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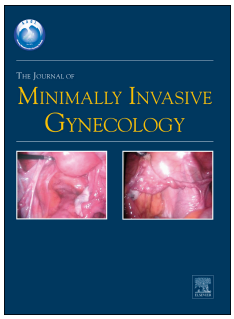

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Pregnancy outcomes following direct uterine fibroid thermal ablation: a review of the literature

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Key words: Myoma, Fibroid thermal ablation, Pregnancy

Abstract

The objective of this review is to describe the reproductive outcomes of women after radiofrequency volumetric thermal ablation (RFVTA) of fibroids or magnetic resonance-guided high-intensity focused ultrasound (MRgHIFU). This is a literature review of the current case

reports of reproductive outcomes following direct fibroid thermal ablation at multiple academic and private centers throughout the world. A literature search was performed using PubMed and Medline. All publications that included data of women who underwent radiofrequency fibroid ablation or magnetic resonance-guided high-intensity focused ultrasound of fibroids and subsequently conceived were included. There were a total of 122 pregnancies following direct uterine fibroid thermal ablation. 20 pregnancies were reported following RFVTA. Of these cases, there was 1 spontaneous abortion and 7 elective terminations. The remaining 12 pregnancies went on to have live full term deliveries, 9 (75%) by cesarean section and 3 (25%) by vaginal delivery. There were no reports of uterine abnormalities at delivery and one delayed postpartum hemorrhage with expulsion of degenerated fibroid. There are 102 reported pregnancies following MRgHIFU. There were 21 spontaneous abortions and 22 elective terminations, 48 deliveries, and 11 ongoing pregnancies at the time of report. There was one preterm delivery at 36 weeks due to placenta previa and the remaining deliveries were full term. The complications reported included vaginal spotting (12.5%), delayed placental separation (4%), and placenta previa (4%). There were no cases of uterine rupture. In summary, RFVTA and MRgHIFU are new minimally invasive alternatives for the treatment of fibroids. Further investigation into the reproductive outcomes following these fibroid therapies is crucial to determine whether these are appropriate treatment options for women with symptomatic fibroids who desire future fertility.

Introduction

Uterine fibroids are the most common benign tumor found in reproductive age women. Studies have shown that fibroids are found in up to 77% of women[1]. While many women are asymptomatic, symptomatic fibroids are the leading indication for benign hysterectomies. Symptoms may include dysmenorrhea and heavy menstrual bleeding which may lead to anemia, infertility, pelvic pain, and pressure on surrounding organs which can lead to urinary and/or bowel dysfunction[1-3].

Based on the symptoms, fibroids can be treated in different ways. For patients whose primary symptoms are abnormal uterine bleeding, medical therapy may be a good first step in management. Medical treatment options include hormonal contraception, levonorgestrel IUDs, GnRH agonists[2]. However, these modalities may only temporarily relieve symptoms and generally have only minimal effect on bulk symptoms. Surgical options include uterine fibroid embolization or uterine artery embolization, hysteroscopic myomectomy, abdominal or laparoscopic myomectomy and hysterectomy[2]. For women who desire future fertility, surgical options are limited. Uterine artery embolization and uterine fibroid embolization are less invasive procedures than myomectomy but can lead to amenorrhea in up to 30% of patients[4] and are not recommended in women who desire future fertility. While myomectomy is the standard of care for patients undergoing surgical management of fibroids who desire fertility, myomectomy is a major surgical procedure which can be associated with a high blood loss and in most cases would require subsequent cesarean delivery for concerns for uterine rupture[2,5].

Over the last few years, new technology for fibroid treatment has been undergoing investigation and development. Volumetric radiofrequency fibroid ablation and magnetic-resonance guided high-intensity focused ultrasound are minimally invasive fibroid treatments that although the technology and energy used is different, provide targeted volumetric thermal ablation to fibroids leading to fibroid volume reduction and symptomatic improvement[6,7]. To date, all of the initial studies excluded women who desired future fertility and thus there have been no published studies evaluating the live birth rates and fertility outcomes following directed fibroid thermal ablation. However, there have been a number of case reports describing reproductive outcomes in women who participated in the initial trials and in women who conceived after commercialization of the technology. In this review, we aim to review the current literature on the reproductive outcomes following radiofrequency fibroid ablation and magnetic resonance-guided high-intensity focused ultrasound and summarize the reproductive sequelae.

Methods

A literature search was performed using PubMed and Medline searching for the terms “fibroid ablation” and “pregnancy”, “radiofrequency fibroid ablation”, “magnetic resonance-guided focused ultrasound surgery”, “high intensity focused ultrasound”, “fibroid treatment”, “fibroid infertility”, “fibroid fertility”, “reproductive outcomes fibroids”. Articles and bibliography of each article was reviewed for further articles that could be included in this review. Inclusion criteria were articles written in the English language, and reporting on pregnancies following radiofrequency fibroid ablation or MRgHIFU. Articles were excluded if pregnancy outcomes were

not included in the report. The articles were reviewed by two different investigators to make sure no cases were reported more than once. The outcomes included pregnancy, termination of pregnancy, spontaneous abortion, live birth, delivery mode, and pregnancy complications.

Thermal Ablation Techniques

Volumetric Radiofrequency Ablation

Radiofrequency volumetric thermal ablation (RFVTA) is a safe and minimally invasive fibroid treatment. The RFVTA system works by delivering monopolor radiofrequency energy directly to tissue using a disposable electrosurgical handpiece[6,8,9]. This has been performed laparoscopically with success and transvaginal modalities are currently under investigation[7,10-12]. At the tip of the handpiece is a deployable needle electrode array which provides real-time temperature feedback to the generator which modifies parameters during the ablation. Disposable dispersive electrode pads are placed on each leg. Using ultrasound guidance, the fibroids are mapped within the uterus either laparoscopically or transvaginally. The dispersive electrode tip is then inserted into the fibroid, the needle tip is deployed which stabilizes the device and controls data input to the generator. The desired ablation diameter is determined by the operator based on fibroid size and location. The generator is set to reach a temperature within the tissue to allow for ablation. The generator displays tissue impedance, ablation time, and tissue temperature in real time during the procedure. This technology reduces the need for multiple ablations of the same fibroid and helps reduce ablative damage to the surrounding myometrium[6,10-12].

The clinical trials investigating the use of radiofrequency ablation for the treatment of fibroids specifically excluded women who desired future fertility or who had not completed their childbearing. The studies have shown that radiofrequency ablation of fibroids does improve symptoms related to fibroids such as heavy bleeding and bulk symptoms. Additionally, long term studies have shown low adverse effects and low surgical re-intervention[6,7,9,12]. Advantages of RFVTA include that it is a minimally invasive procedure that has minimal blood loss, allows for treatment of multiple fibroids of varying sizes, in most locations. Some disadvantages include the need to perform the procedure under general anesthesia and the procedure, if performed laparoscopically, involves intraperitoneal access.

At this time there have been no prospective studies published investigating fertility and pregnancy outcomes following RFVTA of fibroids. However, there are case series of pregnancies following RFVTA treatment. Table 1 lists the reported pregnancies following RFVTA. There is a total of 20 reported cases. Seven were undesired pregnancies and thus underwent elective termination. Of the remaining 13, there was one spontaneous abortion and 12 full term live births. Nine of the 12 pregnancies were delivered by cesarean section (75%). The cases reported by Bing-Song et al and Berman et al were RFVTA performed laparoscopically, while the cases reported by Kim et al and Garza-Leal et al were transvaginal RFVTA procedures[10,11,13,14]. Of the pregnancies reported following RFVTA, Berman et al, describes the size and location of the treated fibroids which is shown in Table 2. The cases reported show the ablation of fibroids

ranging from 0.9cm to 7.6cm and include single as well as multiple fibroids located submucosal, intramural, transmural, and subserosal.

In this series of patients, there were no reported uterine windows, abnormal placentation, uterine rupture, scarring or uterine thinning. The one complication reported was in a 40-year-old G3P3 at 37wks gestation who delivered by cesarean section at 2923g baby. She previously had RFVTA of 1 fundal transmural myoma measuring 4.7cm. Her delivery was complicated by expulsion of a degenerated fibroid and a delayed postpartum hemorrhage of 1500cc for which she received 6 units of blood[10].

Magnetic Resonance-Guided High-Intensity Focused Ultrasound Treatment of Uterine Fibroids

Magnetic resonance-guided high-intensity focused ultrasound is a noninvasive procedure used to ablate fibroids using heat generated from ultrasound waves. During MRgHIFU, magnetic resonance imaging (MRI) is used with a thermal mapping system to visualize the patient's anatomy and monitor the real time thermal effect of the ablation on the targeted tissue. The procedure can take an average of 3 hours and is useful in treating fibroids from 2-10cm[15-17].

During the procedure, the patient is placed in the prone position on the table within the MR scanner. The patient lies on top of a gel pad; this is used as a coupling device to prevent burning of the skin. Coronal, sagittal and axial T2-weighted MR images are taken to localize the fibroid target. The computer system/generator calculates the parameters needed for desired thermal

coagulation. The system generates a high intensity acoustic beam that focuses on the precise target. The sonication (low energy acoustic signal) is typically delivered in a pulsatile fashion with continual thermal feedback throughout and can be adjusted as needed. Tissue necrosis is achieved when the sonication reaches temperatures of 60-80 degrees Celsius. Additionally, a nurse continually monitors the patient's vital signs and pain throughout the procedure. The procedure can be stopped at any point by the patient, the nurse, the physician, or the device's safety over-ride programming. Typically, the patients are monitored for 1-2 hours following the procedure and then discharged home. Patients can be scheduled for repeat procedures if necessary[15,17]. Initially the Food and Drug Administration (FDA) limited these procedures to 3 hours but that restriction has been changed and the cases can last up to 4-5 hours if necessary[17].

Overall, the studies have shown MRgHIFU does successfully treat symptomatic fibroids. Multiple studies have shown reduction in fibroid volume, decreased bleeding, and patient satisfaction with few adverse outcomes[16,17]. The major downsides include time of the procedure, possible need for multiple procedures, and expense. Similar to RFA trials, the initial MRgHIFU studies excluded women desiring fertility. However, after the initial trials were performed, many women desiring fertility underwent the procedure and subsequently conceived which allowed for a larger series of pregnancy outcomes following MRgHIFU to be collected. Table 3 lists the series reporting pregnancy after MRgHIFU.

The two largest collections of cases were Rabinovici[15] and Qin[21]. There were 78 pregnancies following MRgHIFU in these series combined. Of those, 29 (37%) had live births, 14 vaginal

deliveries (48%) and 15 cesarean sections (52%). There were 16 miscarriages and 22 terminations. There was only one preterm delivery which was performed for placenta previa. The infant was 3410g and there were no additional complications of that delivery. Rabinovici et al. reported a case of a 29 year old who was hospitalized at 35 weeks gestational age for pain. She underwent a cesarean section at 38 weeks for breech presentation. The delivery was complicated by a fibroid in the lower uterine segment obstructing the pelvic outlet. A myomectomy was performed at the time of cesarean section. Post-operatively, the patient had uterine atony and hemorrhaged, underwent a repeat laparotomy without abnormal findings. She went on to develop DIC and adult respiratory distress syndrome. She then went on to have a subsequent pregnancy which was complicated by placenta previa but underwent an uncomplicated repeat cesarean delivery at term[15]. Table 4 describes the characteristics of the fibroids treated and the pregnancy outcomes reported by Rabinovici et al.

An additional 24 pregnancies have been reported following MRgHIFU in other case reports[18-20,22-29]. Of these pregnancies, there were 5 miscarriages (21%) and 19 full term deliveries (79%). The only complication reported was by Rabinovici et al, 2006 who described a 36 year old G1P0 who conceived 3 months after MRgHIFU. Her pregnancy was uncomplicated and she went on to deliver a full term 3050g infant vaginally with delayed placental separation requiring manual removal[28].

Conclusions

Radiofrequency volumentric thermal ablation and MRgHIFU are minimally invasive uterine sparing alternatives for fibroid treatment. The studies have shown successful reduction in fibroid size and symptoms with both RFVTA and MRgHIFU. As fibroid treatment can have implications on fertility, it is crucial to better understand the reproductive outcomes following fibroid ablation. There have been no published prospective studies investigating the reproductive outcomes following RFVTA or MRgHIFU, however prospective studies are ongoing at this time.

In assessing the appropriate choice for patients who desire future fertility, physicians will be presented with the difficulty in deciding which will be the ideal procedure for their patients. When looking at RFVTA and MRgHIFU alone, the advantages to RFVTA include that is it a minimally invasive laparoscopic approach which allows for visualization of surrounding anatomy as an additional safety feature and is capable of treating large quantities of fibroids in most uterine locations. Transvaginal RFVTA is still undergoing clinical trials in the United States and is not yet commercially available. MRgHIFU, does not require general anesthesia or intraperitoneal access, however, the costs may be higher due to the requirement of MR guidance, and be unable to treat all fibroids. A disadvantage of any ablative technique is the lack of tissue sampling.

The concerns regarding pregnancy following fibroid ablation are the effects of coagulative necrosis on the uterus. During fibroid ablation, the integrity of the surrounding myometrium may be compromised. These techniques attempt to reduce uterine damage by directing the ablation to the fibroid tissue only; however, there still may be an effect on the surrounding

myometrium. Additionally, as opposed to myomectomy, the ablated fibroids remain in the myometrium. The impact this has on pregnancy and normal uterine physiology needs to be fully investigated. These changes may affect implantation, placentation, and uterine contractility during labor thus increasing the risks of miscarriage, placenta acreta, placenta previa, uterine rupture and postpartum hemorrhage. As seen in these cases, there were complications related to uterine fibroids that remained in situ that may have been avoided had the patient underwent myomectomy instead. Additionally, it is unknown how the size and location of the treated fibroid would effect reproductive outcomes. Table 2 and 4 give a more detailed description of the location and size of the fibroids treated.

In this collection of reported cases following RFVTA, there was only one spontaneous abortion. Given the small sample size (20) and the large number of elective terminations (7), we would be cautious to draw conclusions from this number alone. The one complication reported was hemorrhage with expulsion of degenerated fibroid following delivery[10]. The cesarean section rate is high (75%) as the strength of the myometrium is unknown and given the concerns for uterine rupture, many of the cesarean sections were scheduled prior to the onset of labor. There was a high rate of elective terminations given that the patients selected for the studies did not desire future fertility[13].

MRgHIFU has been better studied in regard to its effects on pregnancy as it has been around longer. The larger cohort studies have shown that women can have uncomplicated pregnancies and safe deliveries following MRgHIFU. There are a total of 102 pregnancies reported with 21

241 miscarriages (20.6%) just slightly above the general population. Additionally, the mean age of the
242 women in these studies was over 35 which would increase the spontaneous abortion rate.
243 Complications reported in the 48 pregnancies that lead to live born deliveries include, vaginal
244 spotting (13%), delayed placental separation (4%), and placenta previa (4%). There were no
245 cases of uterine rupture. The case described by Rabinovici et al, where the patient went into DIC
246 and ARDS was following myomectomy at the time of cesarean[15]. The complications following her
247 delivery are likely a complication of the myomectomy rather than the ablation procedure, yet
248 may have been avoided had myomectomy been performed prior to conception.
249
250 Recent experience of MRgHIFU and radiofrequency ablation of fibroids has shown favorable
251 pregnancy outcomes and, most notably, no uterine rupture. However, there are many
252 limitations to what conclusions can be drawn from these case reports. While the cases of
253 pregnancy following fibroid ablation are growing, the numbers are too low to draw definitive
254 conclusions.
255
256 Another unknown is how fibroid ablation affects one's ability to conceive. We do not know how
257 much fibroids independently contribute to one's infertility. While someone with infertility may
258 be found to have fibroids, the underlying cause of her infertility may not be due to her uterine
259 fibroids. Therefore, it is difficult to draw conclusions regarding the effects of fibroid ablation on
260 fertility outcomes without larger comparative trials. It is unknown which of these methods is
261 superior for the treatment of fibroids in women desiring fertility compared to other treatment

262 modalities. This review highlights the need for a randomized control trial investigating fertility
263 and pregnancy outcomes in all uterine sparing fibroid treatments.
264

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Table 1: Case series of pregnancies following RFVTA of fibroids			
Author, Country, Site, Year	**Number of Pregnancies**	**Pregnancy Outcomes**	**Complications**
Bing-Song Z *et al.* China, Chinese PLA General Hospital, 2015	10 pregnancies	7 elective terminations 3 full term cesarean sections	None
Berman J *et al.,* United States, Guatamala, Mexico. Halt Trial. 2015	6 pregnancies	1 SAB at 10 weeks 4 full term cesarean sections 1 full term vaginal delivery*	*Delayed hemorrhage with 1500cc blood loss and expulsion of degenerated fibroid
Kim CH *et al.*, South Korea, Gangwon National University Hospital, 2010	3 pregnancies	1 full term cesarean section 2 full term vaginal deliveries	None
Garza-Leal JG *et al.,* Mexico, Hospital Universitario "dr. Jose Eleuterio Gonzalez" de Universidad Autonoma de Neuvo Leon, 2014	1 pregnancy	1 full term cesarean delivery	None

Table 2: Characteristics of ablated uterine myomas following RFVTA and pregnancy outcomes					
Patient No.	Maternal Age at Conception	No. Myomas Treated	Diameter of treated myoma (cm)	Myoma Location	Pregnancy Outcome
1	35	1	3.8	Fundal subserosal	FT CD - repeat, 2970g
2	32	1	7.6	Fundal transmural	FT CD, 2778g
3	38	3	2.4, 2.2, 3.2	2 intramural, 1 fundal subserosal	SAB at 10wks
4	34	2	1.9, 0.9	Posterior submucosal, posterior subserosal	FT CD – repeat, 2940g
5	41	1	4.7	Fundal transmural	FT CD, 2923g Postpartum hemorrhage with expulsion of fibroid
6	39	7	1.5, 2, 2.5, 1, 1, 4.7	4 subserosal, 1 intramural/subserosal, 2 intramural/submucosal	FT SVD, 3487g

FT – Full term, CD – cesarean delivery, SVD – spontaneous vaginal delivery, SAB – spontaneous abortion

Berman. Radiofrequency Volumentric Thermal Ablation. Jour of Repro Med 2015

Table 3: Studies of pregnancy outcomes following MRgHIFU			
Author, Country, Year	**Number of Pregnancies**	**Pregnancy Outcomes**	**Complications**
Rabinovici J *et al.* Israel, Clinical trials for InSightec: United States, Israel, United Kingdom, Germany, Japan. 2008.	54 pregnancies in 51 women	7 elective terminations 14 SAB 21 full term live births - 14 vaginal - 7 cesarean 1 preterm delivery 36wks - cesarean 11 ongoing pregnancies	- 1 manual removal of placenta - 2 myomectomies performed intraop - 2 placenta previa - 2 breech presentation - 1 chorioamnionitis - 1 endometritis - 6 vaginal spotting during pregnancy
Qin J *et al.,* China, 2012	24 pregnancies	2 SAB 15 Elective terminations 7 Full term cesarean deliveries	None
Froeling V *et al.,* Germany, 2013	10 pregnancies in 9 women	7 Live births 3 SAB	None
Funaki K *et al.* Japan, 2009	4 pregnancies	2 live full term births 2 first trimester SAB	None
Zaher S *et al.,* United Kingdom, 2010	2 pregnancies	1 full term vaginal delivery, 3589g baby. 1 full term emergency cesarean section,	None

Table 3: Studies of pregnancy outcomes following MRgHIFU			
Author, Country, Year	Number of Pregnancies	Pregnancy Outcomes	Complications
		3050g baby.	
Morita Y *et al.,* Japan, 2008	1 pregnancy	Full term vaginal delivery. 3212g baby.	None
Yoon, S-W *et al.,* Korea, 2013	1 pregnancy	Full term delivery	None
Bouwsma E *et al.,* United States, 2011	1 pregnancy	Full term vaginal delivery. 3450g baby.	None
Gavrilova-Jordan L *et al.,* United States, 2007	1 pregnancy	Full term vacuum assisted vaginal delivery.	None
Hanstede M *et al.,* United States, 2007	1 pregnancy	Full term vaginal delivery. 3170g baby.	First trimester vaginal bleeding until 16 weeks gestation. Diagnosed with type 1 diabetes.

Table 3: Studies of pregnancy outcomes following MRgHIFU			
Author, Country, Year	Number of Pregnancies	Pregnancy Outcomes	Complications
Morita Y *et al.,* Japan, 2007	1 pregnancy	Full term vaginal delivery. 3212g baby.	None
Rabinovici J *et al.,* Israel, 2006	1 pregnancy	Full term vaginal delivery. 3050g baby.	Delayed placental separation requiring manual placental extraction.
Yoon S-W *et al.,* Korea, 2010	1 pregnancy	Full term vaginal delivery. 3190g baby.	None

Table 4: Characteristics of ablated uterine myomas following MRgHIFU and pregnancy outcomes					
Patient No.	**Maternal age at delivery**	**No. myomas treated**	**Myoma volume treated (cm3)**	**Myoma location**	**Pregnancy Outcome**
1		1	169	Intramural	SAB
2	42	1	8	Intramural	FT SVD, 3800g First trimester bleeding
3	37	1		Intramural	FT SVD, 3830g First trimester bleeding
4	36	1	4	Intramural	FT CD, 3480g - Breech
5		3	52	Intramural, Subserosal	SAB
6	37	Adenomyosis	33		FT SVD, 3050g Manual placenta removal
7	29 31	3	82.5	Submucosal, Subserosal	FT CD, 2660g - Breech Myomectomy at time of CD, severe maternal hemorrhage, reoperation, DIC, and ARDS FT CD, 2860g – Placenta previa
8		1	25	Submucosal	SAB SAB
9		1	150	Intramural	SAB
10		2	315	Intramural	TAB
11	37	2	246	Intramural, Subserosal	FT CD, 3970g
12	30	1	111	Subserosal	FT SVD, 3210g
13		1	63	Intramural	SAB
14	42	2	71	Submucosal, Intramural	FT SVD, 3170g First trimester bleeding
15	45	1	95	Intramural	FT VAVD, 3350g Chorioamnionitis
16	44	1	170	Submucosal	FT CD, 3430g – Prior CD NICU admission for lung collapse
17	42	1	62	Subserosal	FT VAVD, 3650g
18		1	232	Intramural	TAB
19		1	340	Intramural	SAB
20		4	87	Intramural, Subserosal	TAB

Table 4: Characteristics of ablated uterine myomas following MRgHIFU and pregnancy outcomes					
Patient No.	**Maternal age at delivery**	**No. myomas treated**	**Myoma volume treated (cm3)**	**Myoma location**	**Pregnancy Outcome**
21		1	119	Submucosal	SAB
22		Adenomyosis	60		TAB
23		1	330	Intramural	TAB
24	40	2	348	Subserosal	FT SVD, 2890g Oligohydramnios Postpartum endometritis
25	38	1	135	Intramural	FT CD, 2990g Myomectomy performed during CD without complication
26		1	154	Intramural	SAB
27		1	78	Intramural	Ongoing
28		1	152	Submucosal	SAB
29	32	1	99	Intramural	FT SVD, 3190g
30	36	4	340	Submucosal, Intramural, Subserosal	FT SVD, 3580g
31		1	41	Submucosal	Ongoing
32	43	2		Submucosal, Intramural	36wk CD, 3410g – Placenta previa Myoma growth, myomectomy performed
33	37				FT SVD, 3760g
34	36	1		Intramural	FT SVD, 3100g
35		1	30	Intramural	SAB
36	41	1	75	Transmural	FT SVD, 3190g Myoma growth
37					Ongoing
38		1	180	Transmural	Ongoing
39		1	129	Subserosal	TAB
40		1	66	Submucosal	Ongoing
41		1	150	Intramural	Ongoing
42	39	1	20	Intramural	SVD* First trimester bleeding Hospitalization at 14wks for threatened miscarriage
43		1	40	Intramural	Ongoing

Table 4: Characteristics of ablated uterine myomas following MRgHIFU and pregnancy outcomes

Patient No.	Maternal age at delivery	No. myomas treated	Myoma volume treated (cm3)	Myoma location	Pregnancy Outcome
44		2	108		Ongoing
45	35	1	72	Transmural	FT CD, 3680g
46		3	291	Submucosal, Intramural, Pedunculated	Ongoing
47		1	4		Ongoing
48		2	23	Intramural, Submucosal	SAB
49		2	7	Submucosal, Subserosal	Ongoing
50		1	5	Submucosal	Ongoing
51		2	9	Submucosal, Intramural	SAB

FT – full term, SVD – spontaneous vaginal delivery, VAVD – vacuum assisted vaginal delivery, CD – cesearean delivery, SAB – spontaneous abortion

*remaining delivery information unknown

Rabinovici. MR-guided focused ultrasound pregnancies. Fertil Steril 2010.