

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.



P O L I S H G Y N E C O L O G Y

GINEKOLOGIA

POLSKA

ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

Magnetic resonance-guided high-intensity ultrasound (MR-HIFU) in the treatment of symptomatic uterine fibroids – five-year experience

Authors: Tomasz Lozinski, Justyna Filipowska, Magdalena Pyka, Monika Baczowska, Michal Ciebiera

DOI: 10.5603/GP.a2021.0098

Article type: Research paper

Submitted: 2020-11-01

Accepted: 2021-01-18

Published online: 2021-04-23

This article has been peer reviewed and published immediately upon acceptance. It is an open access article, which means that it can be downloaded, printed, and distributed freely, provided the work is properly cited.

Articles in "Ginekologia Polska" are listed in PubMed.

Magnetic resonance-guided high-intensity ultrasound (MR-HIFU) in the treatment of symptomatic uterine fibroids — five-year experience

Tomasz Lozinski¹, Justyna Filipowska^{1,2}, Magdalena Pyka¹, Monika Baczkowska³, Michal Ciebiera³

¹Department of Obstetrics and Gynaecology Pro-Familia Hospital, Rzeszow, Poland

²Faculty of Medicine, Institute of Nursing and Health Sciences, University of Rzeszow, Poland

³Second Department of Obstetrics and Gynecology, Center of Postgraduate Medical Education, Warsaw, Poland

Running title: MR-HIFU — five-year experience

Corresponding author:

Michal Ciebiera

Second Department of Obstetrics and Gynecology, Center of Postgraduate Medical Education, Warsaw, Poland

e-mail: michal.ciebiera@gmail.com

ABSTRACT

Objectives: Uterine fibroids (UF) are the most common benign tumors of the female reproductive organ. It is crucial to recognize that the appropriate treatment of UFs requires an individualized approach. The present paper aimed at the presentation of the five-year experience of our center in the treatment of UFs with the use of magnetic resonance-guided high-intensity ultrasound (MR-HIFU) therapy.

Material and methods: The study enrolled a total of 1284 patients with symptomatic UFs. The Sonalleve MR-HIFU system (Philips Ingenia 3.0T System) was used for magnetic resonance imaging (MRI) qualification and treatment.

Results: The group of patients qualified for thermal ablation included 356 (28%) women. No significant differences were observed between the group undergoing thermal ablation and patients who were disqualified. A complete procedure was performed in 22.6% of patients who presented at the center. Non-perfused volume (NPV) is one of the most important parameters assessed during MR-HIFU procedures. The mean NPV value in the present study

was 71%. The average UF volumes decreased by 27% at three-month follow-up ultrasound, by 34% after six months and by 39% as shown by MRI measurements performed 6 months post-treatment.

Conclusions: According to our data, MR-HIFU therapy is associated with good clinical outcomes in patients with symptomatic UFs. The method facilitates a marked symptom reduction and, in many cases, diminishing tumor volume. The presented five-year outcomes as regards our experience in the MR-HIFU therapy of patients with symptomatic UFs indicate that the method offers an attractive alternative to the traditional methods of UF treatment in selected cases.

Key words: uterine fibroid; leiomyoma; non-invasive; magnetic resonance imaging; magnetic resonance-guided high-intensity ultrasound; MR-HIFU

Introduction

Uterine fibroids (UF) are the most common benign tumors of the female reproductive organ [1]. They constitute the most common reason for hysterectomy worldwide [2]. Therefore, the pathology should be regarded as a major socioeconomic problem of the healthcare system [3, 4]. In some populations UFs are thought to occur in as many as 60–70% of women [5]. The lesions are symptomatic in approximately 30–50% of cases triggering the following manifestations: menorrhagia, anemia, dyspareunia, pelvic pain, psychological disorders, and pregnancy complications including fertility disorders, miscarriage or premature delivery [6]. The peak incidence is observed between 40 and 50 years of age, with the number of new cases decreasing after menopause and the symptoms resolving over time in many cases [7]. The reasons for the development of UFs have not been fully elucidated. It is currently known that they develop by means of the conversion of a normal myometrial cell into a monoclonal tumor. Steroid hormones, progesterone in particular, are considered to play an essential role in promoting the formation and growth of those tumors [1, 8]. However, hormones are not the only factors influencing those pathophysiological pathways [9, 10]. UF development is also largely dependent on genetic factors [11, 12], with the disruption of DNA repair mechanisms also playing a role [13]. UFs are markedly more common in dark-skinned women, *e.g.*, African Americans, compared to white women [5, 14]. It is necessary to act because, even in populations characterized by a lower UF incidence their occurrence seems to become higher [15]. Therefore, research is constantly conducted into new possible risk factors [16, 17] and the development of new strategies of prophylaxis and treatment [18, 19].

It is crucial to recognize that the appropriate treatment of UFs requires an individualized, patient-tailored approach and is dependent on patient's age, tumor location and size, symptoms and the expectations of the patient concerning reproductive plans [20, 21]. Currently, numerous modalities are implemented, including conservative treatment, less invasive, but still highly effective methods of invasive radiology [*e.g.*, uterine artery embolization (UAE)], and surgery, which may include endoscopic procedures, classic uterus-sparing surgeries, and partial or complete hysterectomies [6, 21–23].

Conservative treatment with the use of antihemorrhagic tablets, contraceptive pills or intrauterine devices only aims at relieving the symptoms and is often associated with poor effectiveness [18]. Pharmacological modalities in UF treatment, *e.g.*, ulipristal acetate [24], or oral gonadotropin-releasing hormone (GnRH) analogues [25] are easy as regards the administration and effective in the reduction of symptoms. However, the use of those drugs may be perceived as problematic, as they also influence other aspects, *e.g.*, by triggering climacteric symptoms [26, 27], or causing dangerous adverse events [28]. Therefore, regrettably, anti-fibroid drugs are not used for long-term treatment, but rather as preoperative preparation [29]. Some scientific societies specified the guidelines for the treatment of UFs, *e.g.*, the recommendations of the Society of Obstetricians and Gynaecologists of Canada (SOGC) published in 2015 [21]. The algorithm for the management of UFs mostly covered the available methods of treatment and is up-to-date even as regards the issue of selective progesterone receptor modulators, whose use requires further clarification [25, 28]. Some hopes are attached to new oral gonadotropin-releasing hormone antagonists that are already available in Western markets [27].

According to recent analyses, non-surgical methods may lead to positive effects which are similar to those of myomectomy in various aspects. In regards those methods — the treatment effectiveness of uterine artery embolization (UAE) was confirmed to the largest extent [30]. Some authors suggested that UAE was a safe and effective mini-invasive treatment modality for symptomatic UFs [21, 31]. The additional advantage of this method is related to the fact that despite changing the clinical symptoms it also significantly reduces UF volume (especially in larger lesions) [32]. Notably, Poland has considerable experience in this therapy and sets global standards, *e.g.* via the development of specialist uniform, protocol for clinicians performing UAE (Lublin Protocol) [33].

However, this paper focuses on a different method — high-intensity ultrasound (HIFU), which is frequently described together with UAE. It is due to the fact that both methods are relatively new compared to those known for many years [34]. UF treatment with

HIFU involves the precise concentration of high-intensity ultrasound waves on the tumor focus. In such a case the blood vessels are not blocked and the energy of ultrasound increases the temperature and, thereby, destroys the tissue via ablation [34]. Currently, two types of systems are integrated with HIFU, with one being magnetic resonance-guided (MRI) and the other ultrasound-guided. Differences may be substantial, particularly depending on a specific device and the expertise of the personnel, but the principle of the procedure is rather similar. Both methods have their proponents and opponents. The example of ultrasound-guided procedures performed in breast cancer shows that they are inexpensive and convenient and may be performed in real-time, whereas MR-HIFU can provide supreme-resolution images and better thermometry data [35]. In the case of our center, because of the equipment available, we present high-intensity thermal ablation performed with MR-HIFU device. In this technique, a radiologist controls the transducer of an MRI device to target a focused beam of ultrasound at a small area of a UF, and, step by step, the temperature of the tissue is increased leading to protein denaturation and necrosis (Fig. 1). Real-time temperature mapping in the target tissue and adjacent tissues is performed with magnetic resonance during the whole procedure. The procedure is characterized by high precision and is performed completely on an outpatient basis. Pro-Familia Specialized Hospital in Rzeszów was one of few centers in Poland to perform procedures with this technology both for scientific and commercial reasons.

Objectives

The present paper aimed at the presentation of the five-year experience of our center in the treatment of UFs with the use of MR-HIFU therapy. The main aims of this study include the assessment of the effectiveness, success rate, patient satisfaction and symptom resolution, as well as introducing this method to wider audience.

MATERIAL AND METHODS

The study group included women with symptomatic UFs treated in Pro-Familia Specialized Hospital in Rzeszów. The study was approved by the Local Bioethics Committee of the Regional Medical Chamber in Rzeszów (approval no. 1/B/2015, 22/B/2015, 35/B/2015, 38/B/2015).

Patient qualification for the study involved: a gynecological clinical examination, MRI assessment followed by thermal ablation with the simultaneous determination of the effectiveness of the procedure. The whole procedure (despite some exceptions) was

performed completely on an outpatient basis. The patients were admitted after an overnight fast following several days of consuming an easily digestible diet. A follow-up gynecological visit was conducted about three months after the procedure. It involved completing a basic questionnaire to assess the quality of life (QoL). The symptoms might be assessed by the patients on a simplified 5-point Likert-type scale: 1 — ‘much worse’; 2 — ‘worse’; 3 — ‘the same’; 4 — ‘better’; 5 — ‘much better’. The aim of using the scale was to indicate the subjective perception of the above presented symptoms after the procedure. The researchers had assumed that the scale should be as simple as possible in order not to discourage the patients and obtain the highest possible follow-up rate. A six-month follow-up consisted in basic QoL assessment (as above) and undergoing a gynecological examination and a control MRI.

The Sonalleve MR-HIFU system (Philips Ingenia 3.0T System) was used for MRI qualification and treatment. Due to economic reasons, control MRI was only performed in the patients whose baseline non-perfused volume (NPV) was $\geq 70\%$. The study enrolled a total of 1284 patients who presented at the hospital in order to be qualified for ultrasound thermal ablation. The inclusion criteria were a single lesion, UF symptoms, such as menorrhagia, abdominal pain, dyspareunia, and, because of grant requirements, inability to conceive, tumor size > 2 cm. In regards to the grant, the qualification criteria between the years 2015 and 2018 included a symptomatic UF, inability to conceive with the exclusion of other factors impairing fertility, a history of miscarriage, a positive MRI qualification of the UF type according to a classification by Funaki et al. (2007) [36]. In 2018–2020, after completing the research covered by the first grant, we enlarged the study group to women aged until 50 and disregarded the issue of infertility. We considered the cases of symptomatic UFs manifesting as abdominal pain, menorrhagia and dysmenorrhea, intermenstrual bleeding, and other UF-related symptoms. The exclusion criteria for the whole study period were: contraindications for MRI procedures or contrast administration, an active inflammation of the minor pelvic cavity, the diagnosis of an adnexal tumor, asymptomatic lesions, tumor size > 13 cm, Funaki type III UFs [36], the excess of the adipose tissue (distance between the posterior margin of the UF and the skin surface of > 13 cm).

During the procedure, the patients were lying in a prone position on a special gel pad. Subsequently, three lines were determined along which the temperature was monitored: passing through the center of the UF, on the skin surface (so called ‘proximal surface’) and beyond the lesion (so called ‘distal surface’). Another step involved the determination of the predicted thermal dose volume (PTV) of the UF via delineating its external outline. Then, so

called ‘therapeutic cells/volumes’ were determined as the targets of the energy of the ultrasound. The ultrasound wave was adjusted during the sonication of each cell/volume as regards the frequency (1.2 MHz or 1.4 MHz) and power (maximum: 500 Watt). MRI-derived real-time temperature maps facilitated the monitoring of the local distribution of heat to adjust its value to approx. 55-65 degrees Celsius. The patients were administered a contrast agent intravenously (0.1 mmol/kg Gd-DO3A-butrol, Gadovist; Bayer Schering Pharma) and the degree of ablation was determined by measuring NPV during the qualifying examination and after therapy completion. After about two hours of observation the patients could leave the department.

RESULTS

The study enrolled a total of 1284 patients with symptomatic UFs. A total of 1048 MRI tests were performed. Upon gynecological examination, 235 (25%) cases were disqualified. The group of patients qualified for thermal ablation included 356 (28%) women. Pain, stress and impatience of some women, no reaction of the UF tissue to ultrasound were the reasons for the discontinuation of 68 procedures. Therefore, a complete MR-HIFU procedure was performed in 22.6% of patients who presented at our center (Tab. 1).

Table 1. The quantification of the study group patients with uterine fibroids

	MRI qualified	MRI non-qualified	
MR-HIFU not performed	693	235	928 (72%)
MR-HIFU performed	355	1	356 (28%) discontinued procedures included 288 (356-68) (22.6%) discontinued procedures excluded

Total	1048	236	1284 (100%)
-------	------	-----	-------------

MRI — magnetic resonance imaging; MR-HIFU — magnetic resonance-guided high-intensity ultrasound

Throughout the study we obtained the abundance of epidemiological data concerning women seeking alternative methods of UF therapy. The mean age of study group patients was 36.6 years and the average body mass index (BMI) equaled 23.5 kg/m². No significant differences were observed between the group undergoing MR-HIFU procedure and patients who were disqualified. The data are presented in Table 2.

Table 2. Age and body mass index in the analyzed groups of patients

	Mean	Median	Minimum	Maximum	SD
All patients					
Age [n]	36.6	37	19	58	5.3
BMI [kg/m ²]	23.5	22.5	15.8	60.5	4.3
MR-HIFU not performed					
Age [n]	36.7	37	20	58	5.4
BMI [kg/m ²]	23.6	22.4	16.0	60.5	4.6
MR-HIFU performed					
Age [n]	36.2	37	19	51	5.2
BMI [kg/m ²]	23.3	22.6	15.8	39.3	3.7

BMI — body mass index; MR-HIFU — magnetic resonance-guided high-intensity ultrasound; SD — standard deviation

We also analyzed the groups in terms of the most common symptoms, related to UFs. As shown in Table 3, the distribution of individual manifestations was similar in both groups. The manifestations were mostly associated with UF volume, while the age of patients was correlated with pain and voiding symptoms. The NPV value and UF volume reduction were

associated with diminishing all groups of symptoms except voiding and gastrointestinal issues.

Table 3. The quantitative distribution of manifestations and relief after treatment reported in the groups

Manifestations	MR-HIFU performed	Volume/p	Volume change 6 months after treatment/symptom reduction/p	NPV/symptom reduction 6 months after treatment
Menorrhagia	262	0.0182	0.0234	0.0090
Pelvic pain	101	ns	0.0000	0.001
Voiding issues	179	0.0007	0.0338	ns
Anemia	178	0.0051	0.0028	0.0045
Gastrointestinal issues	57	ns	ns	ns

MR-HIFU — magnetic resonance-guided high-intensity ultrasound; NPV — non-perfused volume

Subsequently, the groups were analyzed as regards the volume of UFs assessed both with an ultrasound or MRI examination. A statistically significant correlation was demonstrated between the groups: $p = 0.0165$ and $p = 0.0092$, respectively. The data were presented in Figure 2.

NPV is one of the most important parameters assessed during MR-HIFU procedures. The mean NPV value in the present study was 71%. Moreover, it is worth noting that the parameter significantly improved in 2017–2020 in our center and currently it may even reach 80%. The learning curve of the radiologist and the use of additional medications (*e.g.* oxytocin or misoprostol) are also of importance, as they may influence the effectiveness of the treatment [37]. The mean duration of the procedure (sonication time) was 107 minutes and

depended on the respective baseline UF volume. Correlation factor was $r = 0.57$, $p = 0.00001$. Admission to the department, preparation (positioning, test MRI scans) took the average of 65 minutes.

Another parameter assessed post-treatment was the change of UF volume at the three and six-month follow-up ultrasound tests and six-month follow-up MRI. The average UF volumes decreased by 27% at three-month follow-up ultrasound, by 34% after six months and by 39% as shown by MRI measurements performed 6 months post-treatment. The results are presented in Figure 3.

Most studies and numerous researchers claimed that the main aim of the procedure targeting UFs was not the volume reduction, but alleviating UF-related symptoms (Ikink 2013). Therefore, the present study also involved the assessment of patients' opinions regarding the improvement of the QoL compared to the time prior to the procedure. The patients self-assessed the change in the QoL during the follow-up visits at three and six months. A basic non-validated questionnaire of symptom reduction and well-being assessment was developed by the authors for the needs of rapid clinical assessment for clinical procedures and the study. The patients completed the questionnaire during qualification and after 3 and 6 months following the procedure. The questions tackled the following issues: pain, bleeding, voiding and gastrointestinal symptoms linked to UFs and well-being after the procedure. The improved QoL regarding the occurrence of UF-related symptoms was reported by 69% of women at three months and by 76% at six months post-treatment. Individual symptoms subsided in the patients depending on NPV and UF volume reduction. The data are presented in Figure 4.

During the study period adverse events were reported in 12 patients. One patient had two or more symptoms. Six of those patients were hospitalized until the next post-procedure day. A detailed list of adverse events in those patients is presented in Table 4.

Table 4. Adverse events in patients treated with magnetic resonance-guided high-intensity ultrasound

Abdominal pain	Flu-like symptoms malaise, chills	Low-grade fever	Hematuria	Panic (claustrophobia)
12	7	8	1	1

Our previous publication included a report of initial experience concerning pregnancies in patients who had undergone MR-HIFU in our center [38]. The current number of reported pregnancies and healthy neonates delivered from those pregnancies is higher compared to the previously presented data.

DISCUSSION

The ultrasound thermal ablation of UFs guided by various tools (MRI, ultrasound) is an alternative to well-established therapies. However, it is not widely used due to the high cost of the procedure and no reimbursement in the majority of countries apart from Canada, Israel, Germany and, recently, Italy [39]. Another reason why the procedure is not common is the lack of appropriate cooperation between gynecologists and interventional radiologists. Operative treatment is still preferred by gynecologists, so surgery is the most common modality in the treatment of symptomatic UFs [2, 22]. In our viewpoint, some assumptions should be slightly changed, at least in terms of selected indications due to the most recent data concerning non-invasive treatment of UFs. An increasing number of studies, including those conducted in our center demonstrated that ultrasound thermal ablation was justified in women who wished to preserve fertility [38, 40, 41]. Obviously, it needs to be mentioned that, to the best of our knowledge, no current guidelines propose this method as safe in patients with reproductive plans or treated due to infertility. Nevertheless, a variety of opinions concerning this issue were presented, *e.g.*, with reference to surgery. Therefore, the topic requires a highly individualized approach [42]. The hypothesis that prophylactic UF removal increases the probability of conceiving has not been confirmed by relevant research [42]. However, it is false in case of submucosal or intramural lesions which exert visible pressure on the line of the endometrium (uterine cavity deformity) as they may affect fertility to some extent. UF treatment should be considered in women in whom other reasons for infertility or miscarriages (infections, uterine defects, and disrupted ovulation) were gradually ruled out [42, 43]. In case of such tumors, and, particularly, if an endoscopic procedure may be hindered, we suggest considering the performance of an MR-HIFU procedure as a relatively safe and low-risk alternative [38]. Available research showed a relatively low risk associated with the procedures. Some authors suggested that adverse events related to ultrasound UF ablation under conscious sedation are mostly mild and temporary [44]. For example, a study by Liu et al. (2018) performed in 27,053 patients with benign uterine diseases revealed that major adverse events occurred in about 0.3844% of them. Those major events included mostly skin burn, leg pain, vaginal discharge or bleeding, urinary retention, acute cystitis, an

intrauterine infection, bowel injury, kidney failure, thrombosis, pubic symphysis injury, or sciatic nerve injury [45]. Regardless of the low-risk or high-effectiveness aspects, in cases with no appreciable effect obtained MR-HIFU does not rule out the possibility of a definitive surgery in the future.

According to the presented data, only 288 out of 1288 women underwent MR-HIFU. The presented therapy is known to be very expensive and the limitations concerning the patients are marked. Numerous factors may contribute to patient disqualification from the procedure, including tumor size, UF type and location, anatomic relations within the abdominal cavity, the presence of adhesions [46]. Nevertheless, factors which would have ruled out the procedure several years before (*e.g.* reproductive plans) might currently, or in the nearest future, be the indications for the therapy, depending on the manifestations and other clinical issues [47].

The mean age of presented patients equaled 36.6 years, which stays in line with the general epidemiology of UFs and the peak incidence reported in available literature [5]. However, in case of our center the age was mainly determined by the grant-related requirements, including the analysis of female fertility following thermal ablation and a comparison with patients who had undergone myomectomy. Between the years 2015 and 2018 we only qualified symptomatic women at the maximum age of 43 considering the wish to conceive. As shown above, BMI in the group treated with MR-HIFU was 23.3 kg/m², and in the women disqualified after MRI it was 23.6 kg/m². In this place we should underline that body weight is linked to thermal ablation treatment, because the longer the distance to the lesion, the higher the chance of disqualifying the patient or achieving the unsatisfying effectiveness of the procedure. Importantly, the distance between the posterior margin of the UF and skin surface should not exceed 13 cm. It also refers to adipose tissue thickness over 3 cm, due to the high absorption of ultrasound energy. Therefore, not all patients, especially those considerably obese, may be offered treatment with this method. The care of obese UF-positive patients is always more difficult compared to patients with normal body weight [48]. The present group included some women who had been initially disqualified, and later they were successfully treated with MR-HIFU. This study revealed no differences in BMI between the groups with regard to the correlation between markedly increased body weight and the occurrence of UFs [49]. The measurements were obviously random in some manner, targeted at a specific group. The inclusion and exclusion criteria of the grant also had an influence on the obtained results. Therefore, they should not be assessed in terms of the whole population and should be carefully extrapolated on other comparable populations.

It needs to be emphasized again that MR-HIFU is a non-invasive procedure which may be performed on an outpatient basis [50]. MR-HIFU is highly advantageous over myomectomy or hysterectomy which frequently require hospitalization. Except for several cases, the patients were discharged home and returned to work shortly after the procedure. When performing a detailed comparison of the cost of MR-HIFU and surgeries it should obviously be considered that surgeries, even endoscopic ones, necessitate a hospital stay which may last several days, and the risk of complications typical of operative treatment is higher, which additionally increases the cost if they occur. Moreover, patients undergoing conventional treatment frequently must remain on sick leave, which is of high macroeconomic significance [3]. Another problem associated with MR-HIFU is the price of the device, the cost of personnel training and the cost of the procedure itself. The procedure is rather long-lasting — in case of our center it usually takes about 200 minutes to perform a full procedure. It obviously depends on the conditions, location and, mostly, the size of the UF. Our center does not fall behind other centers in the world and the duration of the sonication performed in here is similar to that in other countries [51]. Regrettably, treatment duration is not its advantage regarding the fact that it involves the exclusion of the MRI device from its everyday use in diagnostic testing. It requires further steps aiming at the improvement of the quality and shortening the procedure. Seemingly, it is worth testing various uterotonics which shorten procedure duration [37].

In regards to the symptomatology of UFs in the present study group, the dominant manifestations were ones typical of this medical condition, *i.e.*, menorrhagia, dysmenorrhea, dyspareunia, voiding and gastrointestinal symptoms. No significant differences were observed between the groups of patients qualified for and disqualified from MR-HIFU. The aim of MR-HIFU treatment of UFs was verified by the reduction in the clinical manifestations and NPV parameter [52]. NPV reflects the ratio of non-perfused UF volume after contrast enhancement to the total volume expressed as a percentage [52, 53]. According to available data, NPV values are commonly consistent with symptom resolution [54]. The mean NPV result of 71% in the present group of patients who underwent treatment may be referred to as good. It correlated with the resolution of symptoms and the reduction in UF volume at post-treatment follow-up. We already mentioned in the results section that the study showed no correlation between age, BMI and NPV, which is also important from the clinical point of view. It is currently believed that the reduction of symptoms is the most important aim of MR-HIFU. During the follow-up visits at three and six months, the majority of patients assessed their QoL as 'improved'. The respective percentages were 61% as 'improved' and

8% as 'highly improved' after three months and 53% and 23%, respectively, after six months post-treatment. Similar results were presented in the recent meta-analysis by Verpalen et al. (2019) who reported the mean symptom reduction at 12-months at 59.9% and lesion volume shrinkage at 37.7% [53]. Moreover, MR-HIFU proved to be effective as regards the sexuality of patients with UFs, as the method was associated with similar post-procedure sexual function scores and re-intervention rates compared to myomectomy [30]. In our opinion the results may be assessed as more than promising. Therefore, the method should be more widely promoted in patients with symptomatic UFs, especially those who rule out the possibility of undergoing a surgery.

The economic dimension of the procedure is also an important aspect. The payback time of such an investment (equipment purchase and personnel training) with the assumption of performing three procedures weekly with a well exploited MRI device in the diagnostic work-up is approximately seven-years. It is of significance to provide a high level of assistance services due to the very specialized and unique type of the device and individualized software. High service costs are necessary because of a high risk of long-lasting downtime resulting in remarkable economic loss [3]. In this place it is also worth noting that personnel training is essential for adequate cost planning, as it is possible only in few centers worldwide and may constitute a substantial financial burden. Therefore, a full training option and the assistance of a company providing an MR-HIFU device should be comprised. However, system optimization may include the use of the device beyond the standard working hours due to the elective nature of the procedures. It also translates into increased income.

The cost of laparoscopic myomectomy covered by the Polish National Health Fund is still highly underestimated. The calculations include no cost of the treatment of complications, medications and high social cost for the system. This means that the real cost of operative procedures is increased by sick leave, no tax paid for the duration of sick leave, and the cost of substitution at work. A prolonged stay of a patient with complications in the hospital, including intensive care unit, is an unpredictable and high cost, which is rare in terms of statistical data, but sometimes inevitable. It needs to be remembered that numerous centers still offer the classic modality of UF treatment, i.e., open surgery, in which the cost of treatment increases due to longer hospitalization and higher complication rates. In this model the benefits of ultrasound thermal ablation are clearly visible, not only because of the cost of medications and care, but also due to diminished suffering, stress and the risk of complications.

The innovative character of the issue and the size of the study population, which seems to be rather large for Polish conditions, are the advantages of the present publication. MR-HIFU procedures may still be considered pioneering ones due to the low availability of the device, trained personnel and the low awareness of practicing physicians of the availability of minimally invasive treatment with HIFU (MRI- or ultrasound-guided) or UAE in Poland. The activity of new centers should be viewed as a huge success due to the invariably high costs. Researchers should also focus on analyzing treatment results and standardizing procedures for the region/country, which will improve the therapy outcomes and may make such therapies available as standard procedures for selected patients. Additionally, we believe it is important to encourage researchers to participate in multicenter cooperation to compare various methods such as MR-HIFU vs ultrasound-guided HIFU, HIFU vs myomectomy, or HIFU vs UAE. Each publication should include the specification of some visible limitations. In our viewpoint, the limitation of the present paper results from the use of a non-validated simple QoL scale instead of a standardized form, *e.g.* ‘The Uterine Fibroid Symptom and Quality of Life (UFS-QOL)’ which is very common [55]. Undoubtedly, it lowers the quality of data obtained and in numerous aspects it may hinder a more precise interpretation or comparisons. In this case the present authors aimed at achieving as many results as possible, to achieve the maximum follow-up rate possible and cover almost the whole study population. It is widely known that the percentage is always reduced in case of more complicated forms. However, the present authors are planning to use previously evaluated scales in the subsequent publications so that the results may be used in multicenter studies and meta-analyses.

CONCLUSIONS

MR-HIFU therapy is associated with good clinical outcomes in patients with symptomatic UFs. The method facilitates a marked symptom reduction and, in many cases, diminishing UF volume.

The key issue of the optimization of treatment outcomes is appropriate patient qualification and the experienced team of gynecologists and radiologists who implement optimal qualification and treatment.

The presented five-year outcomes as regards our experience in the MR-HIFU therapy of patients with UFs indicate that the method offers an attractive alternative to traditional methods of UF treatment and patients should be informed about its availability.

The non-invasiveness of the procedure, lack of social costs connected with sick leave or possible complications make the ultrasound thermal ablation of UFs worth considering as a part of a wide range of benefits despite the high price of the device.

Conflict of interest

All authors declare no conflict of interest.

Funding

This study was supported by European Regional Development Fund Program: Operational Program ‘Innovative economy’ (2007–2013) ‘Establishing a Research and Development Center of noninvasive therapeutic methods’ POIG.04.05.02–00-075/12–00.

This study was also supported by the European Regional Development Fund Programme: Intelligent Development Operational Program (2014-2020): ‘Development and implementation of a noninvasive, personalized thermoablation procedure in the treatment of specific types of neoplasms. POIR.01.01.01-00-0019/15-00.

Figure legends

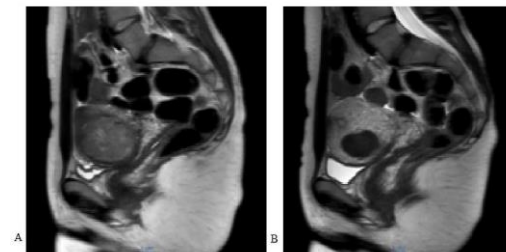


Figure 1. UF prior to thermal ablation (A) and after thermal ablation with visible necrosis (B)

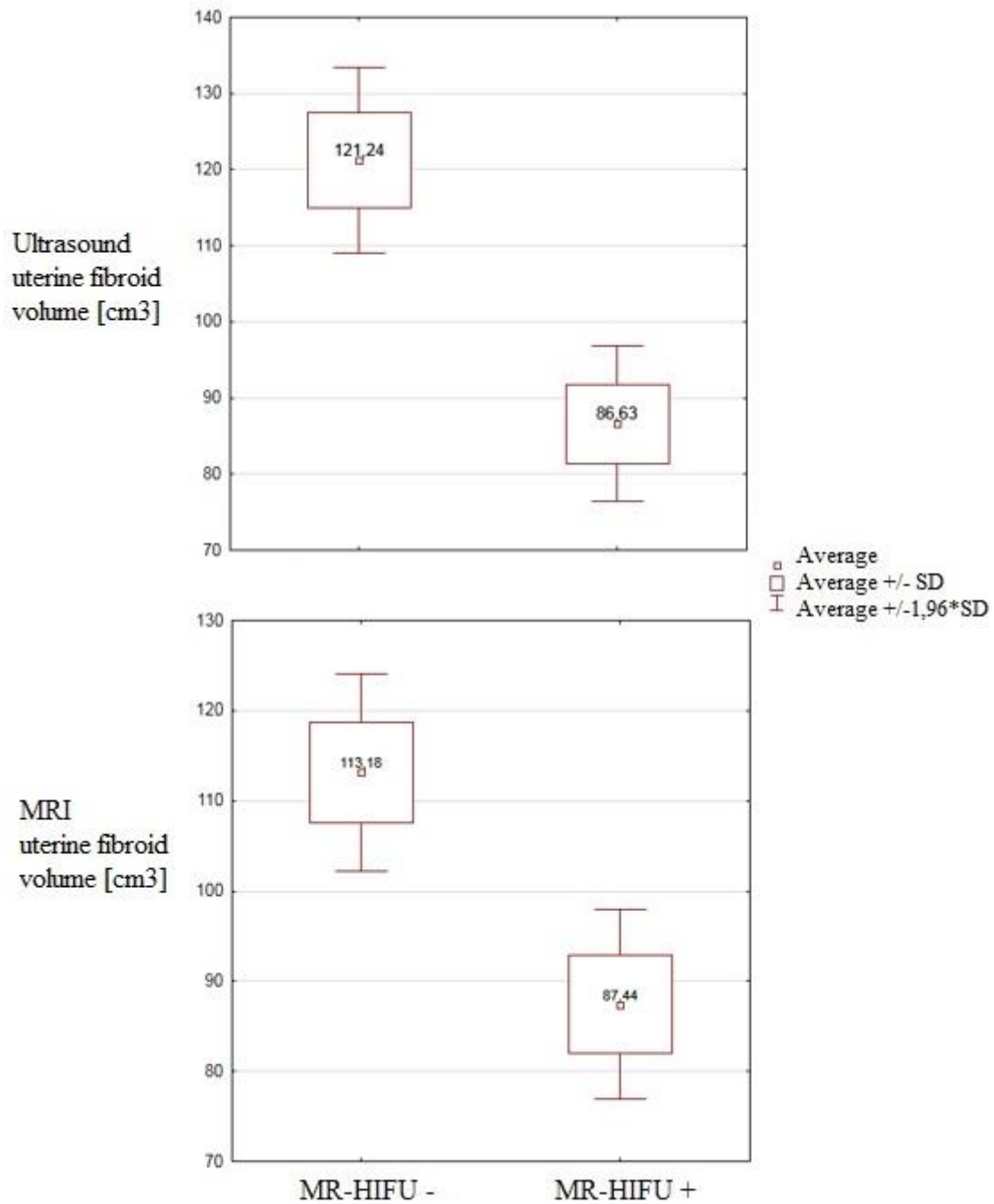


Figure 2. The difference between uterine fibroids volumes assessed with ultrasound and magnetic resonance imaging in groups in which MR-HIFU was and was not performed; SD — standard deviation; MRI — magnetic resonance imaging; MR-HIFU — magnetic resonance-guided high-intensity ultrasound

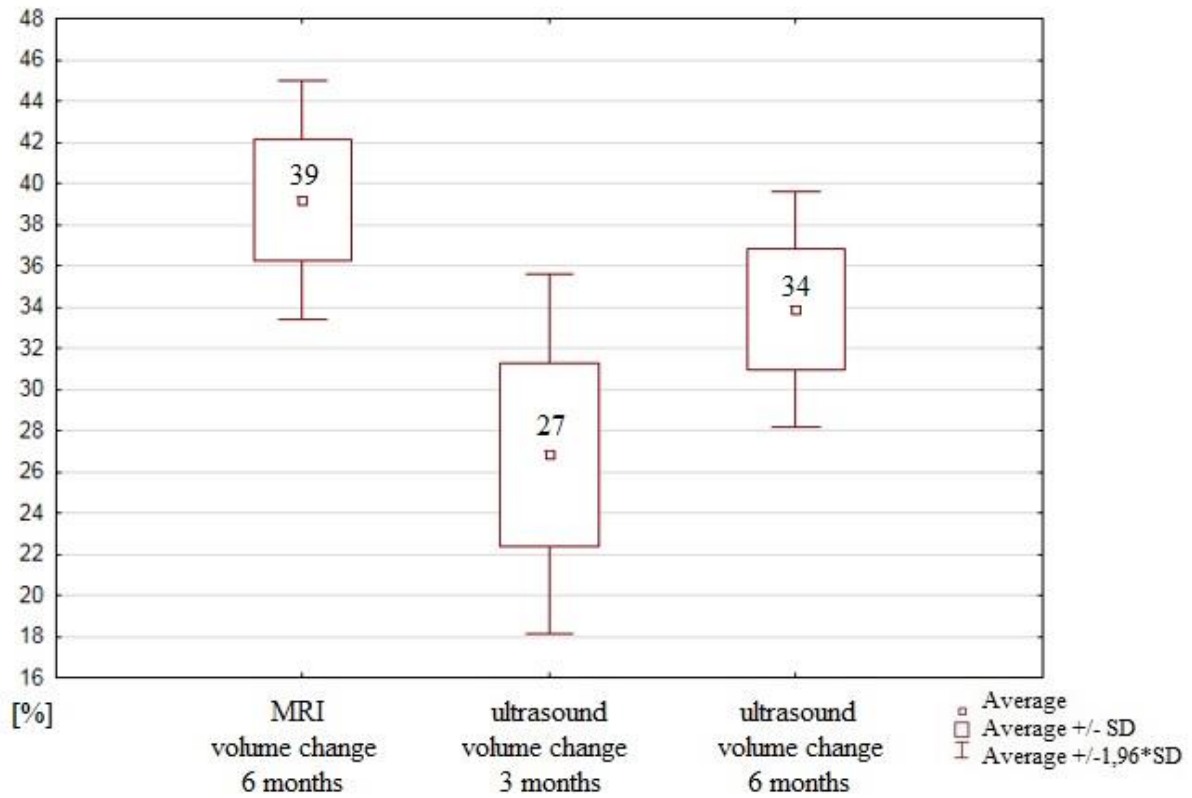


Figure 3. Changes in uterine fibroids volumes depending on the group; SD — standard deviation

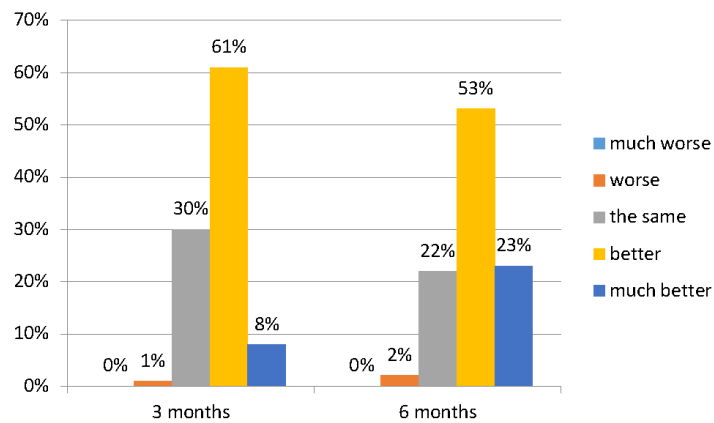


Figure 4. The quality of life in patients who underwent magnetic resonance-guided high-intensity ultrasound at three and six months post-treatment

REFERENCES

1. Stewart EA, Laughlin-Tommaso SK, Catherino WH, et al. Uterine fibroids. *Nat Rev Dis Primers*. 2016; 2: 16043, doi: [10.1038/nrdp.2016.43](https://doi.org/10.1038/nrdp.2016.43), indexed in Pubmed: [27335259](https://pubmed.ncbi.nlm.nih.gov/27335259/).
2. Cardozo ER, Clark AD, Banks NK, et al. The estimated annual cost of uterine leiomyomata in the United States. *Am J Obstet Gynecol*. 2012; 206(3): 211.e1–211.e9, doi: [10.1016/j.ajog.2011.12.002](https://doi.org/10.1016/j.ajog.2011.12.002), indexed in Pubmed: [22244472](https://pubmed.ncbi.nlm.nih.gov/22244472/).
3. Soliman AM, Yang H, Du EX, et al. The direct and indirect costs of uterine fibroid tumors: a systematic review of the literature between 2000 and 2013. *Am J Obstet Gynecol*. 2015; 213(2): 141–160, doi: [10.1016/j.ajog.2015.03.019](https://doi.org/10.1016/j.ajog.2015.03.019), indexed in Pubmed: [25771213](https://pubmed.ncbi.nlm.nih.gov/25771213/).
4. Harrington A, Bonine NG, Banks E, et al. Direct Costs Incurred Among Women Undergoing Surgical Procedures to Treat Uterine Fibroids. *J Manag Care Spec Pharm*. 2020; 26(1-a Suppl): S2–SS10, doi: [10.18553/jmcp.2020.26.1-a.s2](https://doi.org/10.18553/jmcp.2020.26.1-a.s2), indexed in Pubmed: [31958025](https://pubmed.ncbi.nlm.nih.gov/31958025/).
5. Stewart EA, Cookson CL, Gandolfo RA, et al. Epidemiology of uterine fibroids: a systematic review. *BJOG*. 2017; 124(10): 1501–1512, doi: [10.1111/1471-0528.14640](https://doi.org/10.1111/1471-0528.14640), indexed in Pubmed: [28296146](https://pubmed.ncbi.nlm.nih.gov/28296146/).
6. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. *Int J Gynaecol Obstet*. 2020; 149(1): 3–9, doi: [10.1002/ijgo.13102](https://doi.org/10.1002/ijgo.13102), indexed in Pubmed: [31960950](https://pubmed.ncbi.nlm.nih.gov/31960950/).
7. Yu O, Scholes D, Schulze-Rath R, et al. A US population-based study of uterine fibroid diagnosis incidence, trends, and prevalence: 2005 through 2014. *Am J Obstet Gynecol*. 2018; 219(6): 591.e1–591.e8, doi: [10.1016/j.ajog.2018.09.039](https://doi.org/10.1016/j.ajog.2018.09.039), indexed in Pubmed: [30291840](https://pubmed.ncbi.nlm.nih.gov/30291840/).
8. Bulun S. Uterine Fibroids. *N Engl J Med*. 2013; 369(14): 1344–1355, doi: [10.1056/nejmra1209993](https://doi.org/10.1056/nejmra1209993).
9. Cetin E, Al-Hendy A, Ciebiera M. Non-hormonal mediators of uterine fibroid growth. *Curr Opin Obstet Gynecol*. 2020; 32(5): 361–370, doi: [10.1097/GCO.0000000000000650](https://doi.org/10.1097/GCO.0000000000000650), indexed in Pubmed: [32739973](https://pubmed.ncbi.nlm.nih.gov/32739973/).
10. Ciebiera M, Włodarczyk M, Zgliczyńska M, et al. The Role of Tumor Necrosis Factor α in the Biology of Uterine Fibroids and the Related Symptoms. *Int J Mol Sci*. 2018; 19(12), doi: [10.3390/ijms19123869](https://doi.org/10.3390/ijms19123869), indexed in Pubmed: [30518097](https://pubmed.ncbi.nlm.nih.gov/30518097/).

11. Edwards TL, Giri A, Hellwege JN, et al. A -Ethnic Genome-Wide Association Study of Uterine Fibroids. *Front Genet.* 2019; 10: 511, doi: [10.3389/fgene.2019.00511](https://doi.org/10.3389/fgene.2019.00511), indexed in Pubmed: [31249589](https://pubmed.ncbi.nlm.nih.gov/31249589/).
12. Mehine M, Kaasinen E, Mäkinen N, et al. Characterization of uterine leiomyomas by whole-genome sequencing. *N Engl J Med.* 2013; 369(1): 43–53, doi: [10.1056/NEJMoa1302736](https://doi.org/10.1056/NEJMoa1302736), indexed in Pubmed: [23738515](https://pubmed.ncbi.nlm.nih.gov/23738515/).
13. Toprani SM, Kelkar Mane V. Role of DNA damage and repair mechanisms in uterine fibroid/leiomyomas: a review. *Biol Reprod.* 2021; 104(1): 58–70, doi: [10.1093/biolre/iaaa157](https://doi.org/10.1093/biolre/iaaa157), indexed in Pubmed: [32902600](https://pubmed.ncbi.nlm.nih.gov/32902600/).
14. Baird DD, Patchel SA, Saldana TM, et al. Uterine fibroid incidence and growth in an ultrasound-based, prospective study of young African Americans. *Am J Obstet Gynecol.* 2020; 223(3): 402.e1–402.e18, doi: [10.1016/j.ajog.2020.02.016](https://doi.org/10.1016/j.ajog.2020.02.016), indexed in Pubmed: [32105679](https://pubmed.ncbi.nlm.nih.gov/32105679/).
15. Lee M, Chung YJ, Kim HK, et al. Estimated Prevalence and Incidence of Uterine Leiomyoma, and Its Treatment Trend in South Korean Women for 12 years: A National Population-Based Study. *J Womens Health (Larchmt).* 2020 [Epub ahead of print], doi: [10.1089/jwh.2020.8398](https://doi.org/10.1089/jwh.2020.8398), indexed in Pubmed: [32991229](https://pubmed.ncbi.nlm.nih.gov/32991229/).
16. Harmon QE, Brasky TM. Risk factors for uterine fibroids: time to build on what we have learned. *Fertil Steril.* 2020; 114(4): 755–756, doi: [10.1016/j.fertnstert.2020.07.059](https://doi.org/10.1016/j.fertnstert.2020.07.059), indexed in Pubmed: [32907745](https://pubmed.ncbi.nlm.nih.gov/32907745/).
17. Bariani MV, Rangaswamy R, Siblini H, et al. The role of endocrine-disrupting chemicals in uterine fibroid pathogenesis. *Curr Opin Endocrinol Diabetes Obes.* 2020; 27(6): 380–387, doi: [10.1097/MED.0000000000000578](https://doi.org/10.1097/MED.0000000000000578), indexed in Pubmed: [33044243](https://pubmed.ncbi.nlm.nih.gov/33044243/).
18. Chwalisz K, Taylor H. Current and Emerging Medical Treatments for Uterine Fibroids. *Semin Reprod Med.* 2017; 35(6): 510–522, doi: [10.1055/s-0037-1606302](https://doi.org/10.1055/s-0037-1606302), indexed in Pubmed: [29100239](https://pubmed.ncbi.nlm.nih.gov/29100239/).
19. Al-Hendy A, Myers ER, Stewart E. Uterine Fibroids: Burden and Unmet Medical Need. *Semin Reprod Med.* 2017; 35(6): 473–480, doi: [10.1055/s-0037-1607264](https://doi.org/10.1055/s-0037-1607264), indexed in Pubmed: [29100234](https://pubmed.ncbi.nlm.nih.gov/29100234/).
20. Vitale SG, Riemma G, Ciebiera M, et al. Hysteroscopic treatment of submucosal fibroids in perimenopausal women: when, why, and how? *Climacteric.* 2020; 23(4): 355–359, doi: [10.1080/13697137.2020.1754390](https://doi.org/10.1080/13697137.2020.1754390), indexed in Pubmed: [32410475](https://pubmed.ncbi.nlm.nih.gov/32410475/).

21. Laberge PY, Murji A, Vilos GA, et al. SPECIAL CONTRIBUTORS. The management of uterine leiomyomas. *J Obstet Gynaecol Can.* 2015; 37(2): 157–178, doi: [10.1016/S1701-2163\(15\)30338-8](https://doi.org/10.1016/S1701-2163(15)30338-8), indexed in Pubmed: [25767949](https://pubmed.ncbi.nlm.nih.gov/25767949/).
22. Strand T, Kives S, Leyland N, et al. Treatment Choices in a National Cohort of Canadian Women With Symptomatic Uterine Fibroids. *J Obstet Gynaecol Can.* 2020; 42(12): 1475–1482.e2, doi: [10.1016/j.jogc.2020.06.012](https://doi.org/10.1016/j.jogc.2020.06.012), indexed in Pubmed: [33046429](https://pubmed.ncbi.nlm.nih.gov/33046429/).
23. Czuczwar P, Stepniak A, Milart P, et al. Comparison of the influence of three fibroid treatment options: supracervical hysterectomy, ulipristal acetate and uterine artery embolization on ovarian reserve - an observational study. *J Ovarian Res.* 2018; 11(1): 45, doi: [10.1186/s13048-018-0420-1](https://doi.org/10.1186/s13048-018-0420-1), indexed in Pubmed: [29859107](https://pubmed.ncbi.nlm.nih.gov/29859107/).
24. Giarrè G, Franchini M, Castellacci E, et al. Ulipristal acetate in symptomatic uterine fibroids. A real-world experience in a multicentric Italian study. *Gynecol Endocrinol.* 2020; 36(2): 171–174, doi: [10.1080/09513590.2019.1648419](https://doi.org/10.1080/09513590.2019.1648419), indexed in Pubmed: [31392917](https://pubmed.ncbi.nlm.nih.gov/31392917/).
25. Ali M, Chaudhry ZT, Al-Hendy A. Successes and failures of uterine leiomyoma drug discovery. *Expert Opin Drug Discov.* 2018; 13(2): 169–177, doi: [10.1080/17460441.2018.1417381](https://doi.org/10.1080/17460441.2018.1417381), indexed in Pubmed: [29254389](https://pubmed.ncbi.nlm.nih.gov/29254389/).
26. Letterie GS, Coddington CC, Winkel CA, et al. Efficacy of a gonadotropin-releasing hormone agonist in the treatment of uterine leiomyomata: long-term follow-up. *Fertil Steril.* 1989; 51(6): 951–956, doi: [10.1016/s0015-0282\(16\)60724-0](https://doi.org/10.1016/s0015-0282(16)60724-0), indexed in Pubmed: [2498132](https://pubmed.ncbi.nlm.nih.gov/2498132/).
27. Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for Heavy Menstrual Bleeding in Women with Uterine Fibroids. *N Engl J Med.* 2020; 382(4): 328–340, doi: [10.1056/NEJMoa1904351](https://doi.org/10.1056/NEJMoa1904351), indexed in Pubmed: [31971678](https://pubmed.ncbi.nlm.nih.gov/31971678/).
28. Kang S, Brinker A, Jones SC, et al. An Evaluation of Postmarketing Reports of Serious Idiosyncratic Liver Injury Associated with Ulipristal Acetate for the Treatment of Uterine Fibroids. *Drug Saf.* 2020; 43(12): 1267–1276, doi: [10.1007/s40264-020-00960-1](https://doi.org/10.1007/s40264-020-00960-1), indexed in Pubmed: [32647996](https://pubmed.ncbi.nlm.nih.gov/32647996/).
29. Lethaby A, Puscasiu L, Vollenhoven B. Preoperative medical therapy before surgery for uterine fibroids. *Cochrane Database Syst Rev.* 2017; 11: CD000547, doi: [10.1002/14651858.CD000547.pub2](https://doi.org/10.1002/14651858.CD000547.pub2), indexed in Pubmed: [29139105](https://pubmed.ncbi.nlm.nih.gov/29139105/).

30. Cope AG, Young RJ, Stewart EA. Non-extirpative Treatments for Uterine Myomas: Measuring Success. *J Minim Invasive Gynecol.* 2021; 28(3): 442–452.e4, doi: [10.1016/j.jmig.2020.08.016](https://doi.org/10.1016/j.jmig.2020.08.016), indexed in Pubmed: [32841756](https://pubmed.ncbi.nlm.nih.gov/32841756/).
31. Stępnia A. Uterine artery embolization in the treatment of symptomatic fibroids - state of the art 2018. *Prz Menopauzalny.* 2018; 17(4): 141–143, doi: [10.5114/pm.2018.81733](https://doi.org/10.5114/pm.2018.81733), indexed in Pubmed: [30766459](https://pubmed.ncbi.nlm.nih.gov/30766459/).
32. Czuczwar P, Woźniak S, Szkodziak P, et al. Predicting the results of uterine artery embolization: correlation between initial intramural fibroid volume and percentage volume decrease. *Prz Menopauzalny.* 2014; 13(4): 247–252, doi: [10.5114/pm.2014.45001](https://doi.org/10.5114/pm.2014.45001), indexed in Pubmed: [26327862](https://pubmed.ncbi.nlm.nih.gov/26327862/).
33. Szkodziak P, Pyra K, Szkodziak F, et al. The Lublin Protocol of the Uterine Arteries Embolization in the Treatment of Symptomatic Uterine Fibroids. *J Vis Exp.* 2020(163), doi: [10.3791/61530](https://doi.org/10.3791/61530), indexed in Pubmed: [33016950](https://pubmed.ncbi.nlm.nih.gov/33016950/).
34. Sieroń D, Wiggermann P, Skupiński J, et al. Uterine artery embolisation and magnetic resonance-guided focused ultrasound treatment of uterine fibroids. *Pol J Radiol.* 2011; 76(2): 37–39, indexed in Pubmed: [22802829](https://pubmed.ncbi.nlm.nih.gov/22802829/).
35. Li S, Wu PH. Magnetic resonance image-guided versus ultrasound-guided high-intensity focused ultrasound in the treatment of breast cancer. *Chin J Cancer.* 2013; 32(8): 441–452, doi: [10.5732/cjc.012.10104](https://doi.org/10.5732/cjc.012.10104), indexed in Pubmed: [23237221](https://pubmed.ncbi.nlm.nih.gov/23237221/).
36. Funaki K, Fukunishi H, Funaki T, et al. Magnetic resonance-guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted magnetic resonance images. *Am J Obstet Gynecol.* 2007; 196(2): 184.e1–184.e6, doi: [10.1016/j.ajog.2006.08.030](https://doi.org/10.1016/j.ajog.2006.08.030), indexed in Pubmed: [17306674](https://pubmed.ncbi.nlm.nih.gov/17306674/).
37. Lozinski T, Filipowska J, Krol P, et al. Oxytocin Administration in High-Intensity Focused Ultrasound Treatment of Myomata. *Biomed Res Int.* 2018; 2018: 7518026, doi: [10.1155/2018/7518026](https://doi.org/10.1155/2018/7518026), indexed in Pubmed: [30057909](https://pubmed.ncbi.nlm.nih.gov/30057909/).
38. Lozinski T, Filipowska J, Gurynowicz G, et al. The effect of high-intensity focused ultrasound guided by magnetic resonance therapy on obstetrical outcomes in patients with uterine fibroids - experiences from the main Polish center and a review of current data. *Int J Hyperthermia.* 2019; 36(1): 582–590.
39. Focused Ultrasound Foundation. Focused Ultrasound Reimbursement Landscape in Europe 2020 [Updated 8.10.2020]. <https://www.fusfoundation.org/news/focused-ultrasound-reimbursement-landscape-in-europe> (16.01.2021).

40. Rabinovici J, David M, Fukunishi H, et al. MRgFUS Study Group. Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. *Fertil Steril*. 2010; 93(1): 199–209, doi: [10.1016/j.fertnstert.2008.10.001](https://doi.org/10.1016/j.fertnstert.2008.10.001), indexed in Pubmed: [19013566](https://pubmed.ncbi.nlm.nih.gov/19013566/).
41. Liu X, Xue L, Wang Y, et al. Vaginal delivery outcomes of pregnancies following ultrasound-guided high-intensity focused ultrasound ablation treatment for uterine fibroids. *Int J Hyperthermia*. 2018; 35(1): 510–517, doi: [10.1080/02656736.2018.1510548](https://doi.org/10.1080/02656736.2018.1510548), indexed in Pubmed: [30354861](https://pubmed.ncbi.nlm.nih.gov/30354861/).
42. Practice Committee of the American Society for Reproductive Medicine. Electronic address: ASRM@asrm.org, Practice Committee of the American Society for Reproductive Medicine. Removal of myomas in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline. *Fertil Steril*. 2017; 108(3): 416–425, doi: [10.1016/j.fertnstert.2017.06.034](https://doi.org/10.1016/j.fertnstert.2017.06.034), indexed in Pubmed: [28865538](https://pubmed.ncbi.nlm.nih.gov/28865538/).
43. Purohit P, Vigneswaran K. Fibroids and Infertility. *Curr Obstet Gynecol Rep*. 2016; 5: 81–8.
44. Chen J, Chen W, Zhang L, et al. Safety of ultrasound-guided ultrasound ablation for uterine fibroids and adenomyosis: A review of 9988 cases. *Ultrason Sonochem*. 2015; 27: 671–676, doi: [10.1016/j.ultsonch.2015.05.031](https://doi.org/10.1016/j.ultsonch.2015.05.031), indexed in Pubmed: [26093678](https://pubmed.ncbi.nlm.nih.gov/26093678/).
45. Liu Y, Zhang WW, He M, et al. Adverse effect analysis of high-intensity focused ultrasound in the treatment of benign uterine diseases. *Int J Hyperthermia*. 2018; 35(1): 56–61, doi: [10.1080/02656736.2018.1473894](https://doi.org/10.1080/02656736.2018.1473894), indexed in Pubmed: [29792359](https://pubmed.ncbi.nlm.nih.gov/29792359/).
46. Kroncke T, David M. participants of the Consensus M. Magnetic Resonance Guided Focused Ultrasound for Fibroid Treatment - Results of the Second Radiological Gynecological Expert Meeting. *Geburtshilfe Frauenheilkd*. 2015; 75(5): 436–8.
47. Ciebiera M, Łoziński T. The role of magnetic resonance-guided focused ultrasound in fertility-sparing treatment of uterine fibroids-current perspectives. *Ecancermedicalscience*. 2020; 14: 1034, doi: [10.3332/ecancer.2020.1034](https://doi.org/10.3332/ecancer.2020.1034), indexed in Pubmed: [32419846](https://pubmed.ncbi.nlm.nih.gov/32419846/).
48. Pandey S, Bhattacharya S. Impact of obesity on gynecology. *Womens Health (Lond)*. 2010; 6(1): 107–117, doi: [10.2217/whe.09.77](https://doi.org/10.2217/whe.09.77), indexed in Pubmed: [20088734](https://pubmed.ncbi.nlm.nih.gov/20088734/).
49. Ilaria S, Marci R. From obesity to uterine fibroids: an intricate network. *Curr Med Res Opin*. 2018; 34(11): 1877–1879.

50. Filipowska J, Loziński T. Magnetic Resonance-Guided High-Intensity Focused Ultrasound (MR-HIFU) in Treatment of Symptomatic Uterine Myomas. *Pol J Radiol.* 2014; 79: 439–443, doi: [10.12659/PJR.890606](https://doi.org/10.12659/PJR.890606), indexed in Pubmed: [25469176](https://pubmed.ncbi.nlm.nih.gov/25469176/).
51. Yang S, Kong F, Hou R, et al. Ultrasound guided high-intensity focused ultrasound combined with gonadotropin releasing hormone analogue (GnRHa) ablating uterine leiomyoma with homogeneous hyperintensity on T weighted MR imaging. *Br J Radiol.* 2017; 90(1073): 20160760, doi: [10.1259/bjr.20160760](https://doi.org/10.1259/bjr.20160760), indexed in Pubmed: [28256923](https://pubmed.ncbi.nlm.nih.gov/28256923/).
52. Ikin ME, Voogt MJ, Verkooijen HM, et al. Mid-term clinical efficacy of a volumetric magnetic resonance-guided high-intensity focused ultrasound technique for treatment of symptomatic uterine fibroids. *Eur Radiol.* 2013; 23(11): 3054–3061, doi: [10.1007/s00330-013-2915-x](https://doi.org/10.1007/s00330-013-2915-x), indexed in Pubmed: [23793518](https://pubmed.ncbi.nlm.nih.gov/23793518/).
53. Verpalen IM, Anneveldt KJ, Nijholt IM, et al. Magnetic resonance-high intensity focused ultrasound (MR-HIFU) therapy of symptomatic uterine fibroids with unrestrictive treatment protocols: A systematic review and meta-analysis. *Eur J Radiol.* 2019; 120: 108700, doi: [10.1016/j.ejrad.2019.108700](https://doi.org/10.1016/j.ejrad.2019.108700), indexed in Pubmed: [31634683](https://pubmed.ncbi.nlm.nih.gov/31634683/).
54. Kröncke T, David M, Kröncke T, et al. MR-Guided Focused Ultrasound in Fibroid Treatment - Results of the 4th Radiological-Gynecological Expert Meeting. *Rofo.* 2019; 191(7): 626–629, doi: [10.1055/a-0884-3143](https://doi.org/10.1055/a-0884-3143), indexed in Pubmed: [31137044](https://pubmed.ncbi.nlm.nih.gov/31137044/).
55. Spies JB, Coyne K, Guaou Guaou N, et al. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. *Obstet Gynecol.* 2002; 99(2): 290–300, doi: [10.1016/s0029-7844\(01\)01702-1](https://doi.org/10.1016/s0029-7844(01)01702-1), indexed in Pubmed: [11814511](https://pubmed.ncbi.nlm.nih.gov/11814511/).