcomes will be presented per uterus-saving group using absolute numbers and percentage.
NPV[g] and fibroid shrinkage after MR-HIFU treatment	Technical success of MR-HIFU is commonly presented as NPV percentage directly after treatment or fibroid shrinkage 6 months after treatment, as determined on an MRI[h] scan.	NPV% will be measured on an MRI scan performed directly after treatment. Fibroid shrinkage will be measured by comparing volume measured on 6 months' follow-up MRI scan with pretreatment volume.	We will investigate whether technical success (NPV% (NPV/initial volume of the fibroid) or fibroid shrinkage) is associated with (long-term) effectiveness using regression analysis.

Table 2. Secondary outcomes of the MYCHOICEa study, including measurement tool and statistical analyses. (*continued*)

Outcome	Description	Measurement	Statistical analyses
Other study parameters	Several patient characteristics are collected from the medical record of the patients and from the baseline questionnaire such as age, amount and size of fibroids, location of fibroid, position of uterus, duration of treatment, ethnicity, parity, height, weight, relevant medical, and medical history.	Data analysis will be stratified by center to check for differences in results between centers.	In case necessary, multilevel analysis will be used to correct for differences between centers. Multivariate analysis will be performed for symptom reduction, QoL improvement, and reintervention correcting for comedication or menopause as possible confounder. In addition, we will investigate whether certain baseline characteristics such as age, BMI, number of uterine fibroids, and target fibroid size are associated with symptom reduction and reintervention using linear, logistic, and Cox regression analysis.

[a]MYCHOICE: MYoma treatment Comparison study: High intensity image guided fOcused ultrasound versus standard (minimally) Invasive fibroid care - a (Cost) Effectiveness analysis, [b]UFS-QoL: Uterine Fibroid Symptom and Quality of Life questionnaire, [c]EQ-5D-5L: 5-level version of the EuroQoL questionnaire, [d]SSS: symptom severity score, [e]PREM: patient-reported experience measurement, [f]MR-HIFU: magnetic resonance image–guided high-intensity focused ultrasound, [g]NPV: nonperfused volume, [h]MRI: magnetic resonance imaging.

The budget impact model is performed through modeling and analyzed in a probabilistic way.

Because MR-HIFU is an outpatient treatment with a fast(er) recovery, it is expected to be cheaper than the current standard (minimally) invasive treatments, especially from a societal perspective.

Secondary Outcomes

Data on several secondary outcomes will be collected (Table 2). These include adverse events and complications during treatment and recovery, cost-effectiveness–relevant outcomes such as hospital stay duration and use of (co)medication, patient-reported experiences, reintervention rate in case a uterine-sparing treatment was performed, reproductive outcomes when applicable, and technical outcomes after MR-HIFU, such as NPV reached.

Sample Size

The MYCHOICE study is a noninferiority trial for which we hypothesize that MR-HIFU is noninferior to the group of standard (minimally) invasive treatments, accepted by a ≤15 points difference in symptom reduction at 24 months' follow-up as determined with the SSS (range 0-100 points) part of the UFS-QoL questionnaire. We expect that women participating in this trial have a slight preference for the noninvasive MR-HIFU treatment. We therefore choose to use an unbalanced design in which participants are allocated to the intervention or usual care group at a 2:1 ratio, resulting in a larger sample size in the MR-HIFU treatment group. With a larger sample size of the MR-HIFU treatment group, we will be able to gather more data on this new treatment while the effectiveness of standard care is already much better documented. Randomization, stratified by center, will be performed using a computer-generated randomization system, which randomly selects block sizes of 3, 6, or 9. Previous studies concerning (minimally) invasive treatments were performed with women with an average baseline UFS-QoL SSS of 55-65 points (33). Treatment initiated a decrease of 30-47 points on SSS 12 months after these combined treatments. Hitherto, there are 2 MR-HIFU studies published that used a full ablation protocol, had the same 12-month follow-up period as the studies on (minimally) invasive treatments, and in which women participated with a baseline UFS-QoL SSS of 55-65 points. These women showed an SSS reduction of 30-40 points at follow-up (34,35). In our study population we expect comparable baseline SSS in the MR-HIFU and standard care group. However, because hysterectomy results in a somewhat higher SSS reduction than the uterus-saving treatments, we assume in our power calculation an a priori 5-point delta between both the MR-HIFU and standard care group in favor of the standard care group. Using a noninferiority margin of 15 points with α (1-sided)=0.025, β=.1, and an SD

of 20 points, we estimate that 192 participants (128 patients in the MR-HIFU treatment group and 64 patients in the [minimally] invasive treatment group) will be required to test noninferiority of MR-HIFU. Anticipating a 20% loss to follow-up, we need to include 160 patients in the MR-HIFU group and 80 patients in the (minimally) invasive treatment group. The noninferiority margin and the SD of 20 points were determined in consultation with the Dutch Society for Obstetrics and Gynecology and were similar to the noninferiority margin used in the MYOMEX-2 study (36).

Recruitment

In all participating hospitals, patients will be recruited during a visit at the gynecologist. Furthermore, a study website is created to inform patients from all over the country, providing information and contact details to directly contact the study team. By promoting this website among general practitioners, gynecologists, and potential participants, we expect women with an interest in MR-HIFU to become acquainted with our study. Because MR-HIFU treatment for uterine fibroids is not reimbursed in the Netherlands, participating in the MYCHOICE study is the only possibility for women to undergo MR-HIFU treatment.

Statistical Methods

In this study, data will initially be analyzed on an intention-to-treat-basis (including treatment failures) but a per-protocol analysis will also be performed. QoL at the follow-up time point of 24 months after treatment is determined as a change in SSS between baseline and 24 months' follow-up. The difference between the symptom reduction after MR-HIFU and standard (minimally) invasive fibroid care including 97.5% CI is determined using linear regression analysis with a correction for baseline SSS. Although symptom reduction 24 months after MR-HIFU will be expected to be noninferior to standard (minimally) invasive fibroid care, the time course of symptom reduction may differ between the 2 treatment arms. This will be investigated with longitudinal covariance analysis. A faster symptom reduction in the usual care arm may be caused by a faster symptom reduction after hysterectomy. Therefore, a subgroup analysis in which the individual treatments are compared will be performed.

Patients can leave the study at any time for any reason if they wish to do so, without any consequences. In case they decide to withdraw before treatment or within the first 3-month follow-up, they will be included in the database, but an additional patient will be included to achieve the required sample size and reach primary outcome. In case patients withdraw after the 3-month follow-up, they are considered nonresponders. As much precautions as possible will be taken to prevent missing data. However, missing values are expected to occur in our trial due to technical failures and loss to follow-up. In case missing data reach 5%, additional analyzes will be performed to identify a plausible assumption, that is, missing

not at random, missing at random, or missing completely at random. Subsequently, an analysis method that is valid under that assumption will be used.

Data Monitoring

No data monitoring committee will be installed because the risks of participation in this study is categorized as insignificantly low. A data management plan is developed, detailing data management procedures, data standards, minimal data set requirements, and protocols (Isala Institutional Research Board). Data are collected in an online data management platform (Research Manager). Data will be securely stored for at least 15 years, according to hospital Institutional Research Board storage protocols. The study sponsor will be in charge of overseeing data management and access procedures. The Research Manager software will assign a "study ID." The reference between the study ID and the hospital patient number is listed in the patient identification log. The patient identification log will only be accessible by authorized personnel. Each electronic case report form will be completed on-site by the investigator or an authorized staff member. All imaging data will be stored on location but transferred in preparation of the multidisciplinary meeting. After the multidisciplinary meeting these data will be destroyed for privacy reasons. All individual patient data records will be collected on a confidential basis and according to the applicable national data protection, privacy, and secrecy laws.

Safety Reporting

Adverse events are defined as undesirable experiences of a participant within 30 days after treatment and related to participation in this study. All adverse events reported by the participant or observed by the investigator or study staff will be recorded. A serious adverse event is any untoward medical occurrence, within 30 days after treatment and related to participation in this study and results in death, is life threatening (at the time of the event), requires hospitalization or prolongation of existing inpatients' hospitalization, results in persistent or significant disability or incapacity, or any other important medical event that did not result in any of the outcomes listed above. The investigator will report all serious adverse events to the sponsor without undue delay after obtaining knowledge of the events.

Auditing

The clinical monitor will be responsible for verifying adherence to the protocol, reviewing participant records and source data, maintaining records of all actions taken to correct protocol deficiencies during the investigation, and assuring that the data needed to complete the study are complete and accurate.

Patient and Public Involvement

The Foundation Bekkenbodem4All (Pelvicfloor4All) was consulted on the design of the study from a patient perspective and their opinion and feedback were taken into consideration. In addition, an evaluation meeting with previous MR-HIFU patients took place. Outcomes of this meeting were used to improve MR-HIFU treatment routine and to point out important patient outcomes. During inclusion, Bekkenbodem4All will promote the study via their network and participate in the yearly meetings in which the progression of the study is discussed. When the results of the study warrant uptake of the treatment in standard reimbursed care, they will aid in the final implementation of the treatment.

Ethics Approval

This protocol, informed consents, and patient information have been approved by the local medical ethical committee of Isala Hospital (NL74716.075.20) on September 24, 2020, with respect to scientific content and compliance with applicable research and human patient regulations. The research activities of the MYCHOICE study comply with the international conventions and codes of conduct, and the latest Helsinki Declaration of the World Medical Association adopted by the World Medical Assembly.

Dissemination Policy

We aim to make all data Findable, Accessible, Interoperable and Reusable (FAIR) according to the FAIR principles (37). Therefore, we will assign all (meta)data with a unique and persistent (global) identifier and register or index them in a searchable digital data repository at the end of the study for long-time archiving and data reuse purposes. Results will be presented in (inter)national congresses and meetings, and will be published in peer-reviewed journals, publications of the patient associations, in health-related journals, and on various websites such as the MYCHOICE study website.

RESULTS

Inclusion for the MYCHOICE study started in November 2020. Patient enrollment is expected to last approximately 36 months. Because of the 24-month follow-up, we expect to complete data collection in 2026 and plan the dissemination of the results subsequently.

DISCUSSION

Added Value of MYCHOICE

The MYCHOICE study distinguishes itself from previous MR-HIFU trials in that it is an RCT in which full ablation protocols and the latest MR-HIFU equipment are used for uterine fibroid treatment. Moreover, patient follow-up is 24 months. Furthermore, it answers important research questions on both effectiveness and cost-effectiveness with outcomes that are relevant for policy makers, physicians, and patients.

Strengths

As a primary outcome, we will use QoL in terms of symptom reduction 24 months after treatment. We did not choose the commonly used outcome in uterine fibroids studies, reintervention rate, as our primary outcome because re-interventions are not expected to occur after hysterectomy. Symptom reduction will most likely also differ between hysterectomy and uterus-saving treatment options. However, the influence of symptom reduction after hysterectomies in the control group is probably limited, because we expect that most women who will participate in the MYCHOICE study prefer a uterus-preserving treatment option, just like the intervention under study. This is further enhanced by the 2:1 randomization ratio. This ratio will lead to a higher chance to undergo MR-HIFU treatment, and we believe is therefore an important strength of the design. Another strength is the fact that this unbalanced design will enable us to gather more data on our intervention, while the effectiveness of standard care is already much better documented.

Our follow-up duration of 24 months is based on the long-term outcomes of a retrospective study on MR-HIFU treatment results performed by our group (14). In this study, we found that all reinterventions were performed within 24 months after the initial treatment, indicating that the treatment effect reaches a steady state within 24 months after treatment. Thus, it is not useful to prolong follow-up of these patients.

Limitations

A possible limitation of the MYCHOICE study is the uncommon use of a mixed control group. However, in current daily practice, usual care for women with symptomatic uterine fibroids in whom conservative treatment failed or is undesired consist of several (minimally) invasive treatments. The minimally invasive UAE is reimbursed in the Netherlands, and would therefore be an appropriate reference treatment for the noninvasive MR-HIFU treatment. However, hysterectomies are by far the most frequently performed and should thus not be omitted from the standard care group. The standard care group is complemented with myomectomies. We expect that women willing to participate in this study are mostly searching for a uterus-saving treatment option, sometimes because of a

future pregnancy wish. For this category of women, myomectomy is the only alternative and therefore a mixed control group qualifies the most. By using this mixed group, we believe we best represent the real-world situation. Furthermore, the information on treatment preference in the control group can be used to gain more insights into patient preferences.

Although an RCT design is commonly considered to provide the best evidence on the effectiveness of a new intervention compared with usual care, our RCT design also poses several challenges (38). Women may not be willing to be randomized, which may delay enrollment, and our 2:1 randomization ratio with a mixed control group may lead to low sample sizes for the individual treatment options in the mixed control group, which will limit valid comparisons between outcomes of individual treatments. However, sufficient data on primary outcomes are already available for all treatments in this control group. Other possible limitations of the MYCHOICE study are that not all (secondary) outcomes are equally relevant for all included treatments and that the MR-HIFU treatment cannot be performed in all participating centers. However, because of the restricted number of patients eligible for treatment and the complexity of the treatment, it might not be cost efficient to have more than 2-4 uterine fibroid MR-HIFU facilities in the Netherlands.

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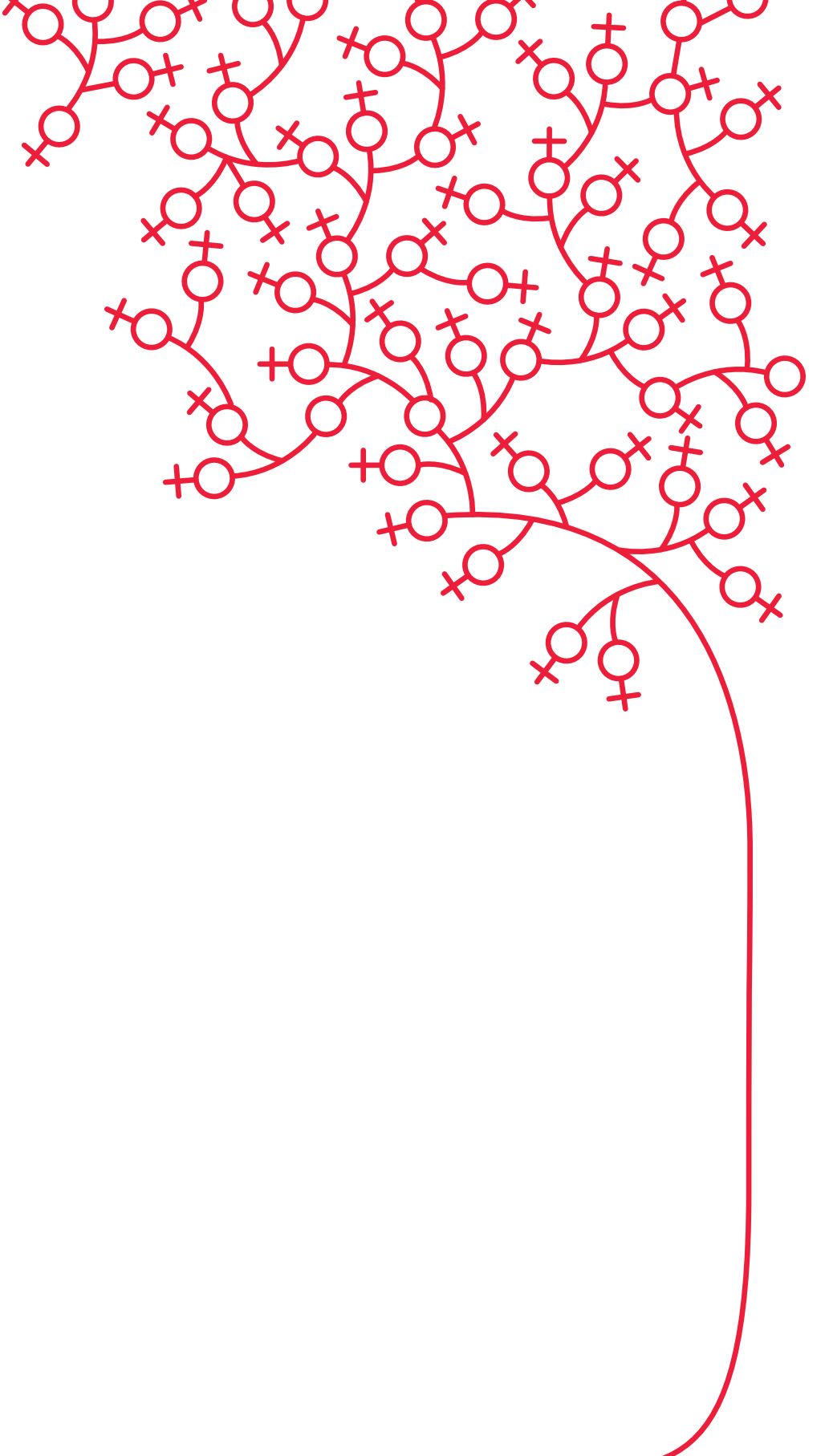

8

Environmental impact of the MR-HIFU treatment of uterine fibroids: First steps in performing an interventional radiology life cycle assessment

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ABSTRACT

Objectives

To assess the environmental impact of the relatively new, non-invasive MR-HIFU (Magnetic Resonance image guided High Intensity Focused Ultrasound) treatment of uterine fibroids, we took the first steps of a full Life Cycle Assessment (LCA), which provides information from cradle-to-grave of all elements involved in the treatment, by evaluating the CO2- (Carbon Dioxide) emission and solid waste production.

Materials and Methods

Our functional unit was a uterine fibroid MR-HIFU treatment performed on a Sonalleve V2 device. The moment the patient entered the day care-unit until she left, defined our boundaries of investigation. We retrospectively collected data of 25 treatments to assess the CO2-emission based on the energy used by the MRI-scanner and the MR-HIFU device and the amount and type of medication administered. Solid waste was prospectively collected from five treatments.

Results

During an MR-HIFU treatment, 33.2 ± 8.7 kg of CO2-emission was produced by the energy consumption of the MRI-scanner and the MR-HIFU device and 0.13 ± 0.04 kg by medication administered. A uterine fibroid MR-HIFU treatment produced 1.2 kg [range 1.1 – 1.4] of solid waste.

Conclusion

Our study is one of the first studies to evaluate the CO2-emission of an MR-guided interventional radiology treatment, i.e. the MR-HIFU treatment of uterine fibroids. Life Cycle Inventory (LCI) databases, to perform a cradle-to-grave LCA, do not include all healthcare data at this point. Future studies are needed to perform a full LCA and to compare the outcomes to the LCA of other uterine fibroid therapies.

Key words

Sustainability; MR-HIFU; Uterine fibroid, Life Cycle Assessment.

INTRODUCTION

Reducing health care's impact on the environment is among the greatest challenges facing health care in the 21st century (1,2). Global warming is caused by the emission of greenhouse gases such as carbon dioxide (CO2) (2,3). Health care is currently responsible for nearly 8% of CO2-emission each year in the United States and 7% of CO2-emission in the Netherlands (3,4). Paradoxically, this CO2-emission contributes to decrease of health. In this way, health care intervenes with the Hippocratic oath, *"primum non nocere"*, first do not harm (2).

Fortunately, measuring the environmental impact of medical practices is gaining attention (5). The number of Life Cycle Assessments (LCAs) providing information on the environmental impact of certain treatments in health care has grown rapidly (6). LCA is a methodology to quantify a multifactorial range of environmental impacts, including climate change (mostly the result of CO2-emission), associated with the full life cycle of products, processes and systems (from cradle-to-grave) (5,7). The main life cycle phases are generally categorized as raw material extraction, manufacturing, use-phase and disposal (Figure 1). When performing an LCA, the environmental impact of all these products, processes and systems at all phases are analyzed together (7).

Within the field of radiology, measurements on environmental impact are performed, however not yet on single interventions (8). Attention is mainly paid on the energy consumption of the different diagnostic modalities and how to decrease (9-11). Because the amount of energy required to perform both diagnostic and interventional procedures is high, reducing energy consumption is a logical first step (12). In addition, as more radiological interventions become available that can compete with, or even replace, more conventional treatments, the environmental impact of these interventions should also be considered.

In 2016, (intervention) radiologists started performing the relatively new non-invasive Magnetic Resonance image guided High Intensity Focused Ultrasound (MR-HIFU) treatment for uterine fibroids in our hospital. MR-HIFU uses focused high intensity waves to ablate tissue under MRI guidance (13). Anno 2023, when introducing a new technique, attention should not only be paid to its (cost-) effectiveness compared to standard care but also to its environmental impact. Hitherto, no LCA has been performed for any MR-HIFU indication, nor any other MR-guided intervention treatment. We took the first steps towards a full LCA of the MR-HIFU treatment of uterine fibroids by evaluating the CO2-emission and the solid waste production of a single treatment.

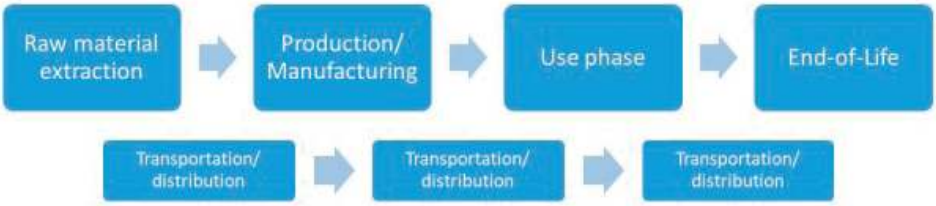

Figure 1: Life cycle system boundaries.

METHODS

An LCA includes four stages (Figure 2). In the first stage, goal(s) and scope are determined, resulting in setting the functional unit and system boundaries. In stage two, a life cycle inventory (LCI) is performed, collecting all materials and energy inputs and outputs and quantifying those for a complete product system (14). In the third stage, the Life Cycle Impact Assessment (LCIA), the potential environmental impact of these materials and energies is determined and in the final stage results are interpreted (15). This research was waived by our Local Medical Ethical Committee (IRB number 075).

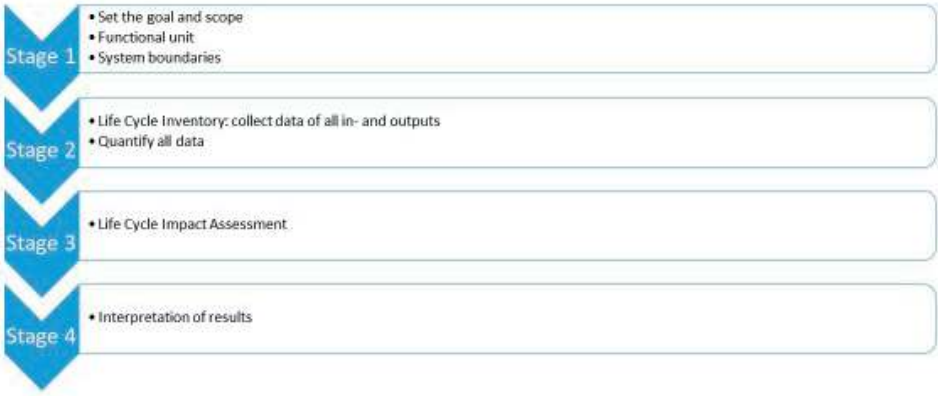

Figure 2: The phases of a Life Cycle Assessment.

Stage 1: Goal, scope and system boundaries

Our goal was to take the first steps of a full LCA by evaluating the CO2-emission and solid waste production of a uterine fibroid MR-HIFU treatment. The functional unit was a technically successful uterine fibroid MR-HIFU treatment performed on the latest version of the CE marked Sonalleve MR-HIFU platform (Profound Medical Corp. Mississauga, Canada) integrated into a 1.5-T MR-scanner (Achieva; Philips Health care, Best, the Netherlands) (13). We included processes, products and systems required from the moment the patient entered the daycare-unit to the moment she left. The

processes, products and systems needed during the patient's visit to the gynecology and anesthesiology department, the screening MRI-scan and all follow-up appointments were excluded. The manufacturing, transportation and construction of the MRI-scanner and MRI-room were also excluded, since we expected that the impact of the limited number of MR-HIFU treatments on total use of the MRI-scanner would be neglectable. The use and production of the non-sterile, linen reusable clothing worn by medical staff, the CO2-emission of commuting by medical staff and all monitors and computers were not part of our analysis either.

Stage 2 Life Cycle Inventory

We focused on three components whose outcomes are likely to differ between the different uterine fibroid treatments: energy used by the equipment during a treatment i.e. in case of an MR-HIFU treatment, the MRI-scanner and MR-HIFU device, the medication used during treatment and admission, and solid waste produced during treatment and admission (Figure 3). The environmental impact of these components in terms of climate change was determined using the LCI unit CO2-emission (kg).

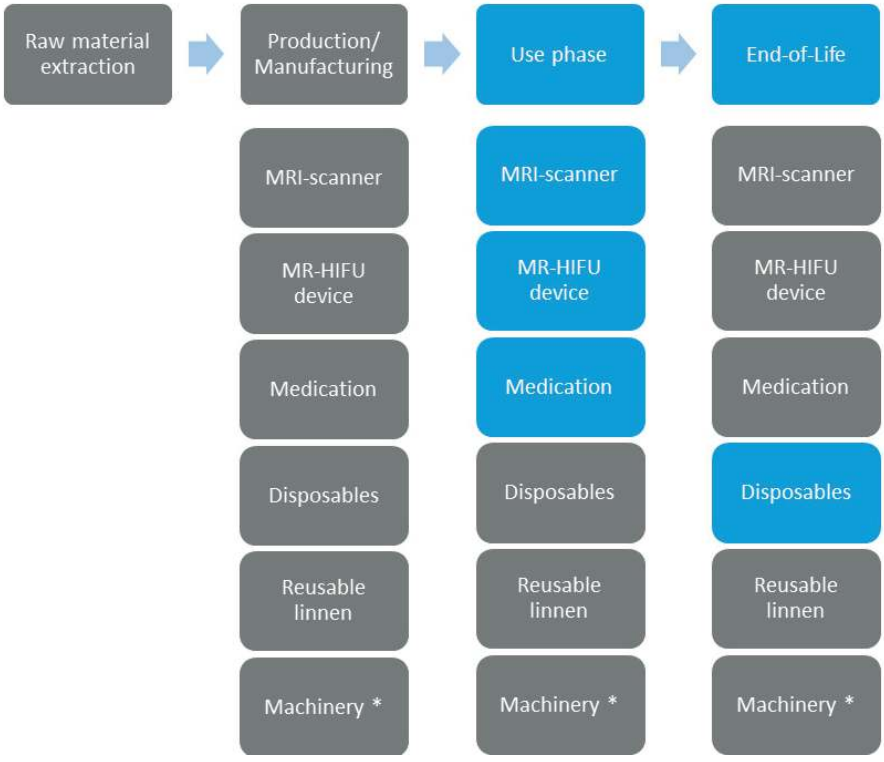

Figure 3: Life cycle of MR-HIFU treatment. *computers and devices used by the radiology and anesthesiology department e.g. blood pressure monitor. Grey: excluded. Blue: included in this study.

Data on energy consumption of the MRI-scanner and MR-HIFU device, and medication use were retrospectively collected of 25 uterine fibroid MR-HIFU treatments in the radiology department of our hospital between September 2020 and January 2022. Solid waste data was collected prospectively during five consecutive treatments in March and April 2022.

LCI Energy consumption: MRI-scanner

To assess the CO2-emission of the energy used by the MRI-scanner, the energy used by the 1.5-T Achieva MRI-scanner was measured in different activation states (active or idle). First, the average total treatment duration of the 25 treatments (time between first T2-survey MRI-sequence and last T1w-CE MRI-sequence) and average duration of the active and idle state were determined (Table 1). The duration of ablation was calculated by adding up the duration of all individual sonications during a treatment. The duration of the idle state of the MRI-scanner was calculated by subtracting the average duration of all MRI-sequences applied during a treatment (T2-survey, skin bubble, DWI, T2-planning and T1w-CE) and the duration of ablation from the total treatment duration. Subsequently, the energy consumption of the MRI-scanner was calculated per mode by multiplying the duration of a given state by the peak kW, using data from a previous report by Walthery (16). He assumed that a general 1.5T MRI-scanner uses 17 kW when active and 12 kW in idle state. An additional 33% kW should be added to the total, to cover energy usage by the cooling system. The energy consumed during ablation was expected to be comparable to the active state. The conversion factor to CO2-emission is 0.523 kg CO2/kWh when regular grey electricity is used (17).

Table 1: Overview of mean power, mean duration, mean and standard deviation energy use and mean and standard deviation CO2-emission of MRI-scanner and MR-HIFU device status during a uterine fibroid MR-HIFU treatment.

1.5T MRI-scanner	Power (kW)	Mean duration (minutes)	Energy use (kWh)	CO2-emission (kg)
Idle	12	149	29.7±8.2	
Active	17	30	8.5±2.4	
Ablation (active)	17	24	6.9±3.4	
Additional energy use 33%	n.a.	n.a.	14.9±3.9	
Total			60.0±15.6	31.4±8.2
MR-HIFU device				
Active	11	24	1.0±0.5	
Idle	1	178	2.5±0.6	
Total			3.5±1.1	1.8±0.6
MRI-scanner and device				
Total			63.5±16.7	33.2±8.7

CO2 Carbon Dioxide, *MR-HIFU* Magnetic Resonance image guided High Intensity Focused Ultrasound *kW* Kilowatt, *kWh* Kilowatt-hour, *n.a.* not applicable,

LCI energy consumption: MR-HIFU device

The manufacturer of the Sonalleve device provided us with the energy consumed during the active and idle states of the MR-HIFU device. The energy used in the idle state is 844 W. The additional energy used during ablation depends on the selected power by the treatment provider and should be multiplied by 11 to calculate total energy used during ablation. To calculate the average total energy consumed by the MR-HIFU device during a treatment, the average duration of idle state and ablation was multiplied by the energy consumed during the active and idle states of the MR-HIFU device, respectively.

LCI medication production and use

All oral and i.v. medication administered to the patient was collected to calculate an average use per treatment, together with the amount of oxygen applied by nasal cannula. The cradle-to-grave greenhouse gasses emissions for six anesthetic drugs and/or painkillers were retrieved from previous studies (6,18). According to Patvatker et al., the CO2-emission of medication is on average 340 g (18,19). Medication administered to only one of the 25 patients and combination therapy were excluded from analysis.

LCI waste audit

All disposables from five treatments were collected, counted and weighted. Packing material of sharp materials were included, sharp materials itself were excluded. Packaging of medication (e.g., glass flacons) was included after emptying. All waste was weighted in total and per five waste types, i.e. soft plastics including packaging, hard plastics, paper, paper including plastics and other. Gloves were weighted as part of the soft plastics and separately. For nitrile gloves only, a conversion factor (11.7 gCO2/g) was available to calculate the CO2-emission (6).

Stage 3 Life Cycle Impact Assessment

Since the LCI unit CO2-emission (kg) was our primary outcome and our LCI data was already converted to this unit, there was no need to perform an LCIA to calculate the additional environmental impact as outcome.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 26. Continuous variables were presented as mean (±SD) in case of a normal distribution. Distribution was assessed by normal probability plots and eyeball testing. Pearson’s rho test was used to analyze the correlation between uterine fibroid diameter and energy use.

RESULTS

Energy consumption

The average energy consumed by the MR-HIFU device during ablation turned out to be 150.0 ± 27.8 W per MR-HFU treatment. The average total energy used was 60.0 ± 15.6 kWh by the MRI-scanner and 3.5 ± 1.1 kWh by the MR-HIFU device per treatment (Table 1). This resulted in a CO2-emission of 31.4 ± 8.2 kg of the MRI-scanner and 1.8 ± 0.6 kg of the MR-HIFU device respectively. In total 33.2 ± 8.7 kg CO2-emission was produced per MR-HIFU treatment. A moderate positive correlation (Figure 4) was found between uterine fibroid diameter and energy use by the MRI-scanner (r= 0.559; p=0.004), the MR-HIFU device (r= 0.601; p=0.001) and both combined (r=0,562; p=0.003).

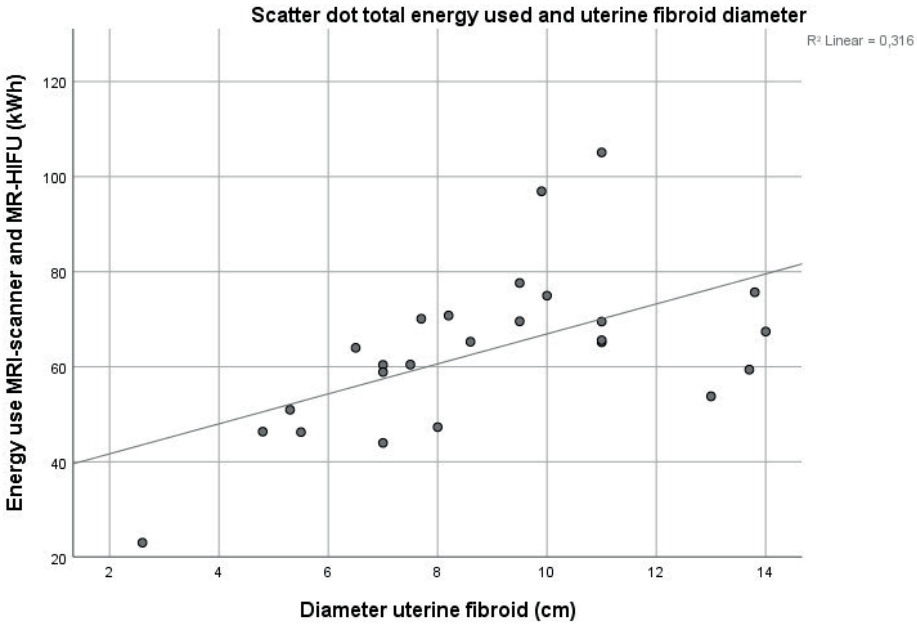

Figure 4: Scatter dot total energy used and uterine fibroid diameter.

Medication

Eleven types of medication were administered to at least five patients. Six additional types of medication were administered only once to different patients and one type of medication was combination therapy. The latter two were excluded from analyses (Table 2). All included medication administered during a uterine fibroid MR-HIFU treatment totaled 0.13 ± 0.04 kg of CO2-emission.

Table 2: Medication use during the MR-HIFU treatment of uterine fibroids.

Name, dosage, route	Average (number of patients (N) / percentage)	Range [min-max]	Conversion factor (gCO2/g)	CO2-emission (kg)
Propofol 2%, perfusor infusion	392.6 mg (25, 100%)	60.36 - 1000 mg	21	0.0083
Fentanyl 25-100mcg/ml	162.0 mcg (23, 92%)	25 - 550 mcg	96	> 0.000
Lidocaine 2%	17.2 mg (16, 64%)	10 – 40 mg	29	0.0005
Carbetocine 100mcg/mL	88.0 mcg (22, 88%)	0 - 100 mcg	340	> 0.000
Gadoteeracid 7.5mmol/15ml	7.5 mmol (25, 100%)	7.5 mmol	340	0.0026
Natriumchloride 0.9% perfusor infusion	266.2 mg (25, 100%)	116.25 – 450.00 mg	200	0.053
Paracetamol, 500mg tablet	1420.0 mg (24, 96%)	1000 – 3000 mg	7.8	0.011
Diclofenac, 50mg tablet	90.0 mg (20, 80%)	50 – 200 mg	340	0.031
Oxycodon short-acting, 10mg meltingtablet	10.8 mg (24, 96%)	10 – 30 mg	340	0.004
Microlax, 5mL sachet*	4.4 mL (22, 88%)	0 - 5 mL	x	x
Granisetron 1mg/mL	0.2 mg (5, 20%)	0 - 1mg	340	> 0.000
Oxygen 2L	221.1 min (24, 96%)	163 – 345 min	2.1	0.016
Buscopan 10mg/0.5mL **	0.4 mg (1, 4%)	0 - 10 mg		x
Pantoprazol 40mg tablet **	1.5 mg (1, 4%)	0 - 40 mg		x
Atropine, 0.5mg/mL**	>0.0 mg (1, 4%)	0 - 0.5 mg		x
Dexamethason 4mg/mL**	0.2 mg (1, 4%)	0 - 4 mg		x
Alfentanil 0.25mg/0.5mL **	0.1 mg (1, 4%)	0 - 0.25mg		x
Total per patient				0.125±0.04

* combination therapy ** medication applied to only one patient, both excluded from analysis. *MR-HIFU* Magnetic Resonance image guided High Intensity Focused Ultrasound, *gCO2/g* Gram Carbon Dioxide per gram.

Waste audit

Mean weight of the solid waste was 1.2 kg [range:1.1–1.4] (Table 3). The weight of the nitrile gloves was 83 grams, which equals 1 kg of CO2-emission.

Table 3: Waste audit of disposable materials used.

Product type	Mean weight (gram)
Soft plastics including packing	150 [range 92 – 178]
Gloves (measured as part of soft plastics)	*83 [range 38 – 111]*
Hard plastics	729 [range 644 – 1010]
Paper	18 [range 17 – 19]
Paper including plastics	163 [range 141 – 196]
Others	165 [range 0 – 298]
Total	1225 [range 1113 – 1346]

DISCUSSION

Despite the major impact of health care on the environment, the sustainability of (new) treatments is currently understudied. We took the first steps towards a full LCA of an MR-guided interventional radiology treatment, i.e. the MR-HIFU treatment of uterine fibroids, by evaluating the CO2-emission and the amount of solid waste produced during a single treatment. Our results can contribute to a comparison of the environmental impact of this non-invasive treatment with current (minimally) invasive standard uterine fibroid care.

Energy consumption

The operating mechanism of an MR-HIFU treatment is induced focused energy. Therefore, the energy consumed by the MR-HIFU device is an important contributor to total CO2-emission during treatment. The average energy consumption of the MR-HIFU device was 13.6 kWh, whereas the energy consumption of the MRI-scanner during treatment was more than four times higher. To put our results in perspective: the 33.2 kg of CO2-emissions produced by the MR-HIFU treatment we calculated, is equivalent to over 222 kilometers traveled by gasoline-powered vehicle (20).

However, this calculated amount of energy underestimate the total CO2-emission of a MR-HIFU uterine fibroid treatment, because we were not able to include all energy variables in our study. Since the MRI-scanner has an average lifespan of fifteen years, it is questionable whether the emission of construction of the MRI-scanner significantly contributes to the CO2-emission of a single treatment. At this point, data on the production of the MR-HIFU device is unfortunately lacking but it is expected to be a significant contributor since almost all treatments performed during its lifetime will be uterine fibroid treatments. Besides energy used by the MRI-scanner and MR-HIFU device itself, heating, ventilation, and air conditioning used in the MRI-room can also be relevant contributors (12).

Furthermore, since there is a significant positive association between size of the uterine fibroid and total energy use, the MR-HIFU treatment may be less sustainable when performed on a large fibroid.

In our analyses, we used the conversion factor “grey energy” (0.523 kg CO2/kWh) which is a representative Dutch combination of coal, gas and nuclear energy without considering the energy used to build the production facilities (17). Some countries showed a decrease in CO2-emission in the last decades, mainly caused by the transition to more “green” energy (6,21). The emission of a kWh energy generated by water, wind or solar energy is respectively 0.004, 0.014 and 0.061 kg CO2 (17). In our hospital, all energy is CO2 neutrally generated. Therefore, one could say that the exact amount of energy needed to perform the

MR-HIFU treatment is less relevant and with more renewable energy used in health care, MR-HIFU might be in favor compared to other treatments due to its operation mechanism. However, even “green” energy needs to be generated and keeping the cradle-to-grave theory in mind, this cannot be done fossil free.

Medication

The CO2-emission of pharmaceuticals is understudied and industry LCA publications cannot be verified, as they require access to confidential manufacturing practices (3,22). Medication accounts for around 25% of emissions within the British National Health Service (23). In our case, the amount of CO2-emission caused by medication used is about 250 times smaller than the amount caused by the energy used and is therefore only a small contributor.

There are also a number of other factors that have an impact on the calculation of CO2-emissions from medication applied which we could not take into account. To assess the CO2-emission of the medication administered during a uterine fibroid MR-HIFU treatment, we used CO2-emission data from previous studies, although they often did not include the emission of packing (6,18,19). McAlister et al. calculated that 90% of morphine CO2-emissions were caused by sterilization and packaging. Therefore, sterilization and packaging should not be neglected (22). Furthermore, we did not analyze the amount of unused and therefore disposed medication after treatment. Approximately 50% of propofol in an operating room can go unused and incorrect drug disposal can contribute to water contamination and toxicity (2). An important advantage of the MR-HIFU treatment over uterine fibroid surgery is that there is no need for anesthetic gases, which are a major contributor to the CO2-emissions from medication in general (6,23).

Waste audit

Hospitals in the USA generate 3.4 billion pounds of solid waste annually (7). The procurement supply chain causes most of the CO2-emission. Therefore, reduction of environmental impact could be achieved by decisions made in the production of products and processes. Clements et al. analyzed the type of waste used for interventional radiology treatments (24). Of the 72 products analyzed, 55% of their total weight consisted of waste and 76% was potentially recyclable. In our waste audit, waste weight was 1.2 kg, and if 76% could be recycled, only 0.3 kg of waste would be left.

Comparison to (minimally) invasive uterine fibroid treatments

The amount of solid waste collected during an MR-HIFU treatment of uterine fibroids is relevantly lower than the 13.7 kg of waste collected after the most often performed uterine fibroid treatment, hysterectomy (7). However, to be able to perform a comparison

between (uterine fibroid) treatments, full LCAs should be performed and no such studies are currently available for (minimally) invasive uterine fibroid treatments. An LCA on all energy use, materials and waste used in a radiological intervention room was performed by Chua et al.(12). They included 98 interventions, but without calculations per intervention. Embolization's were included in their analyses, but it is unclear whether these were uterine artery embolization's with uterine fibroids as indication (12). Within gynecology LCAs are performed comparing the carbon footprint of a disposable and a reusable vaginal speculum and delivery set (25-27).

Limitations

The main limitation of our study is that we did not perform a full cradle-to-grave uterine fibroid MR-HIFU LCA. Ideally, all phases of a product's life cycle would have been included, since interventions in one phase can lead to consequences in another phase (5). However, to some degree all LCA studies are incomplete because boundaries must be set to limit the amount of data and analysis required. Furthermore, primary data are often not available to researchers and therefore secondary data obtained from other sources are widely used in LCA (5). LCIs in general lack health care (system) data and materials and are, together with LCIA software, not available by open access. The reason for this seems to be the lack of awareness and transparency by vendors, hospital mechanics, energy suppliers etc. In our case, not all data needed for a complete MR-HIFU specific LCI was available or could be retrieved. Moreover, several assumptions needed to be made and averages needed to be used. However, despite the limitations, the work we presented here is relevant and important. Not only because we took the first steps towards an MR-guided intervention LCA and comparing its results to what is known about the environmental impact of (minimally) invasive uterine fibroid treatments, but also to provide more insights and awareness in the challenges of performing an LCA in health care and more specific (interventional) radiology (28).

Future perspectives

To reduce the environmental impact associated with providing health care, timely action is much needed. Having carried out this study and facing the challenges that remain, we would like to make some suggestions for change so that the (interventional) radiology community can take its responsibility and make a positive contribution. In our opinion, a combination of approaches should be implemented.

First of all, as physicians we should determine the appropriate indication for treatment and only treat when necessary and beneficial. We should minimize the usage of materials, substitute them by more eco-friendly products, move away from certain heat-trapping anesthetic gases, maximize instrument reuse or single-use device reprocessing and

reduce off-hour energy (7,29). Secondly, the purchasing departments of hospitals also need to focus on the environmental impact of the products they purchase and hospitals should collaborate with suppliers willing to give insights in the environmental impact of their products.

Thirdly, we should feel the need to perform LCAs and should be willing to contribute to them. To do this, conditions should be optimized and sustainability should be valued as much as (cost-) effectiveness. High quality complete LCI databases on health care and LCIA software should be open access available. Last but not least, research grants focusing on sustainability could contribute in the transformational process. By embracing the above described approach the (interventional) radiology community could take their responsibility to diminish their impact on climate change.

CONCLUSION

We took the first steps within MR-guided interventional radiology towards performing an LCA on a single treatment, i.e. the MR-HIFU treatment of uterine fibroids. Energy consumption of the MRI scanner and MR-HIFU device resulted in 33.2 kg of CO2-emission, medication administered in 0.13 kg of CO2-emission. Moreover, 1.2 kg solid waste could be collected during a uterine fibroid MR-HIFU treatment. However, full LCAs on treatments need to be performed to make a definite comparison of the environmental impact of different uterine fibroid treatments.

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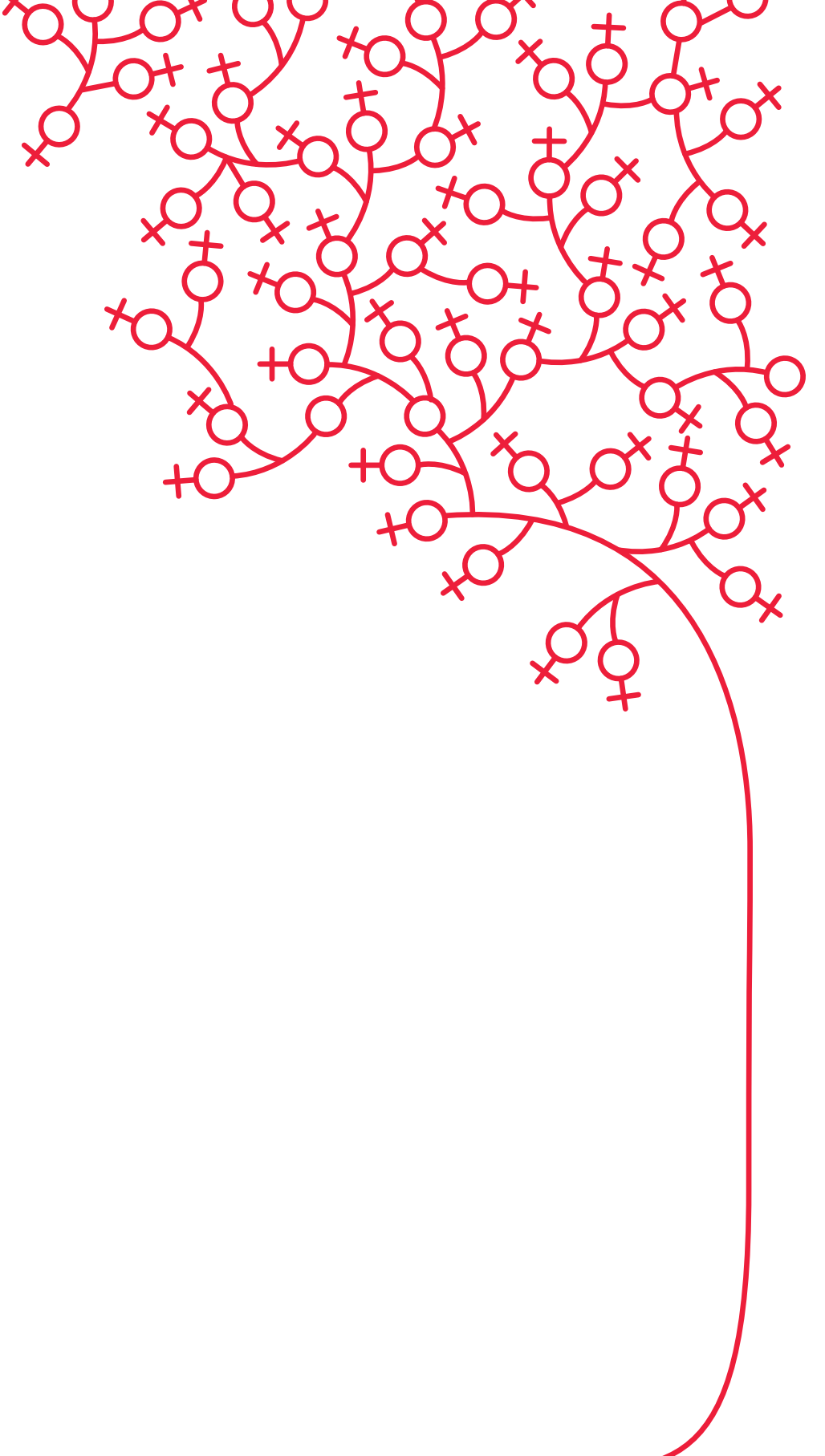

9

General Discussion and future perspectives

MR-HIFU is an effective, non-invasive treatment option for women suffering from uterine fibroids. With this thesis we focused on what, linked to previous work, additional steps are necessary to finally make uterine fibroid MR-HIFU treatment a choice for all women eligible for the treatment.

To be able to get to this point, our group needed to invest in theoretical and practical knowledge concerning uterine fibroid MR-HIFU treatments. First, we performed a systematic review including only full ablation protocol trials to be able to get insights in the latest effectiveness of the treatment (**chapter 2**). Reviews available at that time all included different ablation protocols and could therefore not provide the most up to date data with all known technical updates available.

When we started performing MR-HIFU treatments ourselves, future pregnancy wish was considered a contraindication. However, we soon learned that favorable reproductive outcomes were seen after treatment, without compromising on pregnancy safety. Reviews on reproductive outcomes after MR-HIFU including possible confounders we considered relevant, were however lacking (**chapter 3**). Therefore, we provided an up-to-date systematic review focusing on reproductive outcomes after uterine fibroid MR-HIFU treatment including these possible confounders (**chapter 4**).

A way to ease adoption of MR-HIFU treatment in a clinical setting, is by overcoming the technical hurdles remaining. One of these hurdles is the long treatment duration. By introducing a uterus stimulant during treatment, sonication efficiency improved by a decrease in Energy Efficiency Factor (EEF) and sonication time and an increase in thermal dose volume (**chapter 5**).

Since MR-HIFU is a rather technical treatment and multidisciplinary collaboration is essential, we faced difficulties on different levels when we started performing MR-HIFU treatments. Furthermore, we were not familiar with the length of the expected learning-curve, which complicated expectations on a management level. After finishing our first trial, we therefore decided to not only publish our clinical results, but also give insights into the hurdles we faced on six different levels, the lessons we learned, and the technical improvements we implemented (**chapter 6**).

To finally reach clinical implementation, data on long-term effectiveness and cost-effectiveness is necessary. This data should be collected by the currently gold standard: a randomized-controlled trial (RCT), comparing MR-HIFU to the standard care for uterine fibroids, which we do in the MYCHOICE study (**chapter 7**).

Anno 2023 we believe that the sustainability of (new) treatments should be as important as clinical effectiveness and cost-effectiveness. A Life Cycle Assessment (LCA) is the acknowledged way in the scientific community to inventory sustainability of treatments. Although performing a full LCA is not feasible at this point (**chapter 8**), we made the first steps in performing one for uterine fibroid MR-HIFU. In addition to this, the route to a full LCA within the (interventional) radiological community is discussed in this chapter as well.

First publications on the uterine fibroid MR-HIFU treatment date twenty years back. Performing new studies and publishing recent clinical results, is however still relevant because of, among others, the following reasons:

- Choosing the relevant effectivity outcomes is an evolving process that should transform from the classic, more research based outcomes (i.e. mortality rate), towards patient centered outcomes (i.e. quality of life). Other results might be found when these outcomes are analyzed;

- Over the years, the eligibility criteria for uterine fibroid MR-HIFU are both broadened and narrowed to make sure the most optimal group of women are selected for this treatment;

- Since the start of MR-HIFU treatments, multiple technical improvements of the ablation technique have taken place. One should keep in mind that the treatments MR-HIFU is often compared to, includes treatments that were already out there for decades. These treatments have been exposed to several improvements in the past. MR-HIFU effectivity data collected twenty years ago, do not represent the current technical possibilities of the MR-HIFU device nor current clinical effectivity;

- Implementation of new treatments is now a days more complex, especially for technical treatments, than it was in the past. Therefore, it is of relevance to share experiences on how treatments get adopted within the clinical field. To share what steps are necessary, which hurdles one could expect and how reimbursement, which is often necessary for implementation, can be gained.

PART 1: EFFECTIVITY OF GYNECOLOGICAL AND REPRODUCTIVE OUTCOMES

Measuring effectiveness of a treatment for a benign disease, like uterine fibroids, is not as easy as one might think. Classical medical outcomes, like mortality rate or time to survive, are not applicable. We experienced difficulties in implementing MR-HIFU treatment since

it is always directly compared to currently more invasive treatment options and their classical outcomes. When a new treatment is introduced, instead of using these classical outcomes, one should first consider which outcomes are relevant in this day and age for the specific patient group. In case of uterine fibroid treatments, we know women do prefer less invasive treatment options (1,2). At this point no uterine fibroid specific Patient Reported Outcome Measurement (PROM) is developed by the International Consortium for Health Outcomes Measurements group. In the meanwhile more general PROM's can be used, however relevant questions, like future pregnancy wish, lack (3,4).

The outcomes symptom severity, quality of life, non-perfused volume (NPV) percentage, reintervention rate and adverse events, are today most valued within the uterine fibroid treatment community. Previous studies showed that without a full ablation protocol, no optimal technical treatment result (e.g. a high NPV percentage) could be expected and therefore no optimal clinical results (5,6). When an NPV of 90% is accomplished, 86% decrease of symptoms can be reached (6). An NPV as close as possible to 100% should therefore always aimed for. In our clinical outcome review, we only included studies using a full ablation protocol, and found an overall NPV of 68% (**chapter 2**). This resulted in a symptom decrease of 49% after six months and a reintervention rate at 3–33.6 months follow-up between 0 to 21%, which is comparable to the uterus sparing alternative uterine artery embolization (UAE) (7). If a comparable review would have been performed including only more recent articles, better technical and clinical results are expected due to the many technical improvements and insights that are implemented in the meanwhile. The most recent reviews and meta-analysis did however not exclude older articles (8-10). With a rather technical treatment as MR-HIFU, one should not evaluate or compare a new treatment when technical improvements are still ongoing. When consulting a review, keep in mind that when older articles are included, the final results could be outdated.

For a long time, pregnancy wish was a contraindication to undergo a uterine fibroid MR-HIFU treatment. With the technique improving and knowledge growing, pregnancy is now a possibility after MR-HIFU treatment. Since uterine fibroids might interfere with fertility or can cause adverse pregnancy outcomes, in particular submucosal located fibroids, MR-HIFU might be a very welcome non-invasive treatment option for those women (11). Multiple other treatment options were already available for women with a pregnancy wish and uterine fibroids, but caution is needed when comparing these treatments on reproductive outcomes with MR-HIFU treatment (**chapter 3**). In the letter to the editor we wrote, we pointed out that possible confounders (like maternal age) should not be overlooked in this comparison and again, keep in mind that some treatments are more mature while technical improvements are still ongoing for the MR-HIFU treatment.

The biggest challenge we faced when performing our systematic review on reproductive outcomes, turned out to be the lack of (prospectively collected) data with reproductive outcome as primary outcome (**chapter 4**). To this day, no RCT's has been performed on reproductive outcomes. Indeed, most pregnancies reported after MR-HIFU treatment were part of the post FDA approval data, collected by the vendors and were unplanned pregnancies or at least pregnancies officially prohibited after treatment. More recent systematic reviews or meta-analysis performed included mostly the same data we used. In our review, a total of 124 pregnancies were reported in 114 women after MR-HIFU treatment, resulting in pregnancy rates between 7% and 36% and live-birth rate of 73%. Li et al. compared pregnancy and miscarriage rate after HIFU, myomectomy and UAE (12). Pregnancy rates after myomectomy (ratio 0.43) were significant higher compared to HIFU (ratio 0.18) and UAE (ratio 0.08). Live birth rates analyzed by Akhatova et al. were similar for UAE (70.8%), HIFU (73.5%) and transcervical radiofrequency ablation (TFA, 70%) (13). However, women undergoing myomectomy in the study by Li et al. were on average below 35 years of age, women undergoing HIFU close to 40 years. The study by Akhatova et al. did not include any information on reached NPV%. It is time (MR-) HIFU is considered a serious alternative and a prospective state-of-the-art RCT on reproductive outcomes should give more insights into the added value of this non-invasive treatment option for women suffering from uterine fibroids and a pregnancy wish.

PART 2: MEASURES TO IMPROVE EFFECTIVITY

Improving the MR-HIFU treatment effectivity is important work in progress and includes several aspects. One important aspect we have been focusing on in our group before, is the optimization of the eligibility criteria. The location of the fibroid in relation to other abdominal structures, could be an exclusion criterion. Since the ultrasound beam does not pass air pockets or bones, women were excluded when the fibroid was located on a retroverted uterus or when bowels were located in between. With the implementation of a manipulation protocol, we could increase the number of women eligible for the MR-HIFU treatment (14). Another reason women were often not eligible, was due to the uterine fibroid tissue type, e.g. a high T2 signal intensity (SI). A high SI is thought to be the result of more high water content tissue, which is more difficult/needs more energy to be heated until cell dead occurs (15).The currently most used screening tool is the Funaki classification, categorizing uterine fibroids into three groups based on their SI compared to the SI-scores of the surrounding tissue (i.e. fat and muscle). Better results were seen when Funaki type 3 uterine fibroids are excluded from treatment (16). A comparable theory is used with the numeric signal scale intensity (SSI) by Park et al., claiming that the higher the SSI-score, the more difficult treatment will be (17). However, in reality it turned it out

that using this classification did not automatically result in satisfying treatment results. Some high SI fibroids turned out to be easy to treat, whether others with a low SI were not. Our group published on this topic when analyzing more advanced MRI-screening parameters as a next step towards a more optimal screening protocol (15).

Another aspect of improving effectivity is optimizing treatment time. Compared to, for example UAE, MR-HIFU is a rather time consuming treatment (18). Aiming for a shorter treatment can be done by making ablation more efficient, without jeopardizing safety (**chapter 5**). By the administration of the uterus stimulant carbetocine on a sonication level, we were able to decrease the EEF and treatment time and increase thermal dose volume. Although with this study design, it was not possible to evaluate effect on total treatment duration, it is expected treatment itself could be shortened. Jeong et al. compared women treated with carbetocin during MR-HIFU, to women in a control group who did not receive carbetocin and Zhang et al. analyzed the efficiency of adenomyosis tissue treated by ultrasound guided HIFU after administration of another uterus stimulant, called oxytocin (19,20). In their studies, the use of the uterus stimulant had a significant impact on several efficiency parameters on a treatment level. This resulted in a significant decrease in sonication time.

The use of a uterus stimulant and the previous mentioned manipulation protocol are now part of our standard treatment protocol, and among the several suggestions we made in our article on how we implemented MR-HIFU in our hospital (**chapter 6**). When we started performing uterine fibroid MR-HIFU treatments several years ago, we noticed no guidelines were available on how to efficiently perform the treatment, how to implement the treatment in a hospital structure and how to technically optimize the treatment. The uterine fibroid MR-HIFU treatment is a multidisciplinary treatment, involving both gynecologists and radiologists who need to collaborate closely to make implementation successful. We therefore decided to share our experiences and the lessons we learned on a technical, patient selection, patient counseling, medical specialists and organization level when implementing uterine fibroid MR-HIFU. Our article showcased our individual situation, based on the Dutch healthcare system. Nevertheless we believe that sharing these lessons, both successful and not successful, together with the implementation of the previous mentioned effectivity improvements, will help other hospitals with starting performing MR-HIFU and that our article can act as realistic roadmap. Furthermore, since MR-HIFU is a rather technical treatment, one should expect a learning-curve and this means that the first treatments will take place without satisfying results. It is important to be aware of this learning-curve at the start of implementation, in particular on a management level. When technical improvements and our lessons learned are implemented from the start, it is likely that the estimated learning-curve of 25 treatments could be shortened. Our work must be seen as work in progress, even seven years after performing the first MR-HIFU treatment in our hospital, our staff

is still learning from every case and this again is an example of how the treatment is still optimizing and why new research and publications remain relevant.

PART 3: SOCIETAL IMPACT

How can we eventually make sure all women willing to undergo a non-invasive uterine fibroid MR-HIFU treatment have the choice to do so? Therefore the treatment should become easily accessible and unconditionally reimbursed. And when reimbursement for uterine fibroid MR-HIFU is realized, this could act as a snowball effect, resulting in reimbursement for other MR-HIFU indications as well. At this point, uterine fibroid MR-HIFU is only reimbursed in a few countries, and only under limited conditions (18). For a treatment to become reimbursed in the Netherlands, it must comply with the current "Stand van Wetenschap en Praktijk" (21). This means that an essential step towards final clinical adoption is to perform an RCT with high quality long-term data and (by patients defined) relevant effectivity and cost-effectiveness outcomes. The RCT data currently available are sparse and lack in particular long-term data. By performing a multicenter RCT ourselves, we can take the next step towards reimbursement in the Netherlands (**chapter 7**). Performing an RCT, although seen as high quality evidence based medicine, has its limitations, in particular when results need to be translated to real life data. Often in- and exclusion criteria are too strict, inclusion takes way longer and the process is more expensive, spending community research money on one single study. In the design of our RCT, we decided to work with an uncommon unequal randomization ratio of 2:1. By doing so, more women could undergo the otherwise unavailable MR-HIFU treatment. The control group includes three most often offered uterine fibroid treatments, besides medication. In our opinion this reflects best the real world situation where women can choose between several, already reimbursed treatments. Nevertheless, this study design was not our preferred design to begin with. We try to give women more choices in the treatment of a disease effecting their daily life, but in the route to do so, we force them to participate in a very paternalistic study design. This is outdated and more and more research show us, the design is not even the best way to answer the questions (22,23). From the start we advocated for a more liberal, more patient friendly, more modern, more inclusive and less expensive design: a registry. In a registry all women undergoing any type of uterine fibroid treatment will participate. It is less of a burden for both the patients and the study team, leading to faster inclusions. Furthermore, in our current RCT, for obvious logistic reasons, not all available treatment options are included. Transcervical radiofrequency ablation techniques, like the Sonata® treatment are lacking. In The Netherlands however, extensive research is currently performed on this minimal-invasive treatment option (24). Therefore, if we would like to get more clarity on the position of MR-

HIFU treatment within the uterine fibroid treatment options field, the Sonata® treatment cannot be ruled out.

With our RCT, not only clinical effectiveness but also cost-effectiveness will be analyzed and this is a crucial element in final implementation, but also in gaining equality. Compared to other uterine fibroid treatments, recovery time after MR-HIFU is shorter and due to the lower complication risk, readmission rate is lower as well (25). A health technology assessment is not performed yet on this topic, including this lower work absence, but implementing MR-HIFU is expected to result in a decrease of sickness absence and increase of labor productivity. When taking into account the large number of women suffering from uterine fibroid symptoms during their working lifetime, this could have an impact on equality on the workplace in general.

Although work still needs to be done for the clinical implementation of the uterine fibroid, this does not release us from our responsibility to look towards the future. Clinical effectiveness and cost-effectiveness are the two most important criteria at this point when it comes to comparing treatments. Sustainability however, should and will become another one in the near future. When applying for funding, this is not a criterion yet, but the importance is felt more and more with several recent publications bringing the impact of healthcare on climate change to our attention (26). The way to be able to compare treatments on a sustainability level, is by performing an LCA (27). This includes all materials and elements used by and during a treatment from cradle-to-grave. However, since life cycle inventories, the necessary databases, often lack healthcare materials at this point, it is not feasible to perform a complete LCA of a treatment. This definitely does not discharge us from the responsibility to pay attention to this field (**chapter 8**). We took the first steps towards an LCA and advocated for action within the field of (interventional) radiology to perform LCA's since, in particular intervention radiology, may be a more sustainable alternative for current surgical procedures.

FUTURE PERSPECTIVES

Current developments

Besides the collection of long-term (cost-) effectiveness data, performed by several groups around the world at this moment, important developments within (uterine fibroid) MR-HIFU are mostly on the technical aspect. The most recent MR-HIFU device update focused on more detailed aligning of the different abdominal structures and tissues through which the focused ultrasound beam passes during ablation. This has a direct effect on cooling time. The long cooling time in-between sonications is one of the treatment hurdles

since it results in long overall treatment time. To maintain treatment security, cooling the surrounding tissue is essential, but with more detailed defining and aligning of the type of tissue, cooling time could be decreased. Due to an adjustable DISC temperature and a higher maximum fat temperature, mandatory cooling times are shorter as well. Furthermore, the maximum power that could be used is increased, making treatment of more dense uterine fibroid tissue possible.

Another route to decrease treatment duration is by the development of a tool to evaluate treatment effect during the treatment. Final treatment result is evaluated at this point by the administration of a contrast agent, showing the non-perfused volume on a T1-weighted MRI-scan. By the use of Diffusion Weighted Imaging (DWI) and a deep learning algorithm, the post-HIFU treatment effect can be evaluated without a contrast agent. When successfully applied intra-procedurally, the treatment effect can be assessed during treatment and thereby over-treatment (continuation of sonications while 100% NPV is already reached) or under-treatment (termination of treatment while vital uterine fibroid tissue is still there) could be avoided (28).

Another development within the uterine fibroid MR-HIFU field, is to make patients eligible that might not be eligible at first. By hormonal pretreatment, for example prescribing GnRH analogues before MR-HIFU treatment, uterine fibroid tissue could become less moist and therefore easier to heat by sonications (29).

The use of big data in healthcare, machine learning and other artificial intelligence tools can help to predict treatment outcomes, based on visible and non-visible parameters (30) or can contribute to more precise eligibility criteria. Especially with the use of so called radiomics, hundreds of features could be analyzed together or separately by computer to develop currently unknown eligibility criteria.

At this moment, deep learning-based volumetry can already be used to facilitate automatic NPV percentage calculation. In clinical practice, the post-HIFU NPV percentage is often not measured but only estimated since manual delineation is a time consuming task. Deep learning algorithms are able to automatically segment the uterus, fibroids and NPV's for volumetry purposes, with relatively strong correlations to manually measured volumes (31).

On the reimbursement part, different ablation techniques are evaluated at this point in the Netherlands and this leads to increasing evidence that when results on effectiveness turn out to be positive, ablation techniques on the uterus as a general treatment option, might become reimbursed.

Future recommendations

To make sure relevant outcomes are used in future research, uterine fibroid specific PROMs should be developed. This will help in answering the question which treatment is most suitable for which patient with her specific symptoms, expectations and desires when it comes to a treatment. This could also be used in currently available and future patient decision tools, to make shared decision making possible in the consultation room of the gynecologist (32). To be fully able to inform patients, it is necessary to include more treatments (e.g. the Sonata® treatment) into future comparison studies. The earlier mentioned registry study could and should be the study design that is used after finishing the MYCHOICE study to monitor its place and effectiveness compared to other treatment options.

Uterine fibroid specific PROM's, including pregnancy wish, should also be used for the design of an RCT specific for reproductive outcomes. This RCT will show the position of the MR-HIFU treatment compared to currently used treatment options. It would make most sense to compare with myomectomy, since this treatment is being considered the current golden standard for this group of women, however, UAE and transcervical radiofrequency ablation techniques should not be ruled out (7). In the meanwhile, the location of the uterine fibroids that would be included in this RCT should be clearly defined. Fibroids that could be removed by hysteroscopy, are often not eligible for MR-HIFU and visa versa and this could bias the final outcomes of the trial. Furthermore, the prognostic factors we mentioned earlier in our reproductive outcome review (e.g. NPV percentage reached, maternal age) obviously should be taken into account as well.

On the implementation part in general, it is of relevance to mention that technological innovations are more difficult to implement compared to, for example, the implementation of a new drug. This has to do with the many aspects that are involved in a technical treatment that could impact treatment quality (e.g. logistics, quality of trained staff, learning-curve effect, quality of the device). Fortunately, attention is being paid for this problem, and resulted in the development of the "Veelbelovende zorg" funding program (33). This program does not only offer the financial support to be able to prove the effectiveness of technical innovations, but also assist in the process of gaining reimbursement. It would however be interesting, to gain more knowledge on why some treatment options, even after reimbursement are available, and others are not.

To come to final implementation and adoption of the uterine fibroid MR-HIFU treatment, dissemination is necessary. By performing the MYCHOICE study, we hope the mandatory in between step, gaining reimbursement, can be achieved within the Netherlands. However, this will not guarantee dissemination, as was seen by UAE in the past (34). To get to

dissemination, the MR-HIFU treatment should be part of current regulations and adopted by all the relevant medical specialists and their national associations. Since the treatment is a multidisciplinary treatment, this means that commitment from several (i.e. gynecologists, radiologists) societies is vital and even when the treatment is part of their regulations it is essential to keep them updated regularly.

Furthermore, a possible hurdle for dissemination that should be taken into account from the start, is the fact that not all hospitals (will) offer the MR-HIFU treatment. When keeping in mind the efficiency movement of “De juiste zorg op de juiste plek” and the recently developed “Integraal Zorgakkoord”, it makes more sense to invest in three maybe four MR-HIFU centers in the Netherlands (35,36). The MR-HIFU treatment is a technical advanced treatment and should therefore only be offered in expertise centers, especially, in a country like the Netherlands where travel distances are considered short by international standards. However, one should not discard the hurdles some patients might face and are not be able to overcome to travel to a hospital further away. This might even have an impact on the choice women make, especially since other uterine fibroid treatments are often offered by all hospitals in the Netherlands. Aiming for three to four topographically well spread centers is therefore of importance.

Offering the MR-HIFU treatment in only expertise centers also means that the logistics, when it comes to referring, should be clear. This includes clear eligibility criteria and rereferral in case patients are not eligible or not interested after counseling. Again, this also makes clear why participation of the national associations is crucial. They should be in the lead when it comes to assigning specific hospitals for specific treatment options (e.g. transcervical radiofrequency ablation, UAE, laparoscopic myomectomy) and they should carry this message.

To finalize, even when MR-HIFU is well disseminated and the treatment available among the country, it is essential to monitor the quality of both the treatment and the logistics in all expertise centers. In the best case scenario, all sites have multidisciplinary and multicenter meetings on a regular basis to keep each other sharp and up to date.

In this thesis, the focus is mainly on the Magnetic Resonance Image (MRI) guided HIFU technique. However, developments are ongoing with the Ultrasound guided HIFU technique as well (37). At this point, no direct comparison has been performed between the two techniques. Since steering the devices are very different from each other and both require years of experience and overcoming a learning-curve before relevant effects could be expected, it is unlikely a direct comparison on one site will take place (38,39). Furthermore, differences should not be expected of clinical effectiveness, but more on cost-effectiveness,

treatment duration, adverse events and logistics. The development of uterine fibroid PROM should however first point out whether these outcomes are of great importance for the concerned patients.

When it comes to the sustainability of the MR-HIFU treatment, but also health care in general, only some first steps are taken at this point. Suggestions for improvement range from sustainability labels for medication to easing the rules around re-use (40,41). A full cradle-to-grave LCA on a uterine fibroid MR-HIFU treatment should be aimed for and compared to cradle-to-grave LCAs on other uterine fibroid treatments. Included in this LCA should be the movements of all patient travelling to the previous mentioned expertise centers. In our LCA study, we did not include the travel distance of the 25 women we retrospectively analyzed, although we did collect this data. At that time, our hospital was the only hospital in the Netherlands performing uterine fibroid MR-HIFU treatment on a regular basis. Therefore, women from all over the country came to us, with an average single travel distance of 93 km. Besides the travel for the treatment itself, women needed to visit the gynecologist at least once before treatment. Four times 93 Km equals 55 kg CO2 emission per patient when traveled by gasoline-powered vehicle (42). This shows that decisions made based on effectiveness and cost-effectiveness, have consequences for sustainability and this re-emphasizes why sustainability should be equally important for future research.

CONCLUSION

To finalize, when implementing a new treatment one should consider the following: outcomes that are used to evaluate or compare effectiveness should be relevant for the specific patient group and treatments should not be compared when technical optimization is not yet finalized. To make sure uterine fibroid MR-HIFU will become a choice for all women, the positioning of the MR-HIFU for uterine fibroid should be clear. Performing an RCT (the MYCHOICE study) is therefore essential, as is the performance of an RCT focusing on reproductive outcomes. Anno 2023, we cannot close our eyes for the impact healthcare has on climate change and therefore, future research should not only provide effectiveness and cost-effectiveness data, but data on sustainability as well.

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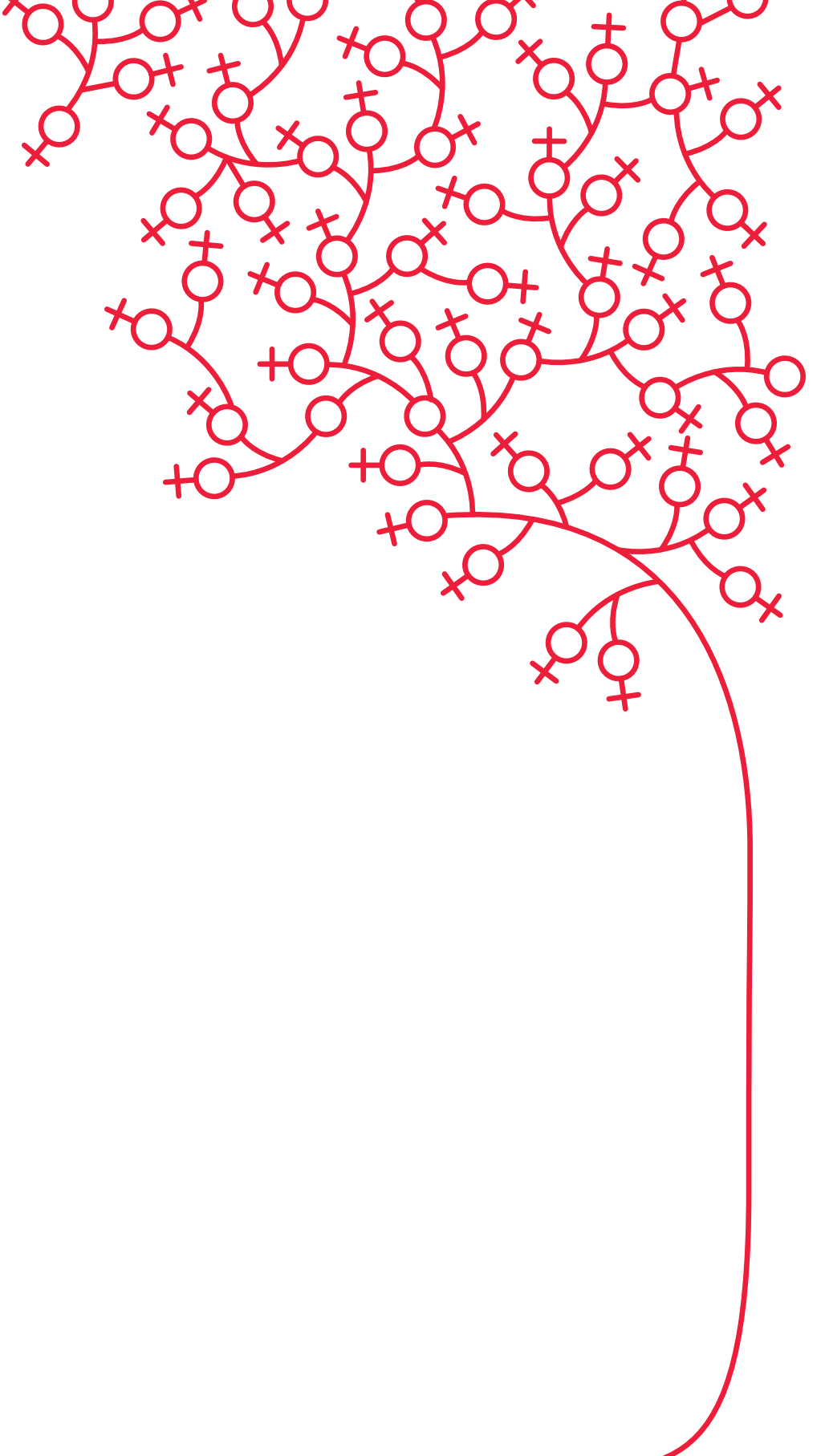

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Summary

Although the MR-HIFU treatment of uterine fibroids have been available for over 20 years, still most women worldwide, including the Netherlands, have no access to this non-invasive treatment option. In this thesis some of the remaining hurdles were addressed.

PART 1: EFFECTIVITY OF GYNECOLOGICAL AND REPRODUCTIVE OUTCOMES

In **chapter 2** we evaluated the results of uterine fibroid MR-HIFU that were available at this point. Our work differed from previous work since we only included studies without a restricted treatment protocol. This means that the studies aimed for a complete treatment and we showed that this resulted in more decrease of uterine fibroid related symptoms and less re-interventions. Long-term data is however still missing.

In **chapter 3** we commented on previous work on reproductive outcomes after different uterine fibroid treatments. Since factors like maternal age can influence pregnancy changes alongside the presence of a uterine fibroid or treatment effect, one should be careful when publishing data without taking this in consideration.

In **chapter 4** previous studies were analyzed as well, however this time solely focusing on reproductive outcomes. An important advantage of (MR-) HIFU treatment is the fact that a pregnancy afterwards is possible. We showed complications did not occur more often in women treated by (MR-) HIFU. Whether (MR-) HIFU results in more pregnancies for women suffering with uterine fibroids, is however still unknown due to the limited number of pregnancies reported.

PART 2: MEASURES TO IMPROVE EFFECTIVITY

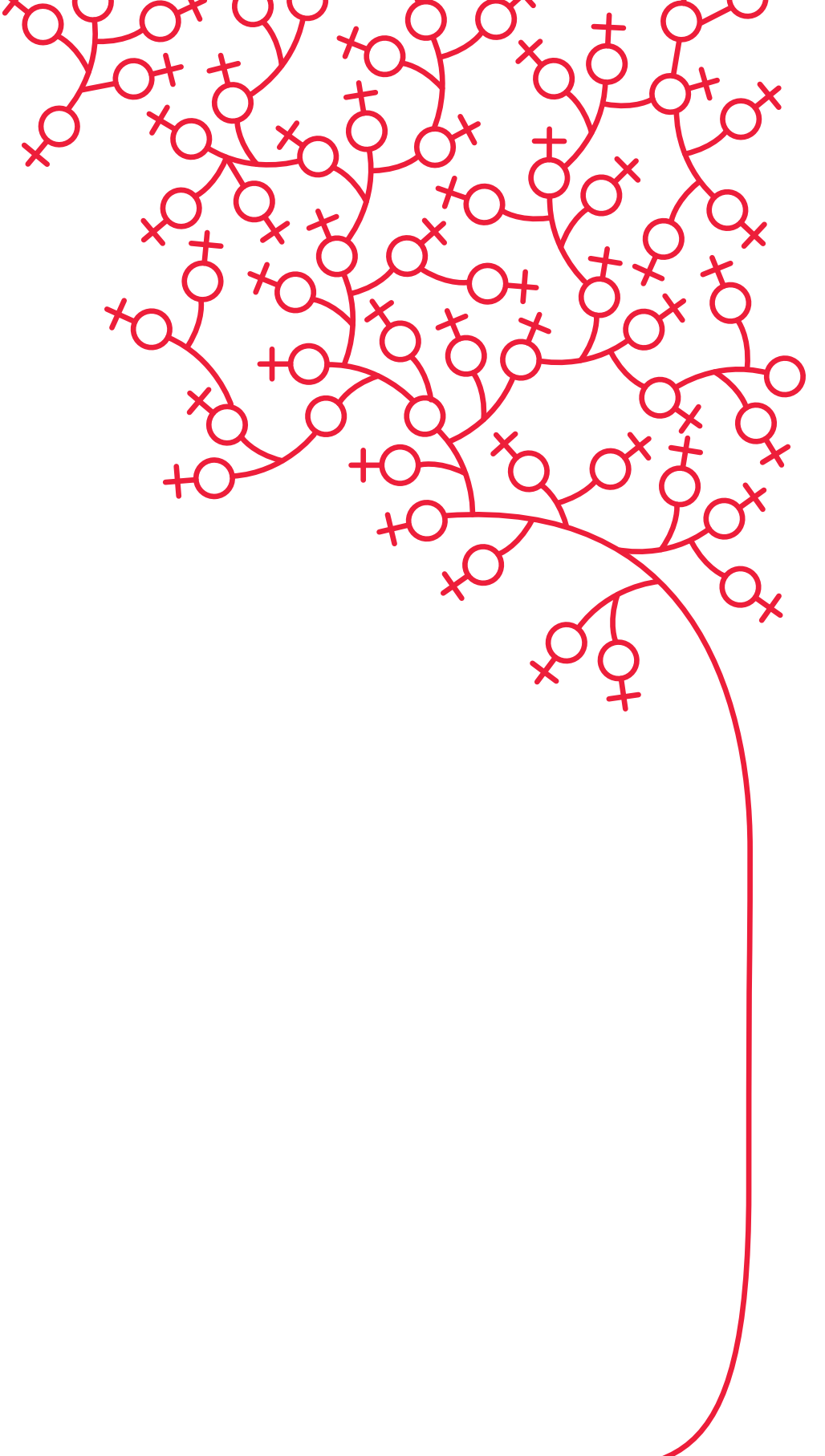
In **chapter 5** the contribution of a uterus stimulant to treatment efficiency was evaluated. When a uterus stimulant is administered, contractions of the uterus result in less blood flow in the tissue that needs to be treated. The aimed temperature can be reached more quickly, resulting in more efficient treatments. In our article we were able to prove this effect on a treatment cell level instead of a patient level.

In **chapter 6** we reflected on the implementation of uterine fibroid MR-HIFU in our own non-academic hospital. We evaluated all the hurdles we needed to overcome on different levels and gave insight on the learning-curve of 25 treatments one should consider when performing uterine fibroid MR-HIFU due to the technical difficulties of the treatment.

PART 3: SOCIETAL IMPACT

In **chapter 7** we are aiming to overcome the most important hurdle for clinical implementation: the lack of reimbursement. Due to the lack of randomized-controlled trials on long-term effectiveness of uterine fibroid MR-HIFU, no reimbursement is reached in the Netherlands. By performing the MYCHOICE study, of which the study protocol can be found in chapter 7, we aim for clinical implementation and reimbursement.

In **chapter 8** we took another look at the future and took the first step in performing a Life Cycle Assessment of a MR-HIFU treatment to get insights in the sustainability of this treatment. At this point, unfortunately not all necessary data is available to perform a full Life Cycle Assessment. We did however inventoried what would be necessary and focused on the importance to perform such analyses.



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Dutch /
Nederlandse samenvatting

Hoewel de MR-HIFU behandeling van myomen (vleesbomen) al ruim 20 jaar bestaat, is de behandeling voor de meeste vrouwen, ook in Nederland, die last hebben van myomen, niet beschikbaar. Dit proefschrift is gericht op het verhelpen van een aantal obstakels die de oorzaak zijn van het gebrek aan toegang tot de MR-HIFU behandeling.

DEEL 1: EFFECTIVITEIT VAN GYNAECOLOGISCHE- EN ZWANGERSCHAPSUITKOMSTEN

In **hoofdstuk 2** werd gekeken naar de effectiviteit van de MR-HIFU behandeling door de resultaten van verschillende studies op een rij te zetten. In tegenstelling tot eerdere reviews, includeerde wij enkel studies waar gestreefd werd naar volledige ablatie: dat wil zeggen, het volledig behandelen van het myoom. Door dit te doen is er meer klachten afname en minder kans op de noodzaak voor een nieuwe behandeling. Lange termijn data ontbreekt op dit moment echter nog.

In **hoofdstuk 3** gaven we commentaar op een andere review die de zwangerschapsuitkomsten van verschillende myoombehandelingen met elkaar vergeleek. In die studie werd echter geen rekening gehouden met belangrijke bijdragende factoren zoals de leeftijd van de vrouwen. We wezen er in ons commentaar op dat dit wel noodzakelijk is alvorens een dergelijke review gepubliceerd kan worden.

In **hoofdstuk 4** publiceren wij onze eigen review waar we de zwangerschapsuitkomsten na een (MR-) HIFU behandeling op een rij zetten. Een zwangerschap is namelijk mogelijk na een (MR-) HIFU behandeling. We zagen dat het aantal complicaties tijdens de zwangerschap of bevalling niet verhoogd leek. Of door de behandeling meer vrouwen zwanger worden, is nog onduidelijk door het lage aantal zwangerschappen waarover na een (MR-) HIFU behandeling is gepubliceerd.

DEEL 2: MAATREGELEN OM EFFECTIVITEIT TE VERBETEREN

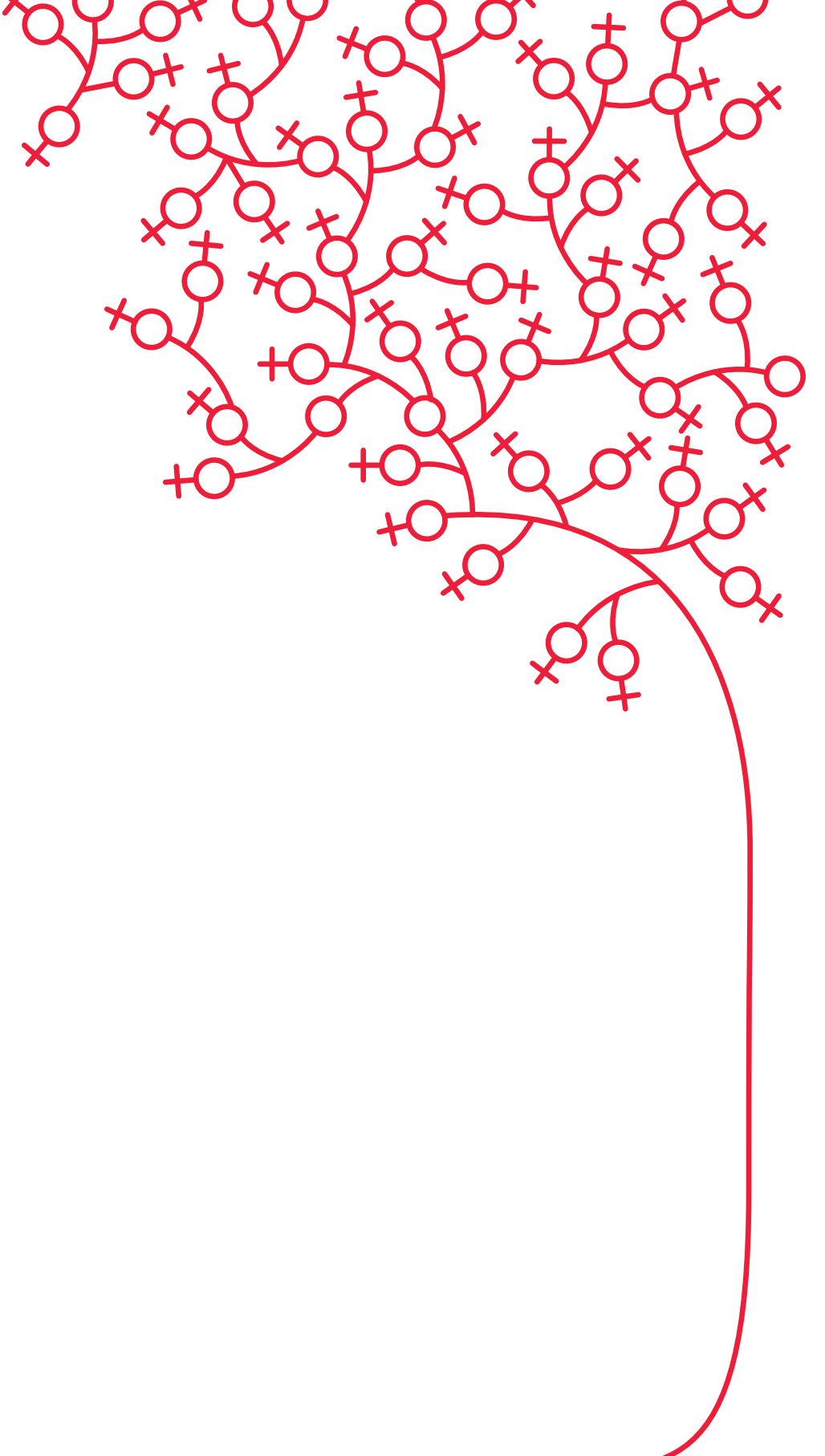
In **hoofdstuk 5** bekeken we het effect van een baarmoeder stimulant op de effectiviteit van de ablatie. Door de stimulant gaat het baarmoederweefsel samenknijpen wat resulteert in minder vocht in het weefsel, dat vervolgens sneller opgewarmd kan worden. Op die manier wordt de behandeling efficiënter. In tegenstelling tot eerdere onderzoeken konden we dat effect op ablatieniveau i.p.v. op patiënt niveau laten zien.

In **hoofdstuk 6** evalueerden we de implementatie van de myoom MR-HIFU behandeling in ons niet-academische ziekenhuis. Op verschillende niveaus hebben we onze geleerde lessen in kaart gebracht en konden we aan de hand van de data van de eerste 70 behandelingen laten zien dat een leercurve van 25 behandelingen nodig is voor de techniek.

DEEL 3: MAATSCHAPPELIJKE IMPACT

In **hoofdstuk 7** publiceerden we het studie protocol van de MYCHOICE studie. Het doel van deze studie is om uiteindelijk het laatste obstakel voor klinische implementatie te verhelpen: vergoede zorg. Daarvoor is lange termijn data van een randomized-controlled trial nodig. Middels deze MYCHOICE studie hopen we klinische implementatie en vergoeding te bewerkstelligen.

In **hoofdstuk 8** keken we nog verder in de toekomst en zetten een eerste stap richting het uitvoeren van een Life Cycle Assessment van een myoom MR-HIFU behandeling. Naast effectiviteit en kosteneffectiviteit zal in de toekomst ook de duurzaamheid van een nieuwe behandeling moeten worden meegewogen. Op dit moment is het uitvoeren van zo'n volledige assessment echter nog niet mogelijk door het ontbreken van essentiële data. In het artikel inventariseerden we welke stappen daar nog voor genomen moeten worden en brachten onder de aandacht waarom het analyseren van duurzaamheid van behandelingen van belang is.



Addendum

LIST OF ABBREVIATIONS

ADC: Apparent Diffusion Coefficient
BRB: Bladder filling, Rectal filling, Bladder emptying
CE: Contrast-Enhanced
CO2: Carbon dioxide
CS: Caesarian Section
DILI: Drug-Induced Liver Injury
DISC: Direct Skin Cooling
DWI: Diffusion-Weighted Imaging
EEF: Energy Efficiency Factor
EM: Equivalent Minutes
EQ-5D-5L: 5-level version of the EuroQoL questionnaire
FAIR: Findable, Accessible, Interoperable and Reusable
FIGO: Fédération Internationale de Gynécologie et d'Obstétrique
FUS: Focused Ultrasound
GnRH: Gonadotropin-Releasing Hormone
HIFU: High Intensity Focused Ultrasound
HMB: Heavy Menstrual Bleeding
IDEAL: Idea, Development, Exploration, Assessment and Long-term study
iMCQ: iMTA Medical Consumption Questionnaire
iPCQ: iMTA Productivity Cost Questionnaire
ISP: IntelliSpace Portal
LCA: Life Cycle Assessment
LCIA: Life Cycle Impact Assessment
LCI: Life Cycle Inventory
MaSS: Myoma Screening Study
METC: Medical Ethics Review Committee
MRgFUS: Magnetic Resonance guided Focused Ultrasound Surgery
MR-HIFU: Magnetic Resonance image guided-High Intensity Focused Ultrasound
MRI: Magnetic Resonance Imaging
MUM: Manual Uterine Manipulation
MYCHOICE: MYoma treatment Comparison study: High-intensity image–guided fOcused ultrasound versus standard (minimally) Invasive fibroid care—a (Cost) Effectiveness analysis
NPV: Non-Perfused Volume
PREM: Patient Reported Experience Measurement
PROM: Patient Reported Outcome Measurement
PSA: Procedural Sedation and Analgesia

QoL: Quality of Life
RCT: Randomized Controlled Trial
RFTVA: Radiofrequency Volumetric Thermal Ablation
SARM: Selective Androgen Receptor Modulators
SI: Signal Intensity
SOP: Standard Operating Procedure
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SPRM: Selective Progesterone Receptor Modulators
SSI: Scaled Signal Intensity
SSS: Symptom Severity Score
T1w-CE: Contrast-Enhanced T1-weighted imaging
T2w: T2-weighted imaging
TE: Echo Time
tHRQL: transformed Health Related Quality of Life
tSSS: transformed Symptom Severity Score
UAE: Uterine Artery Embolization
UF: Uterine Fibroids
UFS-QoL: Uterine Fibroid Symptom Health-related Quality of Life questionnaire
UPA: Ulipristal Acetate
USgHIFU: Ultrasound guided High Intensity Focused Ultrasound

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2019 Methodologie en Statistiek, Isala Academy
2020 Sedatie en Advanced Life Support voor Artsen (SALSA) cursus, Isala Academy
2020-2021 Capita Selecta Course ImagO (digital), UMCU
2021 Medische Beeldvormende technieken (digital), UMCU
2021 Writing a Scientific Paper (digital), UMCU
2021 Good Clinical Practice (digital), Isala Academy
2021 PhD Council Graduate School of Life Sciences PhD Day 2021 (digital), UMCU
2021 Responsible Conduct of Research (digital), UMCU
2021 Analytic Storytelling (digital), UMCU
2022 Effective LCA with SimaPro Desktop, PRé

Training

2020-2022 Monthly supervision of (co)promotores
2019-2022 Weekly research meetings Radiology department, Isala Hospital

(Inter)national presentations & congresses

2019 OOR Noord Oost Nederland Refereeravond “cyclusstoornissen” Gynecology Martini Ziekenhuis, Groningen
2019 Noordelijke Refereeravond Procedurele Sedatie en Analgesie (PSA) Isala, Zwolle
2019 Isala Wetenschapsavond, Zwolle
2020 7th Focused Ultrasound Foundation Symposium, digital
2020 Radiological Society of North America (RSNA) Symposium, digital
2021 IGO Doelencongres, digital
2021 Invited speaker CIRSE congress, digital
2021 Invited speaker MR-HIFU and embolization UMCU course day for gynecology trainees, digital

2021 ESGE congress, Rome, Italy
2021 Invited speaker MR-HIFU treatment MIRO post MBRT webinar InHolland, digital
2021 Invited speaker MR-HIFU UMCU refereeravond, digital
2022 Invited speaker MyCenA Myoomcursus, digital
2022 Invited speaker CIRSE congress, not able to attend
2022 Invited panelist and presentation 8th Focused Ultrasound Foundation Symposium, not able to attend

Teaching

2020 Guiding Heleen van 't Oever, Master thesis Medicine (March -July)
2020 Guiding Loes Knorren, Master thesis Medicine (April - August)
2020 Guiding Susanne ter Laak, Master thesis Medicine (May - August)

Professional development

2019-2020 Vice chair internal affairs Promovendi Netwerk Nederland
2020-2022 Organizing multicenter RCT MYCHOICE
2020 Contribution to writing grant application Veelbelovende zorg ZonMw & Zin
2021-223 Secretary Arts en Organisatie

Grants and awards

2021 Granted the Hilly de Roever-Bonnet fonds, vnVa
2021 Winner of RvE Medische Beeldvorming Science symposium Pitch

Review tasks

2021 BMJ Open
2021 Clinical and Experimental Obstetrics & Gynecology
2021 BMC Medical Imaging
2022 International Journal of Hyperthermia
2022 BioMedical Engineering OnLine
2022 Quantitative Imaging in Medicine and Surgery
2022 The British Journal of Radiology
2022 European Radiology
2022 Scientific Reports
2023 European Radiology

LIST OF PUBLICATIONS

Scientific publications

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Verpalen IM, **Anneveldt KJ**, Vos PC, et al. Use of multiparametric MRI to characterize uterine fibroid tissue types, MAGMA. 2020 Oct;33(5):689-700.

Remaining publications

Anneveldt KJ, Bosch M. Onderzoek naar nieuwe behandeling van vleesbomen. Bekkenbodem op de kaart. 2019:16-17.

Bosch M, **Anneveldt KJ**. MYCHOICE-studie biedt patiëntes met vleesbomen perspectief op nieuwe behandeling. Bekkenbodem op de kaart. 2022: 18-19.

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ABOUT THE AUTHOR

Kimberley Anneveldt was born on April 19, 1993 in Nijmegen, the Netherlands. At age 3 she moved to Hillegom on the Westside of the country, together with her parents and younger brother. Here, she grew up and attended high school (Gymnasium, Fioretti college, Lisse). After graduating in 2011, she moved to Groningen and studied Medicine at the Rijksuniversiteit Groningen. During her studies, Kimberley was a member of various student committees and a board member of IFMSA-Groningen, IFMSA-NL and De Geneeskundestudent. In her fifth year of Medicine, she continued her clinical internships in Isala Hospital, Zwolle. She started her final year with her master thesis at the departments of Gynecology and Radiology in Isala Hospital, working on the Myoma Screening Study and she was involved with the MR-HIFU treatments. Her final internships were conducted on the Gynecology department of Isala Hospital and the Emergency department of Röpcke Zweers hospital, Hardenberg.

After obtaining her medical degree in 2018, Kimberley started working as a resident (ANIOS) at the Gynecology department of Ijsselland Ziekenhuis, Capelle a/d Ijssel. Ten months later, she returned to Isala Hospital since she was given the opportunity to start a PhD-trajectory. Her promotion team was soon completed and her promotion took place at the University of Utrecht. While coordinating the MYCHOICE study, Kimberley finished the Myoma Screening Study, wrote several publications on this study and performed new studies. As part of her PhD-trajectory, she supervised three master students, presented her work at several national and international conferences and advocated for PhD-candidates at a national level as board member of the Promovendi Netwerk Nederland. In 2022 she became a mother and started working as a physician at a nursery home while finishing her PhD. She recently got married and started her advanced training to become a general practitioner. In her free time, Kimberley likes to travel, spend time with friends and family and play tennis.