

Pregnancy outcome after magnetic resonance–guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids

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Objective: To report all pregnancies to date after magnetic resonance–guided focused ultrasound surgery (MRgFUS) for the conservative treatment of clinically significant uterine fibroids.

Design: Prospective registry of all known pregnancies occurring after MRgFUS maintained by the device manufacturer and reported to the Food and Drug Administration.

Setting: World experience of pregnancies after treatment with reports from 13 sites in seven countries.

Patient(s): Fifty-one reproductive-age women with uterine leiomyomas.

Intervention(s): Women underwent MRgFUS treatment for symptomatic uterine leiomyomas before this report.

Main Outcome Measure(s): Pregnancy outcomes and complications.

Result(s): Fifty-four pregnancies in 51 women have occurred after MRgFUS treatment of uterine leiomyomas. The mean time to conception was 8 months after treatment. Live births occurred in 41% of pregnancies, with a 28% spontaneous abortion rate, an 11% rate of elective pregnancy termination, and 11 (20%) ongoing pregnancies beyond 20 gestational weeks. The mean birth weight was 3.3 kg, and the vaginal delivery rate was 64%.

Conclusion(s): Preliminary pregnancy experience after MRgFUS is encouraging, with a high rate of delivered and ongoing pregnancies. (Fertil Steril® 2010;93:199–209. ©2010 by American Society for Reproductive Medicine.)

Key Words: Uterus, leiomyoma, fibroid, ultrasound, myomectomy, pregnancy

Uterine leiomyomata or fibroids are the most common tumors of the female reproductive tract and occur in at least 20%–25% of all reproductive-age women (1). The prevalence of uterine fibroids among pregnant women ranges from 0.1% to 3.9% (2), and with the current tendency to delay childbearing until later in life this prevalence is likely to increase.

Uterine fibroids can impair fertility and cause specific pregnancy complications (3–9). However, the process of treating fibroids can also lead to morbidity and subsequent fertility impairment. The “gold standard” for women desiring fertility remains surgical myomectomy due to long experience with that mode of treatment (10). Rare but sometimes

serious complications have been well described for surgical approaches (10–13).

Minimally invasive procedures such as uterine artery embolization (UAE) are increasingly used to treat symptomatic fibroids (14–16). Reports of successful pregnancies after UAE appeared in the literature shortly after the introduction of the treatment (17, 18). While case reports detailed a number of complications, larger series indicated that after UAE there is an age-related risk of ovarian failure and an increased risk of placentation problems (10, 16, 19–21).

Magnetic resonance–guided focused ultrasound surgery (MRgFUS or FUS) for symptomatic uterine fibroids was first used for uterine leiomyoma treatment in 2000 and has been reported to be an effective and safe method in managing the symptoms caused by uterine fibroids (22–27). To date, more than 4000 women have undergone this treatment globally.

Because of the novel nature of the procedure, initial trials of MRgFUS treatment were restricted to patients who declared that they were not interested in future pregnancies. Thus, the initial device labeling is for treatment of symptomatic leiomyomas in premenopausal women with no desire for future fertility. However, since women maintain their uterus with MRgFUS treatment, the possibility of anecdotal pregnancies remained open.

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Four case reports of pregnancies after MRgFUS have been published, with each reporting a vaginal delivery at term (28–31). In one, the MRgFUS treatment may have facilitated pregnancy in a woman with a history of secondary infertility (28, 31). This report is the first published series of pregnancies after MRgFUS and reports all pregnancies after MRgFUS reported to the manufacturer and the Food and Drug Administration (FDA) as part of the required postapproval medical device monitoring.

MATERIALS AND METHODS

We included in this report all women who conceived after MRgFUS for their symptomatic uterine leiomyomata. All sites were required to report pregnancies to the manufacturer of the device (InSightec, Haifa, Israel) as a part of postapproval monitoring by the FDA. Sites are queried quarterly for additional information regarding ongoing pregnancies and new pregnancy reports.

Anecdotal pregnancies were recorded for patients conceiving after treatment as a part of reported or ongoing clinical trials in the United States (Brigham and Women's Hospital, Boston, Massachusetts; and the Mayo Clinic, Rochester, Minnesota) or outside the United States (Sheba Medical Center, Tel Hashomer, Israel; Saint Mary's Hospital, London, United Kingdom; Charite Hospital, Berlin, Germany; and Shinsuma General Hospital, Kobe, Japan). For these women, a desire for future pregnancy was an exclusion criterion for trial enrollment. Second, a group of pregnancies are reported from an ongoing study conducted at four international sites (Sheba Medical Center, Tel Hashomer, Israel; Charite Hospital, Berlin, Germany; Saint Mary's Hospital, London, England; and Isei Kei, Osaka, Japan) specifically for women trying to conceive. Finally, all pregnancies after commercial treatment in the United States (Sightline, Houston, TX) and outside the United States (Federal State Treatment and Rehabilitation Center of Rozsdrav, Moscow, Russia; Itabashi Chuo Hospital, Tokyo, Japan; Bundang Cha Hospital, Seoul, South Korea; Shinsuma General Hospital, Kobe, Japan; Radiologische Gemeinschaftspraxis, Bochum, Germany; Iseikai Hospital, Osaka, Japan; and Amour Clinic, Yokohama, Japan) are reported. Clinical trials were approved by local institutional review boards or ethics committees at each participating center, and information on pregnancies from commercial treatments was collected in a manner compliant with the Health Insurance Portability and Accountability Act. Two authors (JR and EAS) currently serve as clinical trial investigators for Insightec.

Methods for MRgFUS treatment have been described elsewhere (22–25, 27, 28, 32). Briefly, MRgFUS treatment is a myoma-specific treatment that employs coagulative necrosis to destroy leiomyoma tissue, while leaving the surrounding myometrium untreated (22–24). The ExAblate 2000 focused ultrasound system (InSightec) is integrated with the Signa 1.5 tesla magnetic resonance imaging (MRI) system (General Electric, Milwaukee, WI), which provides con-

tinuous monitoring of the target tissue and thermal feedback. The real-time temperature maps generated during treatment of the treated volumes enable adjustments to both the dose and the target during treatment.

Throughout the treatment planning and procedure, the woman lies prone on the patient table, within the MR scanner, with her abdomen coupled to a gel pad. A phased-array transducer operating at a frequency of 1.15 MHz is located within a degassed water bath in the MRI patient table. Coronal, sagittal, and axial T2-weighted MR images are obtained to localize and define the target area. The system computes the optimal treatment parameters. Initially, a very low-energy acoustic pulse (test sonication) is directed to the target, generating a subtle, nondestructive, temperature elevation in the tissue. An MR thermal map detects the location and confirms registration accuracy or enables the user to adjust the treatment plan as necessary.

During treatment, the FUS system performs real-time thermal imaging of the treatment area based on the proton resonance frequency shift that results from tissue heating. Treatment parameters can be adjusted between sonications based on MR thermometry feedback. Each sonication creates an elongated elliptical focus of high temperature (65–85°C), resulting in immediate tissue necrosis. In an earlier study, we examined the uteri of women who went on to hysterectomy after MRgFUS. Treated tissue showed a series of distinct lesions that were visible macroscopically (22).

At the end of treatment, a gadolinium-contrast MR study of the uterus was performed to assess the extent of tissue damage and lack of perfusion within the treated leiomyomas. This volume, termed the nonperfused volume (NPV), appears to correlate with the volume of histological necrosis treatment (22). Additionally, the NPV ratio that reports the ratio of nonperfused leiomyoma tissue to the volume of uterine leiomyomas in the entire uterus appears to be an important predictor of clinical response to MRgFUS treatment (27).

MRgFUS is performed on an outpatient basis with conscious sedation. The procedure generally requires 2–3 hours. Patients are observed for 1–2 hours after treatment and discharged home with a companion. Most patients return to their routine activities within 24 hours of treatment.

Information regarding each pregnancy was obtained from each site and updated quarterly. Due to differences in protocols and differences in sites, complete information was not available for every pregnancy. For continuous variables, statistical analysis was performed using Excel software (Microsoft, Redmond, WA) with mean values and the standard deviation reported.

RESULTS

In this study, we report on 54 pregnancies in 51 women who were treated with MRgFUS for symptomatic uterine fibroids and/or focal adenomyosis (Table 1). Eight of these pregnancies occurred as part of clinical trials designed for women

TABLE 1

Clinical characteristics of women achieving pregnancy after MRgFUS treatment of uterine leiomyomas with summary statistics.

Patient no.	Pregnancy no.	Age at treatment, years	Race	BMI	Gravidity and parity at MRgFUS	Symptoms	Time to conception from MRgFUS, months	Pregnancy results
1	1	41	White	22	G2P0	ME, IF, SA	22	SA
2	2	40	White	22	G1P1	BC	13	LB
3	3, 4	34	White	21	G2P2	ME, IF	1, 18	SA, LB
4	5	34	White	25	G1P1	ME	8	LB
5	6	44	White	29	G3P1	ME, BC, AP, SA	7	SA
6	7	36	White	21	G2P1	ME, IF, SA	3	LB
7	8, 9	28	Ethiopian	20	G0P0	ME, BC, IF	4, 27	LB, LB
8	10, 11	32	White	20	G2P1	ME, BC, FU, AP, IF, SA	3, 11	SA, SA
9	12	30	Asian	20	G0P0	ME	12	SA
10	13	41	Asian	21	G0P0	AP	0	TA
11	14	36	Asian	20	G1P0	AP, SA	6	LB
12	15	29	Asian	20	G0P0	None	4	LB
13	16	33	Asian		G0P0	ME, AP	4	SA
14	17	40	White	28	G3P3	ME, AP, IF	12	LB
15	18	44	White	25	G0P0	ME	8	LB
16	19	42	White	23	G2P2	ME	23	LB
17	20	40	White	23	G0P0	AP, FU	18	LB
18	21	42	Asian		G0P0	ME	1	TA
19	22	41	Other	29	G0P0	ME, FU	30	SA
20	23	31	White		G1P0	ME, AP	1	TA
21	24	42	White		G0P0	AP	1	SA
22	25	32	Asian		G3P2	ME, AP	5	TA
23	26	42	Asian		G0P0	AP	4	TA
24	27	39	White	26	G0P0	ME, AP	<1	LB
25	28	36	Asian	22	G2P1	ME, SA	10	LB
26	29	45		20	G1P0	FU, IF, SA	7	SA
27	30	36	Asian	20	G1P0	IF, SA	2	ON
28	31	35	White	25	G3P3	ME, AP	7	SA
29	32	31	Asian	20	G0P0	AP, FU	5	LB
30	33	35	Black		G1P0	ME, IF, SA	9	LB
31	34	39	Asian	23	G2P1	UF, SA	2	ON
32	35	41	White	19	G1P1	ME	11	LB
33	36	36	White	22			5	LB
34	37	35	White	24			5	LB

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

TABLE 1

Continued.

Patient no.	Pregnancy no.	Age at treatment, years	Race	BMI	Gravidity and parity at MRgFUS	Symptoms	Time to conception from MRgFUS, months	Pregnancy results
35	38	37	White	20	G0P0	IF	6	SA
36	39	40	White	24	G4P2	IF, SA	1	LB
37	40	33	White	31	G1P0	IF, SA	4	ON
38	41	41	White	25	G0P0	FU	12	ON
39	42	41	Asian	20	G1P1	AP, FU	2	TA
40	43	32	Asian	22	G0P0	IF	1	ON
41	44	31	White		G0P0	IF	6	ON
42	45	37	White	23	G1P1	IF	18	LB
43	46	41	White	29	G4P2	IF	5	SA
44	47	33	White		G2P0	ME, SA	1	ON
45	48	34	White		G5P1	AP	8	LB
46	49	49	White	23	G4P0	SA	17	ON
47	50	39	White	24	G4P3	ME, AP, FU, PN	2	ON
48	51	34	White	22	G1P0	SA, IF	7	SA
49	52	38	Hispanic	38	G3P1	ME, AP, PN	10	ON
50	53	34	White	22			9	ON
51	54	40	White	25	G0P0	IF	16	SA
Mean (\pm SD)		37.2 \pm 4.6		23.4 \pm 3.8			8 \pm 7	
Range		28–49		19–38			0–30	
N		51		41			54	

Note: AP = abdominal pressure; BC = blood clots; FU = frequent urination; IF = infertility; LB = live birth; ME = menorrhagia; ON = ongoing; PN = pain; SA = spontaneous abortion; TA = therapeutic abortion.

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

who had completed their families (one in the pivotal trial, four in the continued access extension of the pivotal trial, two in a study of GnRH agonist pretreatment, and one in a study of treatment of focal adenomyosis). Twenty-six pregnancies are reported after commercial treatments, and 20 pregnancies in 17 patients have occurred in the study designed for women trying to conceive.

The mean age of the women at the time of treatment was 37.2 ± 4.6 years (range, 28–49, $n = 51$), and 39% (20 of 51) were at least 40 years old at the time of treatment (Table 1). Most of those women were white (65%), 27% were Asian, 4% were African, and two patients reported other heritage (Table 1). The mean BMI of the patients was 23.4 ± 3.8 (range, 19.4–37.9; $n = 41$). The mean number of prior pregnancies and deliveries were 1.3 ± 1.4 (range, 0–5) and 0.6 ± 0.9 (range, 0–3), respectively ($n = 48$; Table 1). Approximately a third of the patients (38%) had never been pregnant, and almost two-thirds (58%) had never had a delivery.

Women presented with a variety of symptoms, with most women having more than one symptom (Table 1). Menorrhagia was the most common symptom, affecting 50% of women, followed by abdominal pressure (38%) and infertility (defined as inability to get pregnant for more than 12 months as reported by the patient; 38%) in frequency (Table 1).

Forty-one percent (22 of 54) of pregnancies resulted in deliveries, and 20% (11 of 54) are currently ongoing beyond 20 weeks (Table 1). Elective pregnancy termination and miscarriages represent the remainder at 13% (7 of 54) and 26% (14 of 54), respectively (Table 1). Of the miscarriages, 79% occurred by the 10th week of pregnancy, 14% (2 of 14) occurred at 12–13 weeks, and one woman had a second-trimester loss. The mean time to pregnancy was 8 ± 7 months after MRgFUS treatment (Table 1).

The treated women had a range of uterine disease on pretreatment MRI. Most women (45%) had a single leiomyoma, 37% had between two and six myomas, 14% had more than six, and 4% had adenomyosis (Table 2). The mean volume of all fibroids contained in the uterus was 268 ± 203 cm³ (Table 2). One to four myomas (mean of 1.4 ± 0.8) were treated in each woman (Table 2). Over three-quarters of the women (39 of 51) had a single MRgFUS treatment session (Table 2). Of the 24% (12 of 51) undergoing two treatments, most (58%, 7 of 12) had two treatment sessions scheduled due to the large volume of fibroid disease. In four cases, a second session was scheduled by the treating physician due to inadequate treatment based on the NPV at the first session, and in one case information was not available.

The average NPV after treatment was 117 ± 102 cm³, leading to an average NPV ratio exceeding 40% (Table 2). There was considerable variability in the NPV ratio, ranging from 5.5% (4/72 cm³ in patient no. 47) to 100% (340/340 cm³ in patient no. 30; Table 2).

The mean age of women with delivered pregnancies was 37.7 ± 4.5 years (range, 29–45), with one woman having

two deliveries (Table 3). Common pregnancy complications were seen in the cohort, with abnormal bleeding seen in 27% (6 of 22), gestational diabetes in 14% (3 of 22), and myoma growth a concern in 9% (2 of 22; Table 3). Eighteen percent of women (4 of 22) had an antepartum hospitalization, and 36% (8 of 22) had no antepartum complications (Table 3). Two women had placenta previa (9%; Table 3).

Of the delivered pregnancies in which gestational age was reported, there was a 93% (14 of 15) term delivery rate, and the one preterm birth occurred at 36 weeks (Table 3). For six of the seven pregnancies in which gestational age was not reported, birth weights of 3.05–3.8 kg are reported consistent with term infants, and preterm labor was not reported in any of these seven pregnancies (Table 3). The mean reported gestational age was 39 ± 1.5 weeks (Table 3). Sixty-four percent of the women had a vaginal delivery, and 36% a cesarean delivery (Table 3). The mean birth weight was 3.3 ± 0.4 kg, and no infant met the criteria for low birth weight (<2.5 kg; Table 3).

Fifty-seven percent of pregnancies (12 of 22) had no maternal or neonatal peripartum complications (Table 3). There was no pattern to the complications seen. The most serious complication occurred in the first pregnancy of patient no. 7 (Table 3). This patient underwent an elective cesarean section due to a breech presentation and an intramural fibroid that obstructed the pelvic outlet. She delivered a male infant weighing 2.6 kg, and during the cesarean section she underwent a myomectomy of the low-lying fibroid. After surgery the patient bled vaginally owing to persistent uterine atony. Several hours after the cesarean section, the patient developed hypotension and demonstrated clinical and laboratory signs of disseminated intravascular coagulation (DIC). She received blood coagulation factors and blood replacement. Because of clinical and ultrasonic signs of abdominal fluid accumulation she underwent a repeat laparotomy without any abnormal surgical findings. After recovery from the DIC, the patient developed adult respiratory distress syndrome (ARDS) and spent 3 days in the intensive care unit of the hospital (Table 3). Her second pregnancy was complicated by a placenta previa causing hospitalization in the third trimester (Table 3). A repeat cesarean section at 39 weeks delivered a second healthy infant without need for cesarean hysterectomy.

DISCUSSION

Early reports of pregnancies after novel interventions for uterine leiomyoma must be approached with caution since a complication that causes maternal or fetal morbidity in even one out of several thousand cases can be significant (10).

With this in mind, at the introduction of MRgFUS we initially declined to treat women who desired future pregnancies before establishing the efficacy and safety of the procedure. The current series of pregnancies is reassuring that term (and ongoing) pregnancies can be achieved in a substantial percentage of women conceiving after MRgFUS treatment of uterine fibroids.

TABLE 2

Characteristics of uterine leiomyomas for women achieving pregnancy after MRgFUS treatment with summary statistics.

Patient no.	No. of treatments	No. of myomas	Total myoma volume, cm ³	No. of myomas treated	Myomas location	Nonperfused Volume, cm ³
1	1	1	279	1	Intramural	169
2	1	1	18	1	Intramural	8
3	1	1	43	1	Intramural	
4	1	1	65	1	Intramural	4
5	1	4	293	3	Intramural, subserosal	52
6	1	Adenomyosis	84	—	—	33
7	2	6	230.1	3	Submucosal, subserosal	82.5
8	1	1	73	1	Submucosal	25
9	1	Multiple (>6)	200	1	Intramural	150
10	1	Multiple (>6)	950	2	Intramural	315
11	2	Multiple (>6)	740	2	Intramural, subserosal	246
12	1	1	215	1	Subserosal	111
13	1	1	281	1	Intramural	63
14	1	Multiple (>6)	396	2	Submucosal, intramural	71
15	1	1	480	1	Intramural	95
16	1	1	179	1	Submucosal	170
17	1	1	377	1	Subserosal	62
18	1	2	333	1	Intramural	232
19	2	2	606	1	Intramural	340
20	1	Multiple (>6)	650	4	Intramural, subserosal	87
21	1	Multiple (>6)	216	1	Submucosal	119
22	1	Adenomyosis	370	—	—	60
23	1	1	600	1	Intramural	330
24	1	3	420	2	Subserosal	348
25	1	1	249	1	Intramural	135
26	1	3	210	1	Intramural	154
27	1	1	98	1	Intramural	78
28	2	1	488	1	Submucosal	152
29	2	2	173	1	Intramural	99
30	1	Multiple (>6)	340	4	All	340
31	1	2	75	1	Submucosal	41
32	2	2	297	2	Submucosal, intramural	
33	1	2				
34	2	3	65	1	Intramural	
35	2	1	64	1	Intramural	30
36	1	1	160	1	Transmural	75
37	2	5	125			
38	2	1	320	1	Transmural	180
39	1	1	226	1	Subserosal	129
40	1	1	99	1	Submucosal	66
41	1	1	180	1	Intramural	150
42	1	1	52	1	Intramural	20

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

TABLE 2

Continued.						
Patient no.	No. of treatments	No. of myomas	Total myoma volume, cm ³	No. of myomas treated	Myomas location	Nonperfused Volume, cm ³
43	1	1	283	1	Intramural	40
44	2	4	248	2		108
45	1	2	248	1	Transmural	72
46	1	3	513	3	Submucosal, intramural, pedunculated	291
47	1	3	72	1		4
48	1	3	50	2	Intramural, submucosal	23
49	1	2	111	2	Submucosal, subserosal	7
50	2	1	22	1	Submucosal	5
51	1	3	34	2	Submucosal, intramural	9
Mean (±SD)	1.2 ± 0.4		268 ± 203	1.4 ± 0.8		117 ± 102
Range	1–2		18–950	1–4		4–348
N	51		50	47		46

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

Some case series of deliveries suggest that uterine fibroids themselves may be associated with higher complication rates during pregnancy, labor, and delivery, while others suggest only an increased risk of cesarean delivery (6, 33, 34). Nonetheless, the data in this series are similar to those of reported series of pregnancies after UAE in terms of maternal age, time to conception, and miscarriage rate (17, 20, 21). While patient and uterine factors may be different for women undergoing UAE compared with those electing MRgFUS, examining differences may be helpful in understanding differences in these two techniques. The term delivery rate of 93% seen in this series exceeds that reported in UAE series (71%–82%), and the cesarean section rate is remarkably lower (36% vs. 50%–73%; 17, 20, 21).

It is notable that in this series there are neither infants with low birth weight nor stillbirths, which have been seen at low frequency in UAE case series (17, 20, 21). The mean birth weight of 3.3 kg in this study also exceeds that of the 2.9 kg reported in two series of pregnancies after UAE with complete birth weight information (17, 20). The single pregnancy in which placental insufficiency was suspected in this series resulted in a 38-week delivery with an infant weighing 2.89 kg.

Although the incidence of placenta previa in this study (9%, 2 of 22) is similar to the risk seen in one report after UAE (12% or 3 of 24), both of the subjects in our series had the known risk factor of multiparity and in one case of prior cesarean section, while in the prior study all women with this complication were nulliparous (20, 35, 36).

While additional evidence is clearly needed, this information can support the hypothesis that the fibroid-specific ap-

proach of MRgFUS may have advantages for the woman who wishes to conceive compared with the global uterine approach of UAE in which embolic particles also have an effect on normal myometrium (37). Randomized trials comparing UAE with myomectomy for symptomatic fibroids also suggest that UAE may have a detrimental effect on pregnancy outcome (38). Given the large number of women developing fibroids before childbearing, addressing these important issues in clinical trials is critical (39).

A limitation of the current report is the fact that the correlation between symptomatic relief and pregnancy potential cannot be assessed. Likewise, any effect that MRgFUS has on fertility impairment cannot be assessed. However, the fact that infertility was a presenting complaint in over a third of these women achieving pregnancy is reassuring. Finally, we cannot exclude the possibility that patient factors may account for some of these findings.

Our preliminary results need to be further confirmed by controlled and randomized clinical studies to learn more about fertility and outcomes after MRgFUS. A new randomized clinical trial (NCT00730886, clinicaltrials.gov) for couples with unexplained infertility modeled on prior infertility trials but with at least uterine fibroid distorting the endometrial cavity has been approved by the FDA and will provide us with additional information in the future (40). In the interim, women who conceive after MRgFUS should be informed that normal pregnancy outcomes and normal vaginal deliveries are possible. Since our knowledge is currently limited, these pregnancies need to be followed up carefully, with ultrasonic evaluation of the placental site and

TABLE 3

Pregnancy and delivery characteristics for women achieving pregnancy after MRgFUS treatment with summary statistics.

Patient no.	Maternal age at delivery	Complications during pregnancy	Mode of delivery	Indication for cesarean section	Gestation, weeks	Gender	Weight, kg	APGAR	Intrapartum and postpartum complications
2	42	Bleeding during weeks 8 and 9 leading to hospitalization	Vaginal			Male	3.8		None
3	37	First-trimester bleeding	Vaginal		40	Male	3.83	8, 9	None
4	36	Chlamydia	Cesarean	Breech presentation	38	Female	3.48		None
6	37	Suspected diagnosis of persistent right umbilical vein	Vaginal			Female	3.05		Manual removal of placenta
7	29	Hospitalization at 35 weeks with contractions and lumbar pain	Cesarean	Breech presentation	38	Male	2.66	9,10	Myomectomy performed during cesarean section, causing maternal severe bleeding, reoperation, DIC, and ARDS.
7	31	Early pregnancy bleeding, hospitalization at weeks 28–30 due to placenta previa	Cesarean	Complicated uterine scar and placenta previa	39	Male	2.86	9,10	Patient had respiratory problems for several days postdelivery.
11	37	Vaginal bleeding	Cesarean		41	Female	3.97	8,9	None

TABLE 3

Continued.

Patient no.	Maternal age at delivery	Complications during pregnancy	Mode of delivery	Indication for cesarean section	Gestation, weeks	Gender	Weight, kg	APGAR	Intrapartum and postpartum complications
12	30	None	Vaginal		39	Male	3.21	8,9	None
14	42	First-trimester vaginal bleeding, and diagnosis of diabetes mellitus type II.	Vaginal		39	Male	3.17		Lochia
15	45	Gestational diabetes	Vaginal (Vacuum-assisted)		40	Male	3.35	7, 8	Chorioamnionitis
16	44	None	Cesarean	Previous cesarean section		Female	3.43	8, 8	Baby was in the neonatal intensive care unit because of lung collapse
17	42	Gestational diabetes, hypertension	Vaginal (vacuum-assisted)		38	Female	3.65		None
24	40	Decreased amniotic fluid volume, placental insufficiency	Vaginal		38	Female	2.89	9	Patient hospitalized for puerperal endometritis
25	38	None	Cesarean		38	Female	2.99	10	Myomectomy performed during cesarean section without complication.
29	32	None	Vaginal		39	Female	3.19		None
30	36	None	Vaginal		42	Female	3.58	9–10	None

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

TABLE 3

Continued.

Patient no.	Maternal age at delivery	Complications during pregnancy	Mode of delivery	Indication for cesarean section	Gestation, weeks	Gender	Weight, kg	APGAR	Intrapartum and postpartum complications
32	43	Myoma growth during 21st week of pregnancy lead to myomectomy	Cesarean	Placenta previa	36	Female	3.41		Placenta previa
33	37	None	Vaginal			Male	3.76		None
34	36	None	Vaginal			Male	3.1		None
36	41	Myoma growth to 9.6 × 9.3 cm	Vaginal			Female	3.19		None
42	39	First-trimester bleeding, hospitalization at 14–15 weeks due to threatened miscarriage	Vaginal			Female			
45	35	None	Cesarean		40	Male	3.68		None
Mean (±SD)	37.7 ± 4.5				39 ± 1.5		3.3 ± 0.4		
Range	29–45				36–42		2.66–3.97	7, 8–10	
N	22		22		15		21	10	21
Categorical summary			36% (8 of 22) cesarean, 64% (14 of 22) vaginal			10 Male, 12 female			57% (12 of 21) pregnancies without complications

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

evaluation of their placental status during pregnancy to ensure appropriate care if abnormalities are detected.

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REFERENCES

1. Walker CL, Stewart EA. Uterine fibroids: the elephant in the room. *Science* 2005;308:1589–92.
2. Qidwai GI, Caughey AB, Jacoby AF. Obstetric outcomes in women with sonographically identified uterine leiomyomata. *Obstet Gynecol* 2006;107:376–82.
3. Rice JP, Kay HH, Mahony BS. The clinical significance of uterine leiomyomas in pregnancy. *Am J Obstet Gynecol* 1989;160:1212–6.
4. Farhi J, Ashkenazi J, Feldberg D, Dicker D, Orvieto R, Ben Rafael Z. Effect of uterine leiomyomata on the results of in-vitro fertilization treatment. *Hum Reprod* 1995;10:2576–8.
5. Eldar-Geva T, Meagher S, Healy DL, MacLachlan V, Breheny S, Wood C. Effect of intramural, subserosal, and submucosal uterine fibroids on the outcome of assisted reproductive technology treatment. *Fertil Steril* 1998;70:687–91.
6. Coronado GD, Marshall LM, Schwartz SM. Complications in pregnancy, labor, and delivery with uterine leiomyomas: a population-based study. *Obstet Gynecol* 2000;95:764–9.
7. Pritts EA. Fibroids and infertility: a systematic review of the evidence. *Obstet Gynecol Surv* 2001;56:483–91.
8. Klatsky PC, Lane DE, Ryan IP, Fujimoto VY. The effect of fibroids without cavity involvement on ART outcomes independent of ovarian age. *Hum Reprod* 2007;22:521–6.
9. Klatsky PC, Tran ND, Caughey AB, Fujimoto VY. Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. *Am J Obstet Gynecol* 2008;198:357–66.
10. ACOG Practice Bulletin No. 96: Alternatives to hysterectomy in the management of leiomyomas. *Obstet Gynecol* 2008;112:387–400.
11. Ecker JL, Foster JT, Friedman AJ. Abdominal hysterectomy or abdominal myomectomy for symptomatic leiomyoma: a comparison of preoperative demography and postoperative morbidity. *J Gynecol Surg* 1995;11:11–8.
12. Iverson RE Jr, Chelmos D, Strohhahn K, Waldman L, Evantash EG. Relative morbidity of abdominal hysterectomy and myomectomy for management of uterine leiomyomas. *Obstet Gynecol* 1996;88:415–9.
13. Verkauf BS. Myomectomy for fertility enhancement and preservation. *Fertil Steril* 1992;58:1–15.
14. Ravina JH, Herbreteau D, Ciraru-Vigueron N, Bouret JM, Houdart E, Aymard A, et al. Arterial embolisation to treat uterine myomata. *Lancet* 1995;346:671–2.
15. Spies JB, Bruno J, Czeyda-Pommersheim F, Magee ST, Ascher SA, Jha RC. Long-term outcome of uterine artery embolization of leiomyomata. *Obstet Gynecol* 2005;106:933–9.
16. Goodwin SC, Spies JB, Worthington-Kirsch R, Peterson E, Pron G, Li S, et al. Uterine artery embolization for treatment of leiomyomata: long-term outcomes from the FIBROID Registry. *Obstet Gynecol* 2008;111:22–33.
17. Ravina JH, Vigueron NC, Aymard A, Le Dref O, Merland JJ. Pregnancy after embolization of uterine myoma: report of 12 cases. *Fertil Steril* 2000;73:1241–3.
18. McLucas B, Goodwin S, Adler L, Rappaport A, Reed R, Perrella R. Pregnancy following uterine fibroid embolization. *Int J Gynaecol Obstet* 2001;74:1–7.
19. Pron G, Bennett J, Common A, Wall J, Asch M, Sniderman K. The Ontario Uterine Fibroid Embolization Trial. Part 2. Uterine fibroid reduction and symptom relief after uterine artery embolization for fibroids. *Fertil Steril* 2003;79:120–7.
20. Pron G, Mocarski E, Bennett J, Vilos G, Common A, Vanderburgh L. Pregnancy after uterine artery embolization for leiomyomata: the Ontario multicenter trial. *Obstet Gynecol* 2005;105:67–76.
21. Walker WJ, McDowell SJ. Pregnancy after uterine artery embolization for leiomyomata: a series of 56 completed pregnancies. *Am J Obstet Gynecol* 2006;195:1266–71.
22. Stewart EA, Gedroyc WM, Tempany CM, Quade BJ, Inbar Y, Ehrenstein T, et al. Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique. *Am J Obstet Gynecol* 2003;189:48–54.
23. Hindley J, Gedroyc WM, Regan L, Stewart E, Tempany C, Hynnen K, et al. MRI guidance of focused ultrasound therapy of uterine fibroids: early results. *Am J Roentgenol* 2004;183:1713–9.
24. Fennessy FM, Tempany CM. MRI-guided focused ultrasound surgery of uterine leiomyomas. *Acad Radiol* 2005;12:1158–66.
25. Stewart EA, Rabinovici J, Tempany CM, Inbar Y, Regan L, Gastout B, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. *Fertil Steril* 2006;85:22–9.
26. Rabinovici J, Inbar Y, Revel A, Zalel Y, Gomori JM, Itzhak Y, et al. Clinical improvement and shrinkage of uterine fibroids after thermal ablation by magnetic resonance-guided focused ultrasound surgery. *Ultrasound Obstet Gynecol* 2007;30:771–7.
27. Stewart EA, Gostout B, Rabinovici J, Kim HS, Regan L, Tempany CM. Sustained relief of leiomyoma symptoms by using focused ultrasound surgery. *Obstet Gynecol* 2007;110:279–87.
28. Rabinovici J, Inbar Y, Eylon SC, Schiff E, Hananel A, Freundlich D. Pregnancy and live birth after focused ultrasound surgery for symptomatic focal adenomyosis: a case report. *Hum Reprod* 2006;21:1255–9.
29. Gavrilova-Jordan LP, Rose CH, Traynor KD, Brost BC, Gostout BS. Successful term pregnancy following MR-guided focused ultrasound treatment of uterine leiomyoma. *J Perinatol* 2007;27:59–61.
30. Morita Y, Ito N, Ohashi H. Pregnancy following MR-guided focused ultrasound surgery for a uterine fibroid. *Int J Gynaecol Obstet* 2007;99:56–7.
31. Hanstede MM, Tempany CM, Stewart EA. Focused ultrasound surgery of intramural leiomyomas may facilitate fertility: a case report. *Fertil Steril* 2007;88:497 e5–7.
32. Smart OC, Hindley JT, Regan L, Gedroyc WM. Magnetic resonance guided focused ultrasound surgery of uterine fibroids—the tissue effects of GnRH agonist pre-treatment. *Eur J Radiol* 2006;59:163–7.
33. Davis JL, Ray-Mazumder S, Hobel CJ, Baley K, Sassoon D. Uterine leiomyomas in pregnancy: a prospective study. *Obstet Gynecol* 1990;75:41–4.
34. Vergani P, Ghidini A, Strobelt N, Roncaglia N, Locatelli A, Lapinski RH, et al. Do uterine leiomyomas influence pregnancy outcome? *Am J Perinatol* 1994;11:356–8.
35. Faiz AS, Ananth CV. Etiology and risk factors for placenta previa: an overview and meta-analysis of observational studies. *J Matern Fetal Neonatal Med* 2003;13:175–90.
36. Ananth CV, Smulian JC, Vintzileos AM. The association of placenta previa with history of cesarean delivery and abortion: a metaanalysis. *Am J Obstet Gynecol* 1997;177:1071–8.
37. Stewart EA. *Uterine Fibroids: The Complete Guide*. Baltimore: Johns Hopkins University Press, 2007.
38. Mara M, Maskova J, Fucikova Z, Kuzel D, Belsan T, Sosna O. Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. *Cardiovasc Intervent Radiol* 2008;31:73–85.
39. Viswanathan M, Hartmann K, McKoy N, Stuart G, Rankins N, Thieda P, et al. Management of uterine fibroids: an update of the evidence. Evidence report/technology assessment. *Evid Rep Technol Assess* 2007;1–122.
40. Guzik DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network. *N Engl J Med* 1999;340:177–83.