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Pregnancy Outcomes After Laparoscopic Radiofrequency Ablation of Uterine Leiomyomas Compared With Myomectomy

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OBJECTIVE: To compare pregnancy outcomes after laparoscopic radiofrequency ablation and myomectomy.

METHODS: The ULTRA (Uterine Leiomyoma Treatment With Radiofrequency Ablation) study is an ongoing multicenter prospective cohort study with longitudinal follow-up up to 5 years comparing outcomes of radiofrequency ablation with myomectomy in premenopausal women older than age 21 years with symptomatic uterine leiomyomas. Participants were queried every 6 months after surgery to assess the incidence of pregnancy and pregnancy outcomes.

RESULTS: Among 539 women enrolled in ULTRA, a total of 37 participants (mean age at first pregnancy 35.0±4.7 years) conceived 43 times as of March 2023 (22 radiofrequency ablation, 21 myomectomy). The average length of follow-up time after all procedures was 2.5±1.0 years. The baseline miscarriage rate in the study population was 33.3%. In participants who underwent radiofrequency ablation, 9 of 22 pregnancies (40.9%, 95% CI, 20.3–61.5%) ended in first-trimester miscarriage, 11 resulted in live births (50.0%, 95% CI, 29.1–70.9%), one resulted fetal death at 30 weeks of gestation, and one resulted in uterine rupture during miscarriage treatment with misoprostol 10 weeks after radiofrequency ablation. Among the live births in the radiofrequency ablation group, 45.5% were by vaginal delivery. In the myomectomy group, 9 of 21 pregnancies (42.9%, 95% CI, 21.7–64.0%) ended in first-trimester miscarriage and 12 resulted in live births (57.1%, 95% CI, 36.0–78.3%). There were no significant differences in the likelihood of live birth or miscarriage between the study groups.

CONCLUSION: Full-term pregnancy and vaginal delivery are achievable after radiofrequency ablation of leiomyomas. However, in this interim analysis, the miscarriage rate in both radiofrequency ablation and myomectomy groups was higher than expected for women in this age group. Long-term data collection in the ongoing ULTRA study aims to further understand pregnancy outcomes after radiofrequency ablation compared with myomectomy.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT0210094.

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Uterine leiomyomas, or fibroids, are the most common benign pelvic tumor in women.[1] By age 50 years, most women will have developed uterine leiomyomas, with a lifetime cumulative incidence of leiomyomas of about 80% in Black or African American women and 70% in White women.[2] Black or African American women have increased symptom severity compared with White women, which

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may include pelvic pain and bloating, severe anemia, sexual dysfunction, infertility, and adverse pregnancy outcomes.[3] Women with uterine leiomyomas report symptoms that negatively affect daily activities and overall quality of life. Hysterectomy is the definitive treatment for uterine leiomyomas; however, this limits the reproductive window and options for women with symptomatic leiomyomas. Recent studies have demonstrated that, even with ovarian conservation, hysterectomy is associated with a higher risk of metabolic conditions and cardiovascular disease, especially in individuals younger than age 35 years.[4] Uterine-sparing treatments for leiomyomas are alternatives to hysterectomy for symptomatic control. These methods include myomectomy, endometrial ablation, uterine artery embolization, and, most recently, radiofrequency ablation. Patients might select radiofrequency ablation if their priorities are rapid recovery time and sooner return to work.[5] Others might seek myomectomy if they prefer complete extirpation of leiomyomas.

Although there has been a steady increase in the use radiofrequency ablation, there are few data on reproductive outcomes of patients who undergo radiofrequency ablation compared with other uterine-sparing procedures. Laparoscopic radiofrequency ablation is a minimally invasive, outpatient, uterine-sparing treatment approved by the U.S. Food and Drug Administration (FDA) in 2012 for the management of symptomatic uterine leiomyomas. Several studies have demonstrated its effectiveness in alleviating leiomyoma symptoms, including the Chudnoff et al FDA-approved study,[6] which demonstrated a significant decrease in menstrual blood loss and leiomyoma volume 1 year after the procedure, in addition to an improvement in Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire scores, a validated standardized questionnaire to evaluate leiomyoma symptoms. The follow-up to the initial study by Chudnoff et al demonstrated continued symptomatic improvement in 2- and 3-year follow-up studies.[7] Although these studies describe feasibility, symptom improvement, and efficacy, it is notable that they do not include a myomectomy comparator group. Most recently, an update to the TRUST (Treatment Results of Uterine Sparing Technologies) trial, which is a secondary analysis of the original postmarket randomized comparative trial of radiofrequency ablation and myomectomy, demonstrated the efficacy of radiofrequency ablation as an alternative to myomectomy.[8]

Although subsequent studies have focused on symptomatic improvement after the procedure, there is a paucity of data on reproductive outcomes after laparoscopic radiofrequency ablation. To address this evidence gap, we conducted an interim analysis of an ongoing cohort study of reproductive-aged women undergoing radiofrequency ablation compared with myomectomy in the ULTRA (Uterine Leiomyoma Treatment With Radiofrequency Ablation) study. The aim of this study is to evaluate pregnancy outcomes after laparoscopic radiofrequency ablation for symptomatic uterine leiomyomas.

METHODS

The ULTRA study is an ongoing multicenter prospective cohort study of radiofrequency ablation for symptomatic uterine leiomyomas to evaluate the long-term safety and efficacy of this procedure. Recruitment began in April 2014 as a nationwide observational cohort study for participants undergoing radiofrequency ablation of uterine leiomyomas. Recruitment occurred through Facebook advertisements and referrals from gynecology practices across the country. The participants underwent surgery locally with their health care professionals and completed consent and enrollment remotely through the University of California, San Francisco to participate in longitudinal follow-up. In February 2018, the study was expanded to include 13 clinical sites (see Appendix 1, available online at http://links.lww.com/AOG/D600) that consented and enrolled participants locally and conducted initial study activities within the site. Recruitment closed on July 1, 2022. All long-term follow-up is conducted by the University of California, San Francisco.

Patients were eligible for ULTRA if they had symptomatic leiomyomas, spoke the most common languages for our cohort, English or Spanish, and planned to undergo laparoscopic radiofrequency ablation. In December 2019, enrollment was further opened to participants undergoing laparoscopic or abdominal myomectomy to serve as a comparison group for radiofrequency ablation. Women younger than age 21 years and those planning to undergo hysteroscopic myomectomy were excluded from this study. There were no limits on leiomyoma size or number of leiomyomas present for enrollment in the ULTRA study. All participants provided informed consent before enrollment using procedures approved by the IRB of the University of California, San Francisco (IRB No. 14-13325).

Laparoscopic radiofrequency ablation of uterine leiomyomas has been described in detail in other

published studies.[9] For ULTRA, local health care professionals performed radiofrequency ablation and myomectomy according to standard practice for each surgeon. The radiofrequency ablation procedure is performed under general anesthesia with ultrasound guidance to target leiomyomas. A handpiece tip with coagulating and dispersive electrodes is inserted into the leiomyoma, which is then confirmed with intrabdominal ultrasonography for proper placement. A seven-needle electrode is deployed into the leiomyoma to fit the ablation diameter and volume within the leiomyoma capsule. The radiofrequency ablation device then increases the tissue temperature to 95–100°C to induce coagulative necrosis, sparing the surrounding myometrium.

At baseline, participants completed a preoperative study visit in which they completed questionnaires about demographic characteristics, medical and reproductive history, medication use, desire for future fertility, and leiomyoma symptoms. Race and ethnicity were assessed by self-report; these categories are aligned with U.S. Census data. We assessed race and ethnicity in this study because of higher rates of symptomatic leiomyomas and differential outcomes in women of color, specifically Black- or African American–identifying women. Preoperative leiomyoma characteristics and uterine size and volume were obtained with preprocedural imaging using ultrasonography or magnetic resonance imaging according to health care professional preference. After surgery, participants were queried every 6 months for up to 5 years on desire for pregnancy and reproductive health outcomes, including any pregnancies that had occurred. If a pregnancy was reported, participants reported details of the pregnancy outcome and any related complications. Participants provided permission for medical record release for adverse pregnancy outcomes to adjudicate the clinical events.

Demographic and clinical characteristics of the participants by intervention group were examined with the use of descriptive statistics. Categorical variables were reported as counts and percentages, and groups were compared with the χ^2 or Fisher exact test. Continuous variables were reported using means and SD or means and ranges, and groups were compared with two-sample *t* tests or Wilcoxon rank-sum tests. In comparing the two groups, we accounted for intraclass correlation attributable to participants with multiple pregnancies through robust clustered standard errors[10] obtained from logistic or linear regression; however, in the event of low or zero counts in the logistic regression analyses, we instead reported the more conservative Fisher exact test *P* values. All statistical analyses were performed with STATA 16 or SAS 9.4, with $P<.05$ considered statistically significant.

RESULTS

From April 2014 to March 2023, a total of 539 ULTRA participants were available for analysis, with 372 participants in the radiofrequency ablation group and 167 participants in the myomectomy group (Appendix 2, available online at http://links.lww.com/AOG/D600). Of these, 37 participants achieved 43 pregnancies over an average follow-up time of 2.7±1.2 years for the radiofrequency ablation group and 2.2±0.2 years for the myomectomy group. Participants were 27–43 years old (Table 1), with the mean age at first pregnancy of 35.0±4.7 years. Black or African American participants were 37.8% of the study population; more Hispanic or Latina participants were in the radiofrequency ablation group compared with the myomectomy group ($P=.032$). Mean body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) was higher in the radiofrequency ablation group (31.8±8.9 vs 25.8±4.0, $P=.035$). Otherwise, there were no significant differences in baseline demographic characteristics between the radiofrequency ablation and myomectomy groups. Overall, all participants had five or fewer leiomyomas with a mean uterine volume of 347±435 mL. There was a significant difference in mean leiomyoma volume between the radiofrequency ablation and the myomectomy group (203±200 mL vs 516±586 mL, $P=.016$; Table 2). At baseline, 81.1% of participants reported desire for pregnancy after surgery ("Are you actively trying to get pregnant now or plan to try to get pregnant after recovering from surgery?") and 94.6% were planning to get pregnant in the future ("Do you hope to get pregnant in the future?"). We found that 21.6% of participants reported using assisted reproductive technology to attempt to achieve pregnancy before enrollment, and 83.3% reported no prior surgeries or treatments for uterine leiomyomas. Most of our participants were nulligravid. Of the participants with prior parity, the majority had one prior delivery (median 1.0, range 0.0–5.0), with the radiofrequency ablation group having greater parity than the myomectomy group ($P=.028$). Regarding prior obstetric outcomes, 22.2% of participants reported a prior abortion, 33.3% reported a prior miscarriage, 11.1% reported a prior live birth, and 5.6% (n=2) reported a prior *fetal death*, defined as pregnancy loss after 20 weeks of gestation.

Of the total 43 pregnancies, 22 occurred in the radiofrequency ablation group and 21 in the

Table 1. Baseline Characteristics

Variable	Laparoscopic RFA (n=20)	Myomectomy (n=17)	*P*
Patient characteristics			
Age at first pregnancy (y)	35.60±4.2	34.24±5.2	.216
BMI (kg/m^2)	31.76±8.9	25.76±4.0	.035
Straight or heterosexual	7 (100)	15 (88.2)	.343
Gay or lesbian	0 (0.0)	2 (11.8)	
Race*			
American Indian/Alaska Native	0 (0.0)	0 (0.0)	
Asian	2 (10.0)	1 (5.9)	.647
Black or African American	8 (40.0)	6 (35.3)	.769
Hispanic or Latina	7 (35.0)	1 (5.9)	.032
Native Hawaiian or Other Pacific Islander	1 (5.0)	1 (5.9)	.906
White	7 (35.0)	7 (41.2)	.699
Additional races	0 (0.0)	1 (5.9)	.272
Pregnancy characteristics			
Parity	1 (0–5)	0 (0–5)	.028
Gravidity	0 (0–1)	0 (0–3)	.721
Prior miscarriage	8 (42.1)	4 (23.5)	.238
Prior fetal death	2 (10.5)	0 (0)	.169
Prior live birth	1 (5.3)	3 (17.6)	.238
Ever used assisted methods (medications, IVF)	5 (25.0)	3 (17.6)	.588

RFA, radiofrequency ablation; BMI, body mass index; IVF, in vitro fertilization.
Data are mean±SD, n (%), or median (range) unless otherwise specified.
* Patients were able to select more than one race.

myomectomy group (Table 3). The mean time from procedure to pregnancy was 1.2±0.8 years in the radiofrequency ablation group and 1.1±0.7 years in the myomectomy group. In participants who underwent radiofrequency ablation, 9 of 22 pregnancies (40.9%, 95% CI, 20.3–61.5%) ended in first-trimester miscarriage and 11 of 22 resulted in live births (50.0%, 95% CI, 29.1–70.9%). Among the miscarriages, the median gestational age was 7.7±2.2 weeks. One pregnancy loss at more than 20 weeks of gestation occurred; however, we were unable to reach the participant for further information. Another pregnancy loss occurred 10 weeks after the participant's radiofrequency ablation procedure, resulting in a uterine rupture, the details of which are described later.

The average gestational age at time of birth was 37.9±2.8 weeks. In the radiofrequency ablation group, 45.5% of participants had vaginal deliveries and 54.5% had cesarean deliveries. In the myomectomy group, 9 of 21 pregnancies (42.9%, 95% CI, 21.7–64.0%) ended in first-trimester miscarriage and 12 of 21 resulted in live births (57.1%, 95% CI, 36.0–78.3%); all 12 live births in the myomectomy group were by cesarean delivery. The average gestational age at the time of miscarriage and the time of live birth did not differ between groups. In addition, there

Table 2. Clinical and Surgical Characteristics

Variable	Laparoscopic RFA (n=20)	Myomectomy (n=17)	*P*
Leiomyoma characteristics			
No. of leiomyomas	2.0 (1.0–4.0)	2.0 (1.0–5.0)	.726
Leiomyoma volume (mL)	203±200	516±568	.016
Uterine volume (mL)	457±354	638±557	.421
Primary procedure			
RFA (Acessa)	20 (100)	0	
Laparoscopic myomectomy	0	4 (23.5)	
Robot-assisted laparoscopic myomectomy	0	4 (23.5)	
Abdominal myomectomy	0	9 (52.9)	
Total follow-up time (y)	2.74±1.2	2.15±0.3	.015

RFA, radiofrequency ablation.
Data are median (range), mean±SD, or n (%) unless otherwise specified.

Table 3. Pregnancy Outcomes

Variable	Laparoscopic RFA (n=22)	Myomectomy (n=21)	*P*
Assisted conception (IVF, medications)	7 (31.8)	7 (33.3)	.910
Miscarriage	9 (40.9)	9 (42.9)	.903
Abortion	1 (4.5)		>.99
Live birth	11 (50.0)	12 (57.1)	.661
IUFD after 20 wk	1 (4.5)		1.000
Time from procedure to pregnancy (y)	1.12 (0.8)	1.08 (0.7)	.867
Live births (n=23)			
Gestational age at birth (wk)	37.85±2.8	37.00±1.0	.381
Vaginal delivery	5 (45.5)		>.99
Cesarean delivery	6 (54.5)	12 (100)	.014

RFA, radiofrequency ablation; IVF, in vitro fertilization; IUFD, intrauterine fetal death.
Data are n (%) or mean±SD unless otherwise specified.

were no significant differences in the number of miscarriages (odds ratio 0.92, 95% CI, 0.25–3.35, *P*=.903) and full-term deliveries (odds ratio 0.75, 95% CI, 0.21–2.72, *P*=.661) between the radiofrequency ablation and myomectomy groups.

Regarding full-term pregnancy outcomes, in the radiofrequency ablation group, one participant each reported gestational diabetes, pregnancy-related high blood pressure, placenta previa, and uterine rupture, as described later. In the myomectomy group, two participants reported gestational diabetes, three reported pregnancy-related high blood pressure, and two reported placenta previa. No cases of preeclampsia, seizures, or placental abruption were reported. We did not find any significant differences in the likelihood of miscarriages or live births (*P*=1.00) between the study groups.

One participant experienced uterine rupture 10 weeks after laparoscopic radiofrequency ablation during treatment with vaginal misoprostol to manage early pregnancy loss. This participant was 31 years old, G4P0030, and had four leiomyomas, ranging from 4 to 6 cm in size, that were ablated. The patient was found to be pregnant 2 weeks after the procedure. Six weeks later, the participant presented with an anembryonic pregnancy. The patient elected for medication management 9 6/7 weeks after radiofrequency ablation and was prescribed 800 mg vaginal misoprostol. Twelve hours later, she presented to the emergency department for severe abdominal pain and was found to have free fluid in the abdomen. She subsequently underwent an exploratory laparotomy, which revealed 800 mL hemoperitoneum and a posterior uterine rupture with products of conception extruding from the defect with a necrotic leiomyoma adjacent to the rupture, confirmed by subsequent pathologic examination. This participant experienced another miscarriage in the first trimester 1 year later, which was managed by dilation and curettage.

DISCUSSION

In this ongoing multicenter prospective cohort study of pregnancy outcomes among women in the United States after laparoscopic radiofrequency ablation and myomectomy, we report that full-term pregnancy and vaginal delivery are achievable after radiofrequency ablation for leiomyomas. However, the point estimates for miscarriage rates of 40.9% in the radiofrequency ablation group and 42.8% in the myomectomy group are higher than the reported rates in the general population and after leiomyoma surgery. However, given the small sample size of 43 pregnancies, the CIs around the estimate risk of miscarriage are wide; the low end of the CI for both radiofrequency ablation (20.3%) and myomectomy (21.7%) is within the expected range for the general population. In addition, there is a higher baseline miscarriage rate of 33.3% overall in our study population, which suggests a higher-risk population.

The point estimates for miscarriage in this initial analysis of ULTRA are higher than in a prior study of radiofrequency ablation. Berman et al[11] described reproductive outcomes of 30 pregnancies achieved after radiofrequency ablation; 13% resulted in miscarriage and 87% in live births. However, this study had significant methodologic differences from ULTRA that may explain the varying rates of miscarriage. The pregnancy reports in the Berman et al[11] analyses are a case series of pregnancies from a variety of different data sources, including voluntary reporting from a premarket pivotal trial and postmarket case reports to the manufacturer from gynecologic surgeons. This method of data collection risks underre-

porting miscarriage because health care professionals may be reluctant to report adverse pregnancy outcomes or participants in the pivotal trial may not have remained in follow-up care with the gynecologic surgeon once pregnancy occurred. In contrast, ULTRA is a prospective cohort study in which standardized assessments were made every 6 months for all participants, with attention to minimizing loss to follow-up; this approach aims to minimize bias in reporting pregnancy outcomes. In addition, in the pivotal clinical trial that is included in the Berman et al[11] case reports, eligibility limited participants to leiomyomas smaller than 7 cm and uterine volume less than 300 mL or about 16 weeks of gestation; women with type 0 and 7 leiomyomas were excluded. In ULTRA, women with all leiomyoma types, except those undergoing hysteroscopic myomectomy, were included regardless of the size or location of the leiomyoma or the size of the uterus. The larger leiomyoma volume and leiomyoma number in ULTRA present a significant difference in the clinical presentation between participants in ULTRA and the Berman et al study that may be associated with miscarriage risk. However, there is mixed evidence on the presence of leiomyomas and miscarriage rate, with a recent prospective study finding no characteristics of leiomyomas contributing to increased risk.[12]

We report one participant who experienced uterine rupture about 10 weeks after laparoscopic radiofrequency ablation during treatment with vaginal misoprostol to manage early pregnancy loss. This case calls into question the appropriate timing of pregnancy after radiofrequency ablation and the use of misoprostol, a prostaglandin E_1 analog that is commonly used for inducing the expulsion of uterine contents during early pregnancy loss, medical abortion management, and cervical ripening for induction of labor.[13] Despite its widespread use, there are few data on the risk of uterine rupture with the use of misoprostol for medical management of first-trimester pregnancy loss, especially in women with prior or recent uterine procedures. Uterine rupture in early pregnancy, even with preceding uterine surgery, is exceedingly rare, estimated to be about 1 per 10,000.[14]

Many studies that address risk of uterine rupture with misoprostol use in the second trimester before induction termination have found no increased risk for women with a prior uterine scar. A study of 80 participants found that there was no increased risk of uterine rupture or uterine scar dehiscence in patients undergoing induction termination with misoprostol between 13 and 26 weeks of gestation.[15] This was seen similarly in a study of 100 women with prior cesarean delivery with terminations between 14 and 28 weeks of gestation.[16] Conversely, in a study of 212 participants with prior uterine scar undergoing terminations around 17–24 weeks of gestation, three uterine ruptures were reported compared with none in the unscarred uterus group.[17] However, more definitive studies are needed to evaluate risk of uterine rupture close to the time of uterine surgery. Uterine remodeling occurs for 3 months after myomectomy, with a recommendation to avoid pregnancy for at least 3 months after this procedure, but research is needed to determine whether radiofrequency ablation warrants a similar recommendation regarding delaying pregnancy after surgery.

There are some limitations to note. The point estimates for pregnancy outcomes, small sample size, and wide CIs are study limitations. Therefore, these results are not definitive evidence for change in clinical counseling. In addition, as an observational study, there are both patient and physician factors that contribute to patient and intervention selection, including patient preference and surgeon recommendations. Although key baseline characteristics such BMI and leiomyoma volume differed between study groups, the small sample size precluded multivariable analysis in this study to address confounding. Longer follow-up is required to increase the number of recorded pregnancies in ULTRA; our plan to follow up participants for up to 5 years after surgery will increase the sample size of pregnancies to further evaluate outcomes after uterine preserving procedures.

Laparoscopic radiofrequency ablation is a minimally invasive treatment for symptomatic leiomyomas, with few available data on pregnancy outcomes. We report the largest published series of pregnancy outcomes after radiofrequency ablation compared with myomectomy. Our results highlight that pregnancy and full-term vaginal delivery after radiofrequency ablation are possible, but miscarriage rates in this interim analysis were higher than age-adjusted norms for both the radiofrequency ablation and myomectomy groups. Additional data are needed with larger sample sizes during long-term follow-up after uterine surgery to further assess pregnancy outcomes.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *Not available.*

What other documents will be available? *Not available.*

When will data be available (start and end dates)? *Not applicable.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Not applicable.*

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