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

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ABSTRACT

Introduction: Uterine fibroids (UFs) are benign tumors of female genital tract. Clinically symptomatic UFs may be a cause of serious health problems for many women worldwide. The optimal choice of a treatment method should fit a patient's specific life situation or expectancies (especially fertility) as much as possible. In line with the general current trend in medicine and surgery, great importance is attached to the development of minimally invasive radiological procedures e.g., magnetic resonance guided focused ultrasound (MRgFUS).

Materials and methods: Single-center retrospective cohort study conducted at the Department of Obstetrics and Gynecology of Pro-Familia Hospital in Rzeszów, Poland. The study group consisted of 276 patients suffering from UFs and treated with MR-HIFU over the period from April 2015 to May 2018.

Results: In our group 20 out of 276 patients conceived after the MR-HIFU therapy (7.25%). A general improvement and alleviation of symptoms of the disease after MRgFUS/MR-HIFU procedure were observed in 80% (n = 16) of study participants that conceived. 15% (n = 3) did not report any changes in disease severity. Out of 11 patients who already gave birth – 63.64% (n = 7) underwent cesarean section.

Conclusions: MRgFUS/MR-HIFU seems to be an interesting minimally invasive alternative for women with UFs who wish to conceive and deliver after the procedure. This method does not increase the rate of spontaneous abortions or pregnancy complications. In our opinion, it is important to take off an unjustified badge stating that MRgFUS/MR-HIFU method is contraindicated in women with UFs who wish to conceive.

Introduction

Uterine fibroids (UFs) (also known as myomas or leiomyomas) are benign monoclonal tumors originating from smooth muscle cells of the uterus [1,2]. They are one of the most common tumors found in female genital tract [3]. UFs are heterogeneous in their origin, size, topography and clinical symptomatology. Even up to 70% of women may be diagnosed with UFs depending on selected study populations and chosen diagnostic methods [2,4]. However, many women who have UFs do not present any kind of clinical symptoms and these tumors might grow undiagnosed for years [5]. Clinically symptomatic UFs may be a cause of serious health problems for many women worldwide [6–8]. They manifest through a wide range of symptoms, including painful and prolonged menstruation, heavy menstrual bleeding, passage of clots, spotting, bloating, constipation, anemia, pelvic and abdominal pressure or pain [3,9,10] infertility and obstetric complications [11]. Women with symptomatic UFs experience significant distress that reduces their quality of life (QoL) [10]. Lower QoL scores are observed in patients with the increased number and severity of UF-derived symptoms [7].

For many years, surgical management remained the gold standard for the treatment of symptomatic UFs [12–16]. At present, when the age at which women become mothers shows a constantly growing trend [17], a total deprivation of fertility, which occurs with hysterectomy, often becomes an unacceptable proposal [18,19]. Therefore, the optimal choice of a treatment method should fit a patient's specific life situation or expectancies as much as possible [20]. The factors...
taken into account when choosing proper treatment include
those related to the patient, such as the age and the length
time of to the potential menopause, the severity of symp-
toms, parity, future reproductive plans as well as UF char-
acteristics, including the number, size, location and risk of
malignancy [13,16,21]. It is not possible to perform myome-
tomy which preserves fertility in all patients and it carries
a risk of obstetric complications [22]. However, the risk of uter-
ine rupture after myomectomy is rather low (0.47–0.75%) [22,23]. Therefore, in recent years, the emphasis has been
placed on the development of new minimally invasive tech-
niques and conservative methods in UF treatment [2,13,19].
However, access to UF treatment alternatives, like new min-
imally invasive methods or drugs, may have a significant
effect on choices and outcomes of this disease [14].

Another topic to be discussed elsewhere covers several
drugs with proven efficacy in the treatment of UFs, including
ulipristal acetate (UPA), GnRH analogs [13,24] and others
[25–27]. The disadvantages of available drugs registered in
UF therapy are relatively high price, average efficacy and,
only, difficult accessibility. None of the available drugs may
also be used to prevent the formation of those tumors
[21,28]. To date, none of the available hormonally active
drugs has been classified for long-term treatment due to
side effects accompanying such therapies [19,24,29].

In line with the general current trend in medicine and sur-
gery, great importance is attached to the development of
minimally invasive radiological procedures: uterine artery
eMBOLization (UAE) [30] and magnetic resonance guided
focused ultrasound (MRgFUS) [31,32]. Conventional open and
laparoscopic surgical procedures are important in the man-
agement of UFs. However, radiological procedures may pre-
vent the need for hysterectomy.

MRgFUS is a kind of an ambulatory UF treatment option
with the advantage of preserving the uterus [33–35]. Under
direct magnetic resonance imaging (MRI) targeting, tempera-
ture assessment and monitoring, high-frequency ultrasound
waves produce heat which causes tumor cell death and sub-
sequent UF mass shrinkage [32,36]. During the procedure,
the evaluation of the location and the method of application
depend on the radiologist, who assesses the site, tempera-
ture and onset time [32,37]. In the new generation system
called magnetic resonance guided high-intensity focused
ultrasound (MR-HIFU) the whole procedure is more precise
and involves adequate volumetric heating of UFs with real-
time feedback. Heating every part of the tissue that has
been targeted and ablated volumetrically helps treat larger
volumes more efficiently and quickly [38,39].

Among various opinions on MRgFUS/MR-HIFU method,
attention is particularly focused on satisfactory clinical effi-
cacy, quick recovery and very low morbidity [36,37,40]. The
method is generally safe as side effects occur rarely
[36,40–43]. MRgFUS/MR-HIFU-derived adverse effects include
different kinds of skin burns, fever, nausea, tiredness, pain,
blood clot formation or transient nerve palsy due to pro-
longed stationary position [43–45]. If the patient reports no
complaints after the procedure, she may be discharged
home and return to work in subsequent days.

MRgFUS/MR-HIFU is not recommended in treatment
guidelines, as it is still considered experimental. There are
several studies about the use of MRgFUS/MR-HIFU in women
with clinically symptomatic UFs. In those studies, most of the
women reported satisfaction with the treatment, a significant
reduction in fibroid-related symptoms at follow up and no
need for further surgical intervention [35,40,41,43,46]. This
method is still not recommended for women wishing to pre-
serve fertility [41,47] and is usually banned for these women
due to the lack of randomized research in this topic. Surgical
myomectomy prolongs the time till birth as the patient
requires adequate postsurgical healing. Besides, all patients
after surgical myomectomy should be treated as high-risk of
obstetric complications in case of a future pregnancy [48].
Furthermore, all kinds of UF surgeries, even minimally inva-
sive methods, are procedures that could irreversibly change
or injure the pelvic cavity and cause pelvic adhesions, which
in turn might reduce further reproductive potential [49].

In an expert opinion, MRgFUS/MR-HIFU has the potential
to be a method of treatment that could shift traditional pat-
terns of health care [50]. Regarding the above-mentioned
facts and connecting them with the rising age of women
who wish to conceive with their various individual expecta-
tions (like non-surgical treatment only) MRgFUS/MR-HIFU
becomes a real alternative. Data concerning the effect of
MRgFUS/MR-HIFU treatment on the fertility and pregnancy
outcomes of women with UFs who underwent this treatment
are scarce [51,52]. Available studies by Rabinovici et al. and
Zou et al. showed that MRgFUS/MR-HIFU treatment may
reduce the pre-pregnancy preparation time, secure female
fertility and improve pregnancy outcomes [51,52].

In this manuscript, we present our unique experience
with women with further reproductive plans who received
anti-UF MRgFUS/MR-HIFU therapy. The aim of the study was
to assess the effect of the applied treatment on the allevia-
tion of symptoms and obstetrical outcomes in patients with
UFs wishing to conceive who had undergone MRgFUS/MR-
HIFU procedure at Pro-Family Hospital, Rzeszów, Poland.

Materials and methods
It was a single-center retrospective cohort study conducted
at the Department of Obstetrics and Gynecology of Pro-
Familia Hospital in Rzeszów, Poland. The study group con-
sisted of 276 patients suffering from UFs and treated with
MR-HIFU over the period from April 2015 to May 2018. This
study followed the principles of the Declaration of Helsinki.
The study had the Local Bioethics Committee Approval and
informed written consent was obtained from all the partici-
pants. All mandatory laboratory health and safety procedures
have been complied with in the course of conducting any
experimental work reported in this manuscript.

The inclusion criteria for the retrospective analysis were
as follows:

- Age from 23 to 43 years,
- Diagnosis of UFs and
Bothersome symptoms (painful, massive and/or acyclic uterine monthly bleeding, anemia, stomach pain, painful intercourse, miscarriage or premature delivery in the history of the disease, infertility*).

*Infertility was the main target symptom, all women included in the study had had other causes of infertility excluded.

The exclusion criteria were as follows:

- Multiple UFs (>2),
- Large UFs (>13 cm),
- Location of the UFs on the back wall of the uterus in direct contact with the rectum,
- Pedunculated UF,
- A history of operations due to UFs (a relative contraindication),
- Absence of symptoms and
- Contraindications for MRI.

The first stage of qualification included a medical interview and completion of self-composed questionnaire regarding clinical symptoms of the disease. Each enrolled patient was investigated about their fertility problems. The following steps were undertaken: gynecological examination with additional cervix evaluation and cytological smear check, the assessment of the size of the appendices, uterus and UFs, their consistency, mobility, tenderness. Ultrasound examinations were performed by certified gynecological ultrasonographers for an insightful assessment of UFs, their number, size, position in relation to the uterine cavity and endometrium, the evaluation of tumor structure (evaluation of necrosis and calcifications). The ultrasound assessment also included: flow index (FI), valuation of the vascular index (VI) and valuation of the flow-vascular index (FVI).

The next step was the MRI of the pelvic area. On the basis of the structure in T2-weighted MRI, UFs were divided according to Funaki classification [53]. Type 1 and type 2 UFs were qualified for MRgFUS/MR-HIFU, whereas type 3 UFs were disqualified. MRI also included the assessment of the precise location in relation to the endometrium and internal organs (especially intestines) so that the method would be safe for the surrounding organs.

Our department uses MRgFUS/MR-HIFU Sonalleve system which integrates Ingenia 3.0T MRI scanner (Philips, Amsterdam, Netherlands). All eligible patients underwent an MRI scan with the administration of intravenous gadolinium contrast, including T2- and T1-weighted images with pre- and post-intravenous gadolinium contrast. At the end of the treatment, the patients underwent an additional injection of gadolinium contrast and the non-perfused volume percentage (NPV) of the tumor was calculated as a measurement of the treatment success.

Afterward, the patients were invited to Pro-Familia for follow-up visits, approximately 3 and 6 months after the intervention. After 3 months each patient had a regular gynecological appointment with an additional ultrasound examination and tumor size and mass evaluation. QoL questionnaire was filled in during this visit as well. After 6 months each patient was examined by a gynecologist with an additional ultrasound evaluation.

All the patients included in the study were planning to conceive in the future. Afterward, the authors collected data on whether the patients managed to get pregnant after MRgFUS/MR-HIFU procedure. In case of viable pregnancies standard obstetric data were collected. Data about complications like miscarriages, premature deliveries, intrauterine fetal growth restriction (IUGR), threatened uterine rupture and other severe complications in the patients were collected as well. The patients were obligated to contact our department even in cases where potential medical help would be provided elsewhere.

**Results**

In our group 20 out of 276 patients conceived after the MR-HIFU therapy (7.25%). The mean age of the women was 33.2 (±3.65; range: 26–40 years). 35% \(n = 7\) of the patients were older than 35 years. In addition to UFs, three patients had a history of Hashimoto disease, one of kidney stones and one of cholelithiasis. The remaining patients were otherwise healthy.

Mean sonification time was 114.95 min, mean sonification power 183 W, mean maximal sonification temperature equaled 77.4°C and mean non-perfused volume ratio (NPVR%) was 74.25%. The lowest NPVR% achieved in this group was 50% and the highest was 100%. In 11 out of 20 women (55%) NPVR% was higher or equal to 60–70%, which is conventionally considered as an evidence of the success of MRgFUS/MR-HIFU therapy. Thirty percentage \(n = 6\) of the patients were diagnosed with UF Funaki type I and 70% \(n = 14\) were diagnosed with UF Funaki type II as in the publication by Funaki et al. [53]. The above-mentioned data are presented in Table 1.

A general improvement and alleviation of symptoms of the disease after MRgFUS/MR-HIFU procedure were observed in 80% \(n = 16\) of study participants that conceived. Fifteen percentage \(n = 3\) did not report any changes in disease severity, while 5% \(n = 1\) of patients were lost to follow-up. The results are presented in Table 2.

Twenty percentage \(n = 4\) of the participants had been pregnant at least once before MRgFUS/MR-HIFU treatment. Spontaneous pregnancy after therapy occurred in 20 and none of them conceived through assisted reproductive technologies. Of the 20 patients who became pregnant after the procedure: 3 miscarried (1 of them had miscarried and later gave birth), 11 already gave birth, 7 are currently pregnant. The data are presented in Table 3. Two of three patients who miscarried decided to undergo surgery (no. 14 and 15 in Table 3).

All the pregnancies that had already ended were full-term (38–40 weeks of pregnancy) and uncomplicated by pregnancy complications including: preterm birth, IUGR, preeclampsia or uterine rupture/injury. Two patients developed a pregnancy complication that in our opinion is rather unrelated to MRgFUS/MR-HIFU, i.e., gestational diabetes mellitus (GDM).
Out of 11 patients who already gave birth – 63.64% (n = 7) underwent cesarean section for emergency reasons, e.g., threatening scar dehiscence after previous cesarean section, lack of labor progress and also elective cesarean sections. A percentage of 36.36 (n = 4) of the patients had vaginal delivery. All the children scored 9–10 points on the Apgar scale after the first minute (Table 3).

### Discussion

MRgFUS/MR-HIFU is a quickly developing technology with a potential application in many different indications, especially in UF treatment [47]. The first reports concerning the use of MRgFUS described murine studies and were published in 1995 by Cline et al. [54]. In 2004, US Food and Drug Administration accepted the use of this method in the treatment of UFs, which produced a considerable development. However, to date, the majority of gynecological or radiological associations have advised its use only in research and audit settings [47]. The fact that MRgFUS/MR-HIFU became available for a larger group of patients and taking off its badge stating that it is only an experimental kind of treatment facilitated the extension of the list of indications (e.g., for palliative therapy), beginning clinical research and increasing its availability via the purchase of devices adapted to this kind of treatment [50]. According to the view on medical market, there are a variety of new devices in the development pipeline, as well as a wide spectrum of clinical trials are now in progress or are planned in the nearest future. In some countries, no internal opinions are expressed.

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**Table 1. Sonification effects and fibroid characteristics in patients who conceived after MR-HIFU treatment.**

| Patient number | NPVR% | Sonification time (min) | Maximal sonification power (W) | Maximal sonification temperature (°C) | Fibroid volume at the time of qualification (cm³) | Funaki type |
|----------------|-------|-------------------------|-------------------------------|--------------------------------------|-----------------------------------------------|------------|
| 1              | 90    | 89                      | 220                           | 81                                   | LOD                                           | LOD        |
| 2              | 90    | 293                     | 240                           | 84                                   | 333.4                                         | I          |
| 3              | 50    | 80                      | 160                           | 105                                  | 190                                           | I          |
| 4              | 50    | 54                      | 120                           | 73                                   | 191.2                                         | I          |
| 5              | 90    | 73                      | 170                           | 73                                   | 10.8                                          | II         |
| 6              | 90    | 90                      | 150                           | 69                                   | 19.3                                          | II         |
| 7              | 95    | 75                      | 140                           | 72                                   | 50.5                                          | I          |
| 8              | 90    | 93                      | 180                           | 72                                   | 109.9                                         | II         |
| 9              | 60    | 167                     | 180                           | 72                                   | 50.5                                          | II         |
| 10             | 50    | 104                     | 220                           | 84                                   | 32.5                                          | II         |
| 11             | 50    | 92                      | 170                           | 87                                   | 36.3                                          | I          |
| 12             | 90    | 101                     | 200                           | 72                                   | 63.6                                          | II         |
| 13             | 60    | 193                     | 130                           | 81                                   | 181                                           | II         |
| 14             | 60    | 95                      | 150                           | 69                                   | 80.5                                          | II         |
| 15             | 75    | 176                     | 230                           | 79                                   | 109.9                                         | II         |
| 16             | 100   | 117                     | 220                           | 79                                   | 53.9                                          | II         |
| 17             | 60    | 53                      | 220                           | 70                                   | 95.5                                          | II         |
| 18             | 100   | 113                     | 190                           | 72                                   | 79.8                                          | II         |
| 19             | 55    | 117                     | 170                           | 84                                   | 49.2                                          | II         |
| 20             | 80    | 124                     | 200                           | 70                                   | 81.8                                          | II         |
| Average        | 74    | 115                     | 183                           | 77                                   | 86.5                                          |            |

LOD: lack of data; N/A: not applicable.

**Table 2. General alleviation of symptoms and fibroid volume change after MR-HIFU therapy in described patients.**

| Patient number | Fibroid volume at the time of qualification (cm³) | General alleviation of UF-related symptoms | Fibroid volume 3 months after the procedure (cm³) | % of the initial volume | Fibroid volume 6 months after the procedure (cm³) | % of the initial volume |
|----------------|--------------------------------------------------|------------------------------------------|--------------------------------------------------|------------------------|--------------------------------------------------|------------------------|
| 1              | 333.4                                            | Yes                                      | LOD                                              | LOD                    | LOD                                              | LOD                    |
| 2              | 190                                              | Yes                                      | 99.2                                             | 52.2%                  | 96.7                                             | 50.9%                  |
| 3              | 191.2                                            | Yes                                      | 25.4                                             | 13.3%                  | 28                                               | 14.7%                  |
| 4              | 10.8                                             | No change                                | 13.7                                             | 127.2%                 | 16.8                                             | 155.4%                 |
| 5              | 13.6                                             | Yes                                      | 15                                               | 110.8%                 | 6.6                                              | 48.9%                  |
| 6              | 19.3                                             | Yes                                      | 15.3                                             | 79.1%                  | 13.7                                             | 71.0%                  |
| 7              | 28.7                                             | Yes                                      | 19.9                                             | 69.5%                  | LOD                                              | LOD                    |
| 8              | 28.6                                             | LOD                                      | LOD                                              | LOD                    | LOD                                              | LOD                    |
| 9              | 50.5                                             | Yes                                      | 79                                               | 79.0%                  | 24.3                                             | 48.0%                  |
| 10             | 32.5                                             | Yes                                      | 17.7                                             | 54.4%                  | 18.4                                             | 56.7%                  |
| 11             | 36.5                                             | No change                                | 34.9                                             | 95.6%                  | 46.3                                             | 126.7%                 |
| 12             | 63.6                                             | Yes                                      | LOD                                              | LOD                    | 36                                               | 56.6%                  |
| 13             | 181                                              | Yes                                      | 330                                              | 182.3%                 | 227.5                                            | 125.7%                 |
| 14             | 80.5                                             | No change                                | 97.1                                             | 120.6%                 | 140.5                                            | 174.6%                 |
| 15             | 109.9                                            | Yes                                      | 109.9                                            | 100.0%                 | 86.6                                             | 78.8%                  |
| 16             | 53.9                                             | Yes                                      | 13.8                                             | 25.5%                  | 10.1                                             | 18.7%                  |
| 17             | 95.5                                             | Yes                                      | 82.6                                             | 86.5%                  | LOD                                              | LOD                    |
| 18             | 79.8                                             | Yes                                      | 24.9                                             | 31.2%                  | 27.6                                             | 34.6%                  |
| 19             | 49.2                                             | Yes                                      | 19.7                                             | 40.0%                  | 12.3                                             | 25.1%                  |
| 20             | 81.8                                             | Yes                                      | 59.8                                             | 73.1%                  | 48.5                                             | 59.3%                  |
| Average        | 86.5                                             | N/A                                      | 61.2                                             | 78.8%                  | 52.5                                             | 71.6%                  |

LOD: lack of data; N/A: not applicable.
concerning the implementation of MRgFUS/MR-HIFU in UF treatment. However, national recommendations start to appear more commonly (e.g., in the United Kingdom) with regard to the use of this method in selected cases [55].

There are some various opinions about the use of MRgFUS/MR-HIFU in patients with more than two UFs. Recent data states that limiting the inclusion criteria to one or two UFs might be extremely reductive. Some centers obtain good results with the use only use of MRgFUS/MR-HIFU method in patients with multiple UFs [56,57]. Very recently He et al. published an article stating that ultrasound guided HIFU is safe and effective in treating patients with multiple UFs [58]. In our opinion, the use of MRgFUS/MR-HIFU in patients with multiple UFs needs more data to clarify the findings; however, available sources allow us to consider this method as remarkable in chosen cases.

Numerous women with UFs search for a method which would provide a safe solution in terms of removing the problem associated with the tumors along with preserving the full ability to reproduce [11,59,60]. The problem is of key importance, as currently no UF treatment methods are available which would be 100% successful in terms of giving birth after the treatment. The identification of a method which is the safest for the patient and carries the lowest risk associated with reducing the possibility of a full-term delivery is the key to solving the problem of UF-related infertility [59]. It is worth adding that numerous women completely resign from surgical treatment because of possible complications or surgery-related stress [61]. Therefore, MRgFUS/MR-HIFU appears to be an optimal treatment modality in those patients. Available data confirmed that MRgFUS/MR-HIFU does not impair ovarian function [62] and does not has a negative effect on the overall ability to conceive [43,51]. In case of using MRgFUS/MR-HIFU, as opposed to UAE, ovaries are not exposed to ionizing radiation and the proposed treatment involves no risk of mutagenicity [63].

The main problems related to MRgFUS/MR-HIFU are of logistic nature, e.g., preparation of the patient and device qualification and a possible problem of cooperation between the radiologist and gynecologist. If both of them are sufficiently engaged and experienced in this cooperation, the total UF treatment risk is then calculated as very low and the efficacy as higher [64,65]. Moreover, advanced research is conducted in order to increase the effectiveness of MRgFUS/MR-HIFU therapy, e.g., with the use of oxytocin [66].

Seemingly, in order to determine the influence and the effectiveness of MRgFUS/MR-HIFU on possible symptoms and pregnancy outcome, it should be compared with the most common method of minimally invasive UF treatment, i.e., laparoscopic myomectomy (LM). According to Canadian guidelines, the benefits of myomectomy should be weighed against the risks and the management should be tailored to the patient. The biggest effort should be made to perform precise suturing and minimize the possibility of postoperative adhesion formation [60]. Notably, such a comparison shows the advantage of MRgFUS/MR-HIFU which is not associated with the development of intraperitoneal adhesions, which may be of key importance for some patients. Furthermore, MRgFUS/MR-HIFU has other numerous advantages in comparison with LM, like faster recovery, less discomfort experienced by the patient and a low associated risk [62,63]. Available data showed that LM proved to be an effective procedure feasible for women with UFs who wish to conceive with subsequent good reproductive outcomes, both in terms of potential pregnancy complications and abortion rates [13]. According to Donnez and Jadoul, the pregnancy rate after LM equaled 49% [67]. Data published by Somigliana et al. were even more optimistic – postoperative pregnancy rate was 57% in this study [68]. Considering only large UFs these rates are lower. In a study by Eun et al., 25% of patients with large UF conceives after LM [69]. Live birth rates after LM are lower. In a study by Sangha et al.,

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Table 3. Data concerning pregnancies and labor characteristics in patients who conceived after MR-HIFU treatment.

| Patient number | No. of pregnancies before MR-HIFU | No. of miscarriages before MR-HIFU | No. of pregnancies after MR-HIFU | No. of miscarriages after MR-HIFU | Child born after MR-HIFU | CS/VD | Cause of CC | Week of pregnancy at the time of delivery | Birth weight (g) | Points in Apgar scale |
|---------------|----------------------------------|----------------------------------|---------------------------------|----------------------------------|------------------------|-------|-----------|------------------------------------------|-----------------|----------------------|
| 1             | 1                                | 0                                | 1                               | 0                                | Yes                    | CS    | In past, threatening scar dehiscence    | 38             | 4360                  | 10                  |
| 2             | 1                                | 1                                | 1                               | 0                                | Yes                    | CS    | Elective                             | 40             | 3360                  | 10                  |
| 3             | 0                                | 0                                | 2                               | 1                                | Yes (GDM)              | CS    | Elective                             | LOD            | 3540                  | LOD                |
| 4             | 0                                | 0                                | 1                               | 0                                | Yes                    | VD    | N/A                             | 39             | 3800                  | 9                  |
| 5             | 0                                | 0                                | 1                               | 0                                | Yes                    | VD    | N/A                             | 38             | 3420                  | 10                 |
| 6             | 0                                | 0                                | 1                               | 0                                | Yes                    | CS    | Elective                             | 38             | 3380                  | 10                 |
| 7             | 0                                | 0                                | 1                               | 0                                | Yes                    | CS    | Lack of labor progress               | 38             | 3890                  | 10                 |
| 8             | 1                                | 0                                | 1                               | 0                                | Yes                    | VD    | N/A                             | 39             | 3920                  | 10                 |
| 9             | 0                                | 0                                | 1                               | 0                                | Yes                    | VD    | N/A                             | 40             | 3300                  | 9                  |
| 10            | 0                                | 0                                | 1                               | 0                                | Yes (GDM)              | CS    | LOD                             | 38             | 3370                  | 10                 |
| 11            | 0                                | 0                                | 1                               | 0                                | Yes                    | CS    | LOD                             | 40             | 3500                  | 10                 |
| 12            | 0                                | 0                                | 1                               | 0                                | Pregnant               | N/A   | N/A                             | 38             | 3500                  | 10                 |
| 13            | 0                                | 0                                | 1                               | 0                                | Pregnant               | N/A   | N/A                             | 38             | 3890                  | 10                 |
| 14            | 0                                | 0                                | 1                               | 0                                | No                     | N/A   | N/A                             | 40             | 3300                  | 9                  |
| 15            | 1                                | 1                                | 1                               | 1                                | No                     | N/A   | N/A                             | 38             | 3370                  | 10                 |
| 16            | 0                                | 0                                | 1                               | 0                                | Pregnant               | N/A   | N/A                             | 38             | 3500                  | 10                 |
| 17            | 1                                | 1                                | 1                               | 1                                | No                     | N/A   | N/A                             | 38             | 3890                  | 10                 |
| 18            | 1                                | 1                                | 1                               | 1                                | No                     | N/A   | N/A                             | 38             | 3500                  | 10                 |
| 19            | 0                                | 0                                | 1                               | 0                                | Pregnant               | N/A   | N/A                             | 38             | 3890                  | 10                 |
| 20            | 0                                | 0                                | 1                               | 0                                | Pregnant               | N/A   | N/A                             | 38             | 3500                  | 10                 |

No: number; CS: cesarean section; VD: vaginal delivery; LOD: lack of data; N/A: not applicable.
approximately 25% of women gave a live birth after LM and the rates after transabdominal myomectomy were similar [70]. Similar observations revealing no significant difference in the subsequent cumulative pregnancy rates and severe obstetric complications between LM and abdominal myomectomy were published by Tian et al. in 2015 with the additional recommendation to limit the use of electrosurgery in LM for better results [71]. According to a very recent study by Mohr-Sasson et al. who compared the effect of MRgFUS with LM in 132 (64 – LM, 68 – MRgFUS) patients, the overall satisfaction with long-term outcome in symptoms like abnormal uterine bleeding, dysmenorrhea, abdominal and pelvic pain, voiding symptoms and the rate of additional interventions after MRgFUS for UF treatment was comparable with LM [72]. In the IDEAL prospective exploration Chinese study performed in 2411 patients with UFs, MR-HIFU was found to be better than surgery as regards short-term outcomes. As reported by the authors, major adverse events occurred in 0.2% of patients undergoing MR-HIFU and in almost 12.6% of all surgical cases. The authors concluded that MR-HIFU caused lower morbidity than surgery, with similar longer-term QoL effect [73].

However, while the experts agree that lower pregnancy rates, higher miscarriage rates and more adverse pregnancy outcomes are associated with UAE in comparison with myomectomies [60], data concerning the comparison between MRgFUS/MR-HIFU and LM are practically unavailable in the same context. Therefore, further studies are needed before offering this treatment to women with UFs and otherwise unexplained infertility. Finally, we should also remember that these two methods are still extremely difficult to compare. In surgery nearly each tumor may be removed regardless of the size and location, while MRgFUS/MR-HIFU may only be performed in UFs with a suitable window for an ultrasound beam. In this matter, MRgFUS/MR-HIFU treatment should always be seen as an alternative or complementary therapy. In our opinion, it is of utmost importance to take off an unjustified badge stating that MRgFUS/MR-HIFU method is contraindicated in women with UFs who wish to conceive. More and more reports are published in the press on the therapeutic outcomes of UF treatment with MRgFUS/MR-HIFU and the effect on future pregnancy outcome [51,74].

One of the biggest available studies by Rabinovici et al. is a case series of 51 patients, from 13 sites worldwide, who conceived after the procedure. It was reported that 41% of pregnancies in this group resulted in deliveries and miscarriage occurred in 28%. Thirteen percentage of the pregnancies were electively terminated due to medical reasons [51]. Another study concerning a similar method – laparoscopic ultrasound-guided radiofrequency volumetric thermal ablation performed by Berman et al. showed that five patients delivered full-term healthy infants with the use of this method, whereas one patient had a miscarriage in the first trimester [75]. A systematic review performed by Clark et al. (outcomes of 35 pregnancies) revealed that MRgFUS/MR-HIFU was a well-tolerated method of treatment with a rather low complication rate. The main complication that occurred in the pregnancies after MRgFUS/MR-HIFU was the first trimester bleeding, three patients included in the data suffered from GDM and two from hypertension. The authors concluded that pregnancy after MRgFUS is well-tolerated and further studies should be performed to gain additional data [76].

There are also more recent studies, mostly from China, where MRgFUS/MR-HIFU is a better recognized method of UF treatment. In a study by Zou et al. performed on 78 women, 80 pregnancies occurred. In those patients, 71 cases resulted in live birth (15 vaginal and 56 cesarean deliveries), including three cases of premature cesarean. As stated by the authors of this study pregnancies developed without perinatal complications [52]. In a different study by Li et al. performed in 189 women, the pregnancy rate was 69.3% (mostly after spontaneous conception – 95.4%) (125/131). In 87 (76.3%) cases, the pregnancy ended with a full-term live birth. Cesarean sections were performed in 67 (72%) cases (67/93). The total incidence of complications during pregnancy and delivery in this study equalled 10.8% (five placenta previa, one placental insufficiency, one intrahepatic cholestasis, one premature rupture of membrane, one large ovarian cyst and one cervical insufficiency) [74]. In the most recent study by Liu et al. 88 pregnancies resulted in 9 (10%) miscarriages, 5 (6%) pregnancy terminations and 74 (84%) deliveries. Twenty successful vaginal deliveries were reported in those patients. The authors of this study concluded that MR-HIFU is a promising method of treatment for women with UFs and that vaginal delivery after this kind of therapy appears to be safe as well [77].

In Poland, MRgFUS/MR-HIFU is performed on a larger scale only at our center and is still more of a curiosity for some physicians than a real alternative in UF treatment. The present results are somewhat different from those obtained by Chinese research teams. A considerable reduction in terms of UF-related signs and symptoms were observed in the above-described patients. This article includes data concerning only those patients who conceived, but manifestations like abnormal uterine bleeding, abdominal pain and others, also diminished in the majority of the remaining 256 patients who did not conceive (the data will be published in another paper). The pregnancy rate after implemented treatment reached 7.25% (20 out of 276 patients) which is much lower compared to recent data published by Chinese authors [74,77]. It is worth considering and conducting further research, since the disproportion of data is significant with the method and inclusion criteria being similar. Spontaneous abortion rates after MR-HIFU were really low which is consistent with Chinese data. Chinese studies [74,77] showed an increased percentage of cesarean sections performed in patients who underwent MRgFUS/MR-HIFU treatment, which is explained by the authors as being related to social determinants rather than medical indications. Cesarean section rate was 60% in this study, with some of them performed due to independent obstetric indications during attempts at vaginal delivery. Therefore, it seems that the percentage of cesarean sections following MRgFUS/MR-HIFU does not have to be increased in relation to the standard values in a given country. We agree with Li.
et al. that further clinical experience with MRgFUS/MR-HIFU may lead to the reduction of those values to the benefit of vaginal delivery [74].

One striking feature is that no cases of preterm, iatrogenic or spontaneous delivery were observed in this study. In their study Li et al., concluded that the risk of preterm birth is reduced after MR-HIFU treatment in comparison to LM [74]. Interestingly, this study revealed practically no complications occurring intragestationally in the patients. The case of gestational diabetes mellitus is rather unrelated to the treatment and should not be linked to MR-HIFU. Furthermore, the absence of cases of placental insufficiency or intrauterine growth restriction (IUGR) seems to be of key importance. As regards reports presented by other authors intraterine growth restriction also occurred occasionally [52,74,76]. In our viewpoint, it is an exceptionally interesting observation, because it might seem that MRgFUS/MR-HIFU treatment may somehow contribute to the destruction of the uterine muscle and affect placental function due to treatment-related change of conditions. However, it is possible that such a conclusion is untrue. UFs are less perfused after MRgFUS/MR-HIFU, which makes the blood supply its anatomical target, i.e., the maternal-fetal unit. As regards MRgFUS/MR-HIFU-related complications, no cases of placenta previa were reported in this study, unlike Chinese research, e.g., in a study by Liu et al. [77]. The authors concluded that an increased risk of placental abnormalities after MR-HIFU therapy described in their study might be a topic for further investigation. A possibility of uterine rupture following MRgFUS/MR-HIFU compared to LM is a fundamental issue to be analyzed. According to available data uterine rupture is a serious complication which may be observed in some patients who underwent LM [22,78]. This study showed no uterine rupture cases, which was in line with recent research [74,77]. Therefore, it seems that the risk associated with possible uterine rupture before or during delivery is one of the factors which confirm the beneficial effect of MR-HIFU treatment. Obviously, further research is necessary with regard to additional aspects.

In patients who desire pregnancy, MRgFUS/MR-HIFU offers an attractive alternative to traditional surgical approaches. The results presented in this paper and those of other researchers worldwide are promising and indicate that the method may be considered an effective alternative to traditional methods of UF treatment. Additional data should be collected, especially as regards possible complications associated with the implementation of the method and the ways of preventing such complications. However, data regarding MRgFUS/MR-HIFU are more and more abundant with more facilities performing this type of treatment. Therefore, over a few years, it may be possible to obtain sufficient sample sizes to make proper and reliable conclusions concerning this therapy, especially as regards patients with UF who wish to conceive without having to undergo a surgery.

Conclusions

MRgFUS/MR-HIFU seems to be an interesting minimally invasive alternative for women with UF who wish to conceive and deliver after the procedure. This method helps to minimize the risks associated with a surgical intervention and does not increase the rate of spontaneous abortions or pregnancy complications. In our group of patients, all the pregnancies which already ended and the ongoing ones were uncomplicated by IUGR, uterine rupture or preeclampsia until the day of the publication of this article. In the majority of cases, the treatment contributed to radiological improvement and a significant reduction in tumor volume, which translated into a substantial alleviation of disease symptoms.

Due to considerable limitations in patient qualification process (UF location, number, size, etc.), this therapy should still be treated as an alternative or complementary treatment in women with UF with unexplained infertility. However, it is important to take off an unjustified badge stating that MRgFUS/MR-HIFU method is contraindicated in women with UF who wish to conceive.

Disclosure statement

All authors declare no conflict of interest. The study has not been published elsewhere.

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Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

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