Title

Pregnancy Outcomes after Laparoscopic Radiofrequency Ablation of Uterine Leiomyomas versus Myomectomy

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~~Uterine Leiomyoma Treatment with Radiofrequency Ablation (ULTRA)~~
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Short title: Pregnancy Outcomes After Radiofrequency Ablation of ~~fibroids~~Leiomyomas

Precis: Pregnancy is achievable after radiofrequency ablation of symptomatic uterine fibroids and pregnancy outcomes are similar to those after myomectomy.

Abstract

Objective: To compare pregnancy outcomes following laparoscopic radiofrequency ablation (RFA) and myomectomy.

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

Results: Among 539503 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 RFA, 21 myomectomy). The average length of follow-up time after surgery all procedures was 2.5 years (+/- 1.0 years). The baseline miscarriage rate in the study population was 33.3%. In those who underwent RFA, 9 of 22 pregnancies (40.9%, 95% CI 20.3% - 61.5%) ended in 1st trimester miscarriage, 11 resulted in live births (50.0%, 95% CI 29.1% - 70.9%), 1 had a fetal demise at 30 weeks and 1 had a uterine rupture during miscarriage treatment with misoprostol 10 weeks after RFA. Among the live births in the RFA 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 1st-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: Conception, Ffull-term pregnancy, and vaginal delivery are achievable after RFA of fibroids. However, in this interim analysis, the miscarriage rate in both RFA 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 following RFA compared with myomectomy.

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Introduction

Uterine leiomyomas, or fibroids, are the most common benign pelvic tumor in women [1]. By age 50, most women will have developed uterine fibroids, with a lifetime cumulative incidence of fibroids of approximately 80% in Black or African American women and 70% in White women [2]. Black or African American women suffer from increased symptom severity compared with White women, which may include pelvic pain and bloating, severe anemia, sexual dysfunction, infertility, and adverse pregnancy outcomes [3]. Women with uterine fibroids report symptoms that negatively impact daily activities and overall quality of life. Hysterectomy is the definitive treatment for uterine fibroids; however, this limits the reproductive window and options for women that suffer from symptomatic fibroids. 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 under the age of 35 [4]. Uterine-sparing treatments for fibroids are alternatives to hysterectomy for symptomatic control. These methods include myomectomy, endometrial ablation, uterine artery embolization, and, most recently, radiofrequency ablation (RFA). Patients might select RFA if their priorities are rapid recovery time and sooner return to work[5]. Others might seek myomectomy if they prefer complete extirpation of fibroids.

While there has been a steady increase in the use radiofrequency ablation, there is little data on reproductive outcomes of patients who undergo RFA compared with other uterine sparing procedures.

Laparoscopic RFA is a minimally invasive, outpatient, uterine-sparing treatment approved by the FDA in 2012 for the management of symptomatic uterine fibroids. Several studies have demonstrated its effectiveness in alleviating

fibroid symptoms, including the LAP-RFA trial [6] which demonstrated a significant decrease in menstrual blood loss and fibroid volume one-year post-procedure, in addition to an improvement in Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire scores, a validated standardized questionnaire to evaluate fibroid symptoms. The HALT trial [7], a follow-up to the LAP-RFA trial, demonstrated continued symptomatic improvement in 2 and 3-year follow-up studies. While these studies describe feasibility, symptom improvement and~~or~~ efficacy, notably they do not include a myomectomy comparator group. Most recently, an update to the TRUST trial, which is a secondary analysis of the original post-market randomized comparative trial of RFA vs myomectomy, demonstrated~~s~~ RFA's efficacy as an alternative to myomectomy [8].

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

Methods

The ULTRA study is an ongoing multicenter prospective cohort study of RFA for symptomatic uterine fibroids 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 RFA of uterine fibroids. Recruitment occurred through Facebook advertisements and referrals from gynecology practices across the country. The participants underwent surgery locally with their provider

and completed consent and enrollment remotely through the University of California, San Francisco (UCSF) to participate in longitudinal follow-up. In February 2018, the study was expanded to include 13 clinical sites (see acknowledgements) that consented and enrolled participants locally and conducted initial study activities within the site. Recruitment closed on July 1st, 2022. All long-term follow-up is conducted by UCSF.

Eligibility criteria for ULTRA were participants who had symptomatic fibroids, who spoke the most common languages for our cohort, English or Spanish, and planned to undergo laparoscopic RFA. In December 2019, enrollment was further opened to participants undergoing laparoscopic or abdominal myomectomy to serve as a comparison group for RFA. Women younger than 21 or those planning to undergo hysteroscopic myomectomy were excluded from this study. There were no limits on fibroid size or number of fibroids present for enrollment into the ULTRA study. All participants provided informed consent before enrollment, using procedures approved by the institutional review board of UCSF (IRB # 14-13325).

Laparoscopic RFA of uterine fibroids has been described in detail in other published studies [9]. For ULTRA, local providers performed RFA and myomectomy according to standard practice for each surgeon. The RFA procedure is performed under general anesthesia with ultrasound guidance to target fibroids. A handpiece tip with coagulating and dispersive electrodes is inserted into the fibroid, which is then confirmed with intrabdominal ultrasound for proper placement. A 7-needle electrode is deployed into the fibroid to fit the ablation diameter and volume within the fibroid capsule. The RFA device then increases the tissue temperature to 95-100 ° Celsius to induce coagulative necrosis, sparing the surrounding myometrium.

At baseline, participants completed a pre-operative study visit in which they completed questionnaires about demographic characteristics, medical and reproductive history, medication use, desire for future fertility, and fibroid symptoms. Race and ethnicity were assessed by self-report; these categories are aligned with US Census data. We assessed race and ethnicity in this study due to higher rates of symptomatic fibroids and differential outcomes in women of color, specifically Black or African American identifying women. Pre-operative fibroid characteristics and uterine size and volume were obtained with pre-procedure imaging using ultrasound or MRI based on provider preference. Following surgery, participants were queried every 6 months for up to 5 years on desire for pregnancy, 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 using descriptive statistics. Categorical variables were reported as counts and percentages and groups were compared using chi-square or Fisher’s exact tests. Continuous variables were reported using means and standard deviation or means and ranges and groups were compared using two sample t-tests or Wilcoxon rank sum tests. In comparing the two groups, we accounted for intraclass correlation due to subjects 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’s exact test p-values. . All statistical analyses were performed using STATA 16 (StataCorp LLC College Station, TX) or SAS

statistical software (version 9.4; SAS Institute Inc, Cary, NC), with P values of <0.05 considered statistically significant.

Results:

From April 2014 to March 2023, a total of 539503 ULTRA participants were available for analysis, with 372 participants in the RFA group and 167 participants in the myomectomy group. (Fig. Appendix 1, available online at http://links.lww.com/xxx). Of these, 37 participants achieved 43 pregnancies over an average follow-up time of 2.7 years (+/- 1.2 years) for the RFA group and 2.2 years (+/- 0.2 years) for the myomectomy group. Participants were aged 27 to 43 years (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 RFA group compared with the myomectomy group (p=0.032). Mean body mass index (BMI) was higher in the RFA group (31.8 +/- 8.9 versus 25.8 +/- 4.0, p = 0.035). Otherwise, there were no significant differences in baseline demographic characteristics between the RFA and myomectomy group. Overall, all participants had ≤5 fibroids with mean uterine volume of 347cc, +/- 435cc. There was a significant difference in mean fibroid volume between the RFA and myomectomy group (203cc +/- 200 vs 516cc +/- 586, p=0.016) (Table 2). At baseline, 81.1% of participants reported desire for pregnancy following surgery (“Are you actively trying to get pregnant now or plan to try to get pregnant after recovering from surgery?”) and 94.6% were trying to get pregnant in the future (“Do you hope to get pregnant in the future?”). 21.6% of participants reported using assisted reproductive technology to attempt to achieve pregnancy prior to enrollment and 83.3% reported no prior surgeries or treatments for uterine fibroids. Most of our participants were nulligravid. Of the participants with prior parity, the

majority had 1 prior delivery (median 1.0, range 0.0 – 5.0), with the RFA group having greater parity than the myomectomy group (p=0.028). Regarding prior obstetric outcomes, 22.2% 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 greater than 20 weeks.

Of the total 43 pregnancies, 22 occurred in the RFA group and 21 in the myomectomy group (Table 3). The mean time from procedure to ~~conception~~ pregnancy was 1.2 +/- 0.8 years in the RFA group and 1.1 +/- 0.7 years in the myomectomy group. In those who underwent RFA, 9 of 22 pregnancies (40.9%, 95% CI 20.3% - 61.5%) ended in 1st trimester miscarriage, 11 of 22 resulted in live births (50.0%, 95% CI 29.1% - 70.9%). Among the miscarriages, the median gestational was 7.7 weeks (+/- 2.2). One pregnancy loss over 20 weeks occurred, however we were unable to reach the participant for further information. Another pregnancy loss occurred at 10 weeks after the participant's RFA procedure, resulting in a uterine rupture; the details of which are described below. The average gestational age at time of birth was 37.9 weeks +/- 2.8. In the RFA group, 45.5% had a vaginal delivery and 54.5% had a cesarean delivery. In the myomectomy group, 9 of 21 pregnancies (42.9%, 95% CI 21.7% - 64.0%) ended in 1st-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 section. The average gestational age at the time of miscarriage and time of live birth did not differ between groups. Additionally, there were no significant differences in the number of miscarriages (OR 0.92, 95% CI 0.25-3.35, p = 0.903) and full-term deliveries (OR 0.75, 95%CI 0.21-2.72, p = 0.661) between the RFA and myomectomy groups. Regarding ~~pregnancy~~ full-term pregnancy outcomes, in the RFA group, one participant each reported

gestational diabetes, pregnancy-related high blood pressure, placenta previa and uterine rupture, as described below. 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 who experienced uterine rupture 10 weeks after laparoscopic RFA during treatment with vaginal misoprostol to manage early pregnancy loss. This participant is a 31-year-old G4P0030 who had 4 fibroids were ablated, ranging from 4 to 6cm in size. 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 weeks and 6 days after RFA and was prescribed 800mg of 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 800cc of hemoperitoneum and a posterior uterine rupture with products of conception extruding from the defect with a necrotic fibroid adjacent to the rupture, confirmed by subsequent pathological examination. This participant experienced another miscarriage in the first trimester managed by dilation and curettage one year later.

Discussion

In this ongoing multicenter prospective cohort study of pregnancy outcomes among women in the United States after laparoscopic RFA and myomectomy, we report that conception, full-term pregnancy and vaginal delivery are achievable

after RFA for fibroids. However, the point estimate for miscarriage rates of 40.9% in the RFA group and 42.8% in the myomectomy group are higher than the reported rates in the general population and following fibroid surgery. However, given the small sample size of 43 pregnancies, the confidence intervals around the estimate risk of miscarriage are wide; the low end of the confidence interval for both RFA (20.3%) and myomectomy (21.7%) are within the expected range for the general population. Additionally, 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 a prior study of RFA. Berman et al. [11] described reproductive outcomes of 30 pregnancies achieved after RFA where 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. analyses are a case series of pregnancies from a variety of different data sources including voluntary reporting from a premarket pivotal trial and post-market case reports to the manufacturer from gynecologic surgeons. This method of data collection risks underreporting miscarriage as providers 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 where 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. ~~Additonally~~Additionally, in the pivotal clinical trial that is included in the Berman case reports, eligibility limited participants to fibroids <7cm and uterine volume less than 300 cc or approximately 16 weeks gestation; women with Type 0 and 7

fibroids were excluded. In ULTRA, women with all fibroid types, except those undergoing hysteroscopic myomectomy, were included irrespective of the size or location of the fibroid or the size of the uterus. The larger fibroid volume and fibroid number in ULTRA present a significant difference in the clinical presentation between participants in ULTRA and the Berman study that may be associated with miscarriage risk. However, there is mixed evidence on the presence of fibroids and miscarriage rate, with a recent prospective study finding no characteristics of fibroids contributing to increased risk [12].

We report one participant who experienced uterine rupture approximately 10 weeks after laparoscopic RFA during treatment with vaginal misoprostol to manage early pregnancy loss. This case calls into question the appropriate timing of pregnancy after RFA as well as the use of misoprostol, a prostaglandin-E1 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 is little data on the risk of uterine rupture with 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 approximately 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 in uterine rupture or uterine scar dehiscence in patients undergoing induction termination with misoprostol between 13 and 26 weeks [15]. This was seen similarly in a study of 100 women with a prior Cesarean delivery with

terminations between 14 and 28 weeks [16]. Conversely, in a study of 212 participants with a prior uterine scar in terminations around 17 to 24 weeks, three uterine ruptures were reported compared to 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 following this procedure but research is needed to determine if RFA warrants a similar recommendation regarding delaying pregnancy following surgery.

~~This study has several strengths. This study population is a racially and geographically diverse sample including 38% Black or African American women in a variety of practice environments. It is important to critically assess and meet the needs of Black or African American women diagnosed with symptomatic uterine fibroids who desire minimally invasive treatments with uterine preservation. Many studies have demonstrated that Black or African American women are less likely to be offered minimally invasive surgery for a variety of benign gynecological issues [18], however, research studies have been slow to recruit participants that reflect the true distribution of fibroid burden in Black women. Finally, to our knowledge, this is the only comparative study of pregnancy outcomes after laparoscopic RFA versus myomectomy.~~

There are some limitations to note. The point estimates for pregnancy outcomes, small sample size and wide confidence intervals are a study limitation. As such, these results are not definitive evidence for change in clinical counseling. Additionally, as an observational study, there are both patient and physician factors that contribute to patient and intervention selection including patient preference

and surgeon recommendations. While key baseline characteristics such BMI and fibroid volume differed amongst 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 participants for up to 5 years after surgery will increase the sample size of pregnancies to further evaluate outcomes following uterine preserving procedures.

~~Conclusion~~

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

~~Figure~~Appendix 1. Study flow chart

Table 1: Patient Baseline Characteristics

Variable	Lap RFA (n=20)	Myomectomy (n=17)	P-Value
Age at First Pregnancy, year, mean (SD)	35.60 ±4.2	34.24 ±5.2	0.216
Body Mass Index kg/m^2 , mean (SD)	31.76 ±8.9	25.76 ±4.0	0.035
Straight/heterosexual	7 (100.0)	15 (88.2)	0.343
Gay or lesbian		2 (11.8)	
Race*			
American Indian/Alaska Native	0 (0.0)	0 (0.0)	
Asian	2 (10.0)	1 (5.9)	0.647
Black or African American	8 (40.0)	6 (35.3)	0.769
Hispanic or Latina	7 (35.0)	1 (5.9)	0.032
Native Hawaiian or Other Pacific Islander	1 (5.0)	1 (5.9)	0.906
White	7 (35.0)	7 (41.2)	0.699
~~Other~~ Additional races	0 (0.0)	1 (5.9)	0.272
Pregnancy characteristics at baseline			
Parity (median, range)	1 (0-5)	0 (0-5)	0.028
Gravida (median, range)	0 (0-1)	0 (0-3)	0.721
Prior miscarriage	8 (42.1)	4 (23.5)	0.238
Prior fetal death	2 (10.5)	0 (0)	0.169
Prior live birth	1 (5.3)	3 (17.6)	0.238
Ever used assisted methods (medications, IVF)	5 (25.0)	3 (17.6)	0.588

Expressed in absolute numbers and percent unless otherwise specified
***Patients able to select more than one race**

Table 2: Clinical and Surgical Characteristics

Variable	Lap RFA (n = 20)	Myomectomy (n = 17)	P-Value
Fibroid Characteristics			
Number of fibroids, (median, range)	2.0 (1.0-4.0)	2.0 (1.0-5.0)	0.726
Fibroid Volume (cc) SD	203 ±200	516 ±568	0.016
Uterine Volume (cc) SD	457 ±354	638 ±557	0.421
Primary Procedure			
Radiofrequency ablation (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 (years) SD	2.74 (± 1.2)	2.15 (0.3)	0.015

Expressed in absolute numbers and percent unless otherwise specified

Table 3: Pregnancy outcomes

Variable	Lap RFA (n=22)	Myomectomy (n=21)	P-Value
Assisted conception (IVF, Meds)	7 (31.8)	7 (33.3)	0.910
Miscarriage	9 (40.9)	9 (42.9)	0.903
Abortion	1 (4.5)		1.000>.99
Live Birth	11 (50.0)	12 (57.1)	**0.661**
IUFD>20 weeks	1 (4.5)		1.000
Time from procedure to pregnancy (years)	1.12 (0.8)	1.08 (0.7)	0.867
Live Birth (n=23)			
Gestational age at birth, mean (SD)	37.85 ±2.8	37.00 ±1.0	0.381
Vaginal delivery	5 (45.5)		1.00>.99
Cesarean section	6 (54.5)	12 (100)	0.014

***Expressed in absolute numbers and percent unless otherwise specified**

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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.*