



# Focused Ultrasound Surgery for Uterine Fibroids: Potential Impact on Fertility and Pregnancy Outcome - A Review

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## Abstract

Uterine fibroids are a common gynecological disorder affecting a large number of infertile women. Their pregnancy outcomes may also be poor because of complications such as miscarriage, preterm labor, obstructed labor, or postpartum bleeding. Myomectomy was traditionally used to enhance women's reproductive ability or reduce the above complications. However, operative myomectomy, either laparoscopic or open approach, may cause operative morbidity and raise hysterectomy risks. After myomectomy, women would also require a Caesarean section because of uterine ruptures' risks. High Intensity Focused Ultrasound ablation (Focused Ultrasound Surgery - FUS) is currently increasingly used as a new technology to treat fibroids. Therefore, the impact of HIFU ablation on patients' fertility and pregnancy outcomes has become a topic of interest. This paper reviewed the currently existing but limited evidence of this issue in the literature. It showed that USgHIFU/MRgFUS treatment for fibroids could be a safe alternative to myomectomy or UAE for women who wish to have babies. It also appears that FUS treatment can shorten the treatment to pregnancy interval after FUS ablation. Given the large number of women developing fibroids before childbearing, addressing this important issue in a large clinical trial is critical.

**Keywords:** Pregnancy; Ultrasound Surgery; Uterine Fibroids; Gynecology

## Introduction

Uterine fibroids are a common gynecological disorder. They affect approximately 30-70% of reproductive age-women [1], and approximately 5% - 10% of infertile women have fibroids. Their size and location determine whether they affect fertility. Examples include fibroids that are inside the uterine cavity (submucosal) or very large (>6 cm in diameter) within the wall of the uterus (intramural). Fibroids can block the fallopian tubes, interfere with the sperm or embryo's movement, and impact the uterine endometrial lining because of their locations and sizes. This can then reduce the chance of embryo implantation. For large fibroids, the pregnancy outcome may also be poor because of miscarriages and premature labor. Therefore, uterine fibroids in reproductive age women might adversely affect their fertility, causing pregnancy and labor complications

such as miscarriage, preterm labor, obstructed labor, or postpartum bleeding.

Myomectomy was traditionally used to remove fibroids before pregnancy or after delivery to enhance women's reproductive ability or reduce the above complications. However, operative myomectomy, either laparoscopic or open approach, will cause operative morbidity; sometimes, intraoperative heavy blood loss might raise the risks of hysterectomy. After myomectomy, women would also have to wait for at least 9 -12 months before their pregnancy because of uterine ruptures' risks.

## Focused Ultrasound Surgery

Focused ultrasound surgery (FUS), also known as High Intensity Focused Ultrasound (HIFU) ablation, is a new

non-invasive approach used for the treatment of benign gynaecologic diseases, including uterine fibroids [2] and adenomyosis [3]. The principle of FUS is to focus the ultrasound energy into a focus within the body after safely penetrating the body tissue. The focused energy will induce thermal, cavitation, and mechanical effects, producing a temperature 60 to 90 °C within a very short time at the focused target tissue such as a fibroid. This action results in coagulation necrosis of the fibroid without inflicting injury to the surrounding tissues. The necrotic fibroid tissue is gradually absorbed and reduces in sizes.

After FUS ablation, the fibroid volume shrinks in size. In a retrospective case series of 189 nulliparous women, the mean uterine fibroid volume shrinkage was 58.0% ± 31.3% after USgFUS treatment at 12 months [4]. Wang, et al. [5] in a prospective comparative study of 94 women with symptomatic uterine fibroids treated with USgFUS or MRgFUS, the mean fibroid volume reduction at 6 months was 52.7% ± 11.4% in the USgFUS group compared with 59.1% ± 9.0% in the MRgFUS group. Lyon, et al. [6] reported their clinical experience in a prospective case series of 10 patients. The mean volume reduction rate (MVR%) of the 14 treated fibroids reduced in size; It accounts for 23.3 % reduction in size at 3 months, 49.3% at 12 months, and 51.9% at 24 months.

At the same time, the fibroid related symptoms were also reduced significantly. A large cohort study of 2,411 women reported that uterine fibroid symptom score decreased significantly more in the USgFUS group than in the myomectomy group at 6 months (difference from baseline:  $-9.84 \pm 13.37$  compared with  $-8.23 \pm 13.10$ ,  $p=0.002$ ) and 12 months ( $-12.17 \pm 9.71$  compared with  $-9.71 \pm 13.69$ ,  $p=0.000$ ) [7].

### Complications of FUS Treatment

No mortality has been reported until now, and the majority of complications were not serious. After FUS therapy, common complications were skin burn, subcutaneous edema, lower abdominal pain, sciatic pain, and vaginal discharge with various vaginal bleeding amounts. However, severe adverse events were also reported, such as severe skin burn requiring surgical repair, bowel perforation, bladder burn, and deep vein thrombosis.

According to the International Association of Interventional Radiology Severity Classification (SIR) standards [8], in a large cohort study conducted by Chen, et al. [7], complications arising from FUS treatment were all grade A or grade B, and no grade C or higher complications occurred. Another safety analysis of 9988 cases of uterine

fibroids and adenomyoma treated by Chen, et al. [9] showed that in a total of 1062 patients, 1305 adverse reactions occur. Of the 1305 patients, 1228 were SIR class A and 45 cases SIR class B, 24 cases SIR class C, and the remaining 8 cases SIR class D. Many of these complications are more adenomyosis-related complications with a higher incidence. Otherwise, most of FUS side effects are mild. The incidence of serious complications for fibroids is extremely low. Therefore, the FUS treatment for fibroids has demonstrated a high degree of safety.

Since there have been only a few reports about serious complications after FUS, many clinicians were not seriously concerned about the possibility of rapid growth after FUS or unresponsiveness to FUS treatment, especially for very large fibroids, because they recognize that not all fibroids are suitable for FUS treatment. However, they agree that repeat FUS treatment can be available and accepted by the patients. In general, to avoid serious complications, careful selection of patients with fibroids will be recommended. Treatment by experienced FUS surgeons and safety protocols should be adopted. For consideration, the following should be considered as factors limiting FUS therapy; they are a large fibroid very close to the sacrum, extensive cutaneous keloid scars, pedunculated fundal subserosal fibroid, fibroid over 15 cm in size, or suspected bowel interposition in the acoustic pathway.

### Impacts on Fertility and Pregnancy Outcome

FUS treatment is increasingly used as a new technology for treating fibroids in young women who want to have babies. Despite its effectiveness and safety, FUS's impact on patients' fertility and pregnancy outcomes has become a topic of interest. In the early days of FUS treatment to fibroids, clinical reports had concentrated on the treatment of symptomatic women who had completed their families, and FUS ablation was contraindicated for women expecting a baby. Before 2009, the FDA regulatory body in America listed FUS treatment as an absolute contraindication in patients with fertility demand. With increasing experience, it is recognized that the safety of pregnancy outcomes may be due to any tumor necrosis after FUS ablation is within the fibroid's pseudocapsule and that FUS does not damage the surrounding healthy tissues. After FUS treatment, it successfully reduces the sizes of fibroids and improves the endometrial environment; thus, the pregnancy rate appears to have improved. More and more studies suggested that women who had FUS ablation could also conceive naturally and showed that FUS treatment has no adverse effects on pregnancy and newborns. With increasing experience and proof of safety, FDA changed FUS treatment as a relative contraindication for these women.

### Impacts on Fertility

Lee, et al. [10] compared the AMH levels of 79 patients with symptomatic adenomyosis and uterine fibroids before FUS treatment and six months after FUS treatment. They also found no significant difference between the two treated groups, suggesting that FUS treatment had no obvious impact on ovarian functions. Cheung, et al. [11] also studied the ovarian reserve measuring the anti-Mullerian hormone (AMH) before and after FUS treatment for uterine fibroid. They confirmed that it showed that FUS treatment had no adverse effect on the ovarian reserve.

Compared to myomectomy, which is associated with risks of infection, bleeding, adhesion formation, and early recurrence of fibroids, FUS treatment is a comparatively non-invasive method with minimal fertility impairment. As FUS is a non-invasive treatment with no wound or bleeding, there would not be any surgery-induced adhesion after treatment. The recurrence rate of fibroids after FUS treatment is compatible or even lower than that of myomectomy reported in the literature [12]. Compared to the uterine artery embolization (UAE), which has also been increasingly used

to treat symptomatic fibroids, another minimally invasive treatment, case reports of its uses, had detailed several complications. Larger series also confirmed that after UAE, there was an age-related risk of ovarian failure [13] and increased placentation problems [14]. Therefore, it appears that FUS treatment for fibroids is comparatively safer towards the fertility of patients receiving treatment.

### Impacts on Pregnancy and Labour Outcome

There are many existing reports showing that FUS treatment has no adverse impact on pregnancy and labor outcomes. In the early date, case reports of pregnancies after MRg-FUS treatment showed successful vaginal delivery at term, and none has complications during pregnancy and labor [15-17]. Some larger studies-including individual and multicentre collaborative trials-had also confirmed successful pregnancies after FUS therapy [18-22].

Table 1 showed that successful pregnancies occur after FUS treatment, and only a few reported complications in pregnancy and labor outcomes in patients wishing to have a vaginal delivery.

No	Author, Year	Treatment	Tumors/ treatment	Months to Pregnancies	Outcome
1	Hanstede MMF, et al. [15]	USA	Fibroid/MRgFUS	1.5 years	1 spontaneous pregnancy; vaginal delivery at 39 weeks
2	Morita Y, et al. [16]	Japan	Fibroid/MRgFUS	3 months	1 spontaneous pregnancy; vaginal delivery at 39 weeks
3	Yoon SW, et al. [17]	Korea	Fibroids/MRgFUS	4 months	1 spontaneous pregnancy, vaginal delivery at 39 weeks
4	Funaki K, et al. [23]	Japan	Fibroids/MRgFUS	Within 24 months	4 pregnancies. 1 pregnancy occurred 3 months after MRgFUS, 2 at 12 months, and 1 within 24 months. There were 2 live full-term births and 2 first-trimester miscarriages.
5	Rabinovici J, et al. [18]	Israel, Germany, Japan, USA	Fibroids/MRgFUS	(Mean) 8 months	54 pregnancies in 51 women have occurred after MRgFUS treatment of uterine leiomyomas. Live births 41% of pregnancies, of which 64% vaginal delivery, 28% spontaneous abortion rate, 11% termination of pregnancy, and 11 (20%) ongoing pregnancies beyond 20 weeks.
6	Qin J, et al. [19]	China	Fibroids/USgFUS	< 3 months (n = 4), 3-6 months (n = 13), and > 7 months (n = 7)	24 pregnancies. 8 women had desired pregnancy while the remaining 16 had not. Of the 8 desiring pregnancy, 7 continued to elective Caesarean section at full term with birth weights at least 2,500-g and Apgar scores within normal ranges (8-9) in all cases

7	Froeling V, et al. [24]	Germany	Fibroids// MRgFUS	average 16.1 months (range, 8.5–23.8)	10 pregnancies. There were 7 live births and 3 miscarriages.
8	Bohlmann MK, et al. [20]	Germany	Fibroids/ USgFUS, MRgFUS	n.a.	101 pregnancies, from an analytic study of 40 published papers. Miscarriage 17.8%, premature labor 5.9%, and Caesarean section rate 33.3%.
9	Zou M, et al. [21]	China	Fibroids/ USgFUS	5.6 +/- 2.7 months	80 pregnancies, including 4 IVF pregnancies, 15 vaginal deliveries, 56 cesarean sections, 3 miscarriages, 1 induced abortion, 5 ongoing pregnancies, no uterine rupture or postpartum complications
10	Li JS, et al. [4]	China	Fibrods/USgFUS	3 years	131 pregnancies out of 189 (69.3%) FUS treated nulliparous, spontaneous conception rate 95.4%, show 87 reached full term, Pregnancy complications, 10.8% Caesarean section 67/93 (72%). Labor complications – 5 premature birth, 1 fetal distress, and 6 bleeding at delivery
11	Liu X, et al. [22]	China	Fibroids/ USgFUS	Median of 76 months	88 pregnancies, 74 full-term deliveries (84%) including 37 cesarean sections, 9 miscarriages (10%), 5 induced abortions (6%), none has complications during pregnancy and labor.
n.a. not available					

**Table 1:** The pregnancy and obstetrical outcomes of patients after ultrasound guided Focused Ultrasound Surgery (USgFUS) and Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS) treatments for fibroids from the English literature.

From the table, early case reports demonstrated the safety of vaginal delivery after FUS treatment without complications [15-17]. Not until 2012, Chinese authors began to present their data after in larger series of patients. They also did not show any obstetric or labor complications in patients after USgFUS treatment. However, it might appear that there was a high rate of abortion rate from 17.8 % to 28% after FUS treatment [18,20]. Bohlmann, et al. [15] in their study showed that the risk of miscarriage after USgFUS/MRgFUS was 17.8%, which did not appear to be higher compared to an age-matched control group of patients wanting to have children. He further commented that FUS treatment for fibroids should be recommended to women with fibroid-associated subfertility who strictly reject surgical treatment or those who have very unacceptably high surgical risk. Besides, the mothers' age and the presence of sizeable fibroids may influence the miscarriage rate in these studies, as both of these factors can independently adversely impact miscarriages.

High Caesarean section rates after FUS ablation were also reported in Table 1. Despite the widespread reassurance

that vaginal delivery is safe, it could be due to the patients' desire for a healthy baby or the need for more safety than uncertain labor risks after FUS treatment. Caesarean section rate was reported as high as 50% to 78% [21,22]. Therefore after FUS ablation, all pregnancies that reach up to term would have a high caesarean section rate compared to term pregnancy without FUS surgery.

## Conclusion

The Practice Committee of the American Society for Reproductive Medicine had stated that removal of fibroids in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline [24]. The impact of FUS ablation on patients' fertility and pregnancy outcome becomes a topic of interest because FUS ablation is currently increasingly used as a new technology for the treatment of fibroids. This paper reviews the FUS treatment for fibroids and its potential impact on fertility and pregnancy outcomes.

Whether pregnancies are at particular risk for those women who have previously had USgFUS/MRgFUS

treatment, prospective randomized clinical trials should be performed. However, no such trials have been done yet. The currently existing but limited evidence suggests that USgFUS/MRgFUS treatment for fibroids and adenomyosis could be a safe alternative to myomectomy or UAE for women who wish to have babies. However, this is to be confirmed by the current consensus. However, it appears that FUS treatment can shorten the treatment to pregnancy interval after FUS ablation.

Even though early reports of pregnancies after FUS interventions for uterine leiomyoma and adenomyosis appear to be safe. However, these data must be carefully studied because a single complication causing maternal or fetal morbidity can be a disaster in even one out of a thousand cases. Given the large number of women developing fibroids and adenomyosis before childbearing, addressing these important issues in a large clinical trial is critical.

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