Sonalleve MR-HIFU Therapy

Uterine therapy application: Review of published literature on MR-guided focused ultrasound and pregnancy

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Abstract

Depending on their location and morphology, uterine leiomyomas may have a substantial negative impact on a patient's ability to conceive and bear children. Traditionally, the most common treatment option for uterine leiomyomas has been hysterectomy, with myomectomy as the primary treatment for patients who wish to preserve their future fertility. Recently the risks and side effects related to surgical interventions have led to the development of less invasive treatment options, such as Sonalleve MR-HIFU therapy.
In this paper we review the current literature on pregnancy outcomes in patients following minimally-invasive and non-invasive treatment for uterine fibroids. The analysis emphasizes the evidence base for treatment with MR-guided high intensity focused ultrasound.

Background

Uterine leiomyomas occur in 40 – 60% of women by the age of thirty-five[1], with estimated rates of 20 –50% overall during reproductive years. Incidence during pregnancy remains less clear, with estimates ranging from 0.1 to 11%.[1–4]
Fibroids may negatively impact a patient's ability to conceive, as well as increase her chances of obstetric complications if she is able to conceive. Fertility problems induced by uterine fibroids cannot be attributed to just one mechanism; instead several mechanisms have been proposed. Anatomical distortions of the cervix, uterine cavity or tubal ostia may alter the likelihood of sperm reaching the proximal fallopian tube, as well as hinder ovum retrieval and transport to the uterus. It is also suggested that fibroids may reduce the possibility of successful implantation by promoting abnormal uterine contractility, altering endometrial blood supply and by inducing localized endometrial inflammation and changes in the biochemistry of the intrauterine fluid. According to one theory, fibroid sufferers may have anovulatory cycles resulting from the hyperestrogenic environment. Fibroids alone may even lead to infertility, although it is difficult to rule out other contributing factors. In many cases, increase in fertility rates has been observed in patients following fibroid therapies.[5–9]
It is generally accepted that location of the fibroid within the uterus is the most important factor influencing its effect on fertility. The literature indicates that subserosal fibroids have no statistically significant effect on fertility, whereas intramural fibroids appear to negatively impact fertility and lead to increased pregnancy loss. Submucosal fibroids reduce both implantation rate and clinical pregnancy rate whilst increasing the possibility of spontaneous abortion.[8, 10]

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Uterine fibroid treatment options

The most common treatments for uterine fibroids include medical hormone treatment, myomectomy, hysterectomy, uterine artery embolization (UAE), and magnetic resonance-guided high intensity focused ultrasound. Therapy choices are dictated by the size and location of the fibroid, symptom severity and the patients desire to preserve fertility. When preservation of fertility is a concern for the patient, hysterectomy is not an appropriate treatment for these patients, whilst hormonal therapy is not an appropriate treatment for patients wishing to become pregnant.[7]

Myomectomy is most often considered the current standard of care for patients with fibroids seeking to become pregnant. For patients suffering from infertility and having submucosal fibroids, there is strong evidence for improved pregnancy outcomes following myomectomy. Data related to possible fertility improvement in patients with intramural fibroids is so far inconclusive. Nevertheless, myomectomy has known risks, both directly related to the procedure and for patients who do become pregnant. Depending on the surgical technique chosen, patients undergoing a myomectomy may have an increased risk of uterine rupture, adhesion formation, intra-operative conversion to hysterectomy, as well as fibroid recurrence. In addition, patients who have had a myomectomy may have an increased risk of miscarriage, uterine rupture during pregnancy, caesarian section and pre-term birth if they do conceive.[7–9]

Uterine artery embolization (UAE) has increased in popularity as a treatment option for women with symptomatic myomas. A number of successful pregnancies after UAE treatment have also been reported. However, this approach is associated with an increased rate of caesarean delivery along with a relatively higher incidence of complications, such as miscarriage, preterm delivery, intrauterine growth restriction, abnormal placentation, malpresentation, and postpartum hemorrhage. Lee et al. even concludes that UAE is absolutely contraindicated in women desiring future fertility.[11–14]

Recently, MR-guided high intensity focused ultrasound (MR-HIFU or MRgFUS) has been used for treatment of uterine fibroid patients who want to preserve fertility and pursue future pregnancy. MR-HIFU has been reported to be an effective and safe method in managing the symptoms caused by uterine fibroids.[15–20]

To date, more than 9000 women have undergone this treatment globally. MR-HIFU is a relatively new technology and it has only recently been approved for use in patients seeking future pregnancy, thus much of the documented evidence currently available related to MR-HIFU and pregnancy is based on case reports. Despite the limited volume of publications, as a body of evidence the reports indicate that very few related adverse events occurred during pregnancy and peripartum, and infants were healthy, suggesting that successful pregnancy is feasible following MR-HIFU therapy.

During an MR-HIFU procedure, real-time temperature mapping can be used to control the heating at the core of the fibroid, and to closely monitor that there is no damage of the uterine wall or endometrium. This approach enables the physician to limit the thermal damage to a distinct targeted region of the fibroid, which can be followed throughout therapy. The ablated tissues can also be observed post-treatment with MR-contrast imaging. Accurate correlation of the location of the thermal damage to the intended area has been proven by pathology specimens.[21, 22]

When MR-HIFU technology was introduced, regulatory agencies restricted its use to patients who were family complete. Based on the body of evidence described below, these restrictions have now been removed. In the countries which accept the CE marking, Philips Sonalleve MR-HIFU therapy is indicated for the ablation of symptomatic uterine fibroids or adenomyotic tissue in pre- or peri-menopausal women who desire a uterine sparing treatment. Women planning future pregnancy should consult with their physician before seeking the treatment.

Case reports of pregnancies following MR-HIFU therapy

Hanstede et al. (2007) reported a case in which the treatment of two uterine fibroids by MR-HIFU resulted in the restoration of normal shape to the endometrial cavity, which possibly facilitated a subsequent pregnancy. In this case, MR-HIFU was used to treat the patient's intramural myomas and the authors reported that at 1 year follow-up, a conformational change of the uterine cavity was observed on MRI and after this a pregnancy was successful.[23]

Gavrilova et al. (2007) was the first to address conception after treatment of a solitary large 9 x 10 x 10 cm^3 symptomatic uterine myoma.

At 39 weeks, the patient delivered a healthy male infant following labor induction and vacuum-assisted vaginal delivery. According to the report, there were no associated antepartum or intrapartum obstetrical complications after pregnancy following MR-HIFU.[24]

Morita et al. (2007) reported a case of a 29-year-old patient who had never been pregnant and whose history revealed no significant medical or gynecologic problems such as pain, abnormal bleeding or infertility. On clinical examination the size of her uterus was comparable to the size at 14 weeks of pregnancy. After successful MR-HIFU treatment, the patient conceived and at 39 weeks of pregnancy she had a vaginal delivery of a healthy baby.[25]

Zaher et al. (2010) described the first pregnancy and successful delivery in a woman who was part of a fertility trial and specifically treated with MR-HIFU for symptomatic fibroids. Prior to MR-HIFU, this patient had a premature delivery at 28 weeks.[26]

Yoon et al. (2010) described a patient with two distinct intramural myomas that were treated successfully with two consecutive MR-HIFU treatments one month apart. According to the case report, four months post treatment; the patient spontaneously conceived and continued her pregnancy to term. After 39 weeks of normal pregnancy, a baby girl was born, weighing 3190 grams, through a vaginal delivery. No complications were recorded during the labor or post-partum periods. The conclusion of his case report recommended large-scale clinical studies on women suffering from myoma-related infertility to verify the safety and the effectiveness of utilizing MR-HIFU treatments for enhancing fertility in patients with uterine myomas.[26]

Zaher et al. (2011) described a case of successful in vitro fertilization and pregnancy following MR-HIFU therapy. A 45-year old patient presented with a single symptomatic intramural fibroid measuring 9 x 6.2 x 7.1 cm^3 in the anterior wall of the uterus, causing distortion of the uterine cavity. The patient had already undergone four previous IVF cycles, resulting in one pregnancy which ended in miscarriage in the first trimester. MR-HIFU was subsequently performed, resulting to 90% non-perfused volume. Three months after the therapy, 80% shrinkage of the fibroid was observed, and the distortion of the endometrial cavity resolved. Ten months following therapy, the patient had her fifth IVF cycle, which resulted in a successful pregnancy. Initially the patient was admitted in spontaneous labor at term, although emergency caesarian section was performed due to suboptimal cardiotocograph. Patient delivered healthy male infant.[27]

Bouwsma et al. (2011) reported a case of a 37-year-old woman with several symptomatic leiomyomas, with the two largest intramural fibroids measuring 4.8 x 4.4 x 5.1 cm^3 and 3.5 x 3.2 x 3 cm^3. The patient had a history of 18 months of home-inseminations from a known donor, resulting in one miscarriage at 6 weeks. Two months after MR-HIFU treatment, the patient underwent intrauterine in`semination, resulting in pregnancy with a full-term vaginal delivery.[28]

Kim et al. (2011) reported a case study of a 40-year-old woman with 600 ml subserosal fibroid with symptoms of urinary frequency and a growing palpable mass. She underwent MR-HIFU therapy in which 72% of the fibroid was ablated as measured by non-perfused volume. Four months post-procedure the patient's fibroid volume had reduced to 43% of the baseline, and the patient was also 4 weeks pregnant. In addition to the reduction in fibroid volume, the patient reported completely resolved symptoms of urinary frequency and that the mass was barely palpable. Pregnancy outcome was not known at the time the original article was published.[29]

Retrospective clinical studies

In addition to the case reports summarized above, Rabinovici et al. (2008) summarized 54 pregnancies in 51 women after MR-HIFU treatment for their symptomatic uterine fibroids. The mean time to pregnancy after the procedure was 8 ± 7 months (range, 0 – 30 months). Of the 54 pregnancies, 22 (41%) resulted in live births and 11 (20%) were ongoing at more than 20 weeks. The spontaneous abortion rate was 27% and the rate of therapeutic abortion was 11%. The mean birth weight was 3.3 kg and 64% of the women had a vaginal delivery.[30] This study's findings suggest that fertility may be maintained, yet the number of cases is too small to draw concrete conclusions.

At this time, no study has been conducted to address the possible impact of MR-HIFU treatment on a patient's ability to become pregnant. It is expected that a prospective, randomized clinical trial of this nature would be difficult to design and perform. In the absence of such a study, retrospective analyses must be continued to refine our understanding of MR-HIFU and its potential impact on fertility enhancement.

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