Sonata® SYSTEM

Clinical Compendium

Transcervical Fibroid Ablation (TFA) with the Sonata® System provides an incisionless, uterus-preserving, minimally-invasive outpatient or ambulatory surgery center option for patients with symptomatic fibroids.

gynesonics®

www.SonataTreatment.com

EXECUTIVE SUMMARY

Transcervical Fibroid Ablation (TFA) with the Sonata® System provides an incisionless, uterus-preserving, minimally-invasive outpatient or ambulatory surgery center option for patients with symptomatic fibroids.

Clinical results show a significant reduction in heavy menstrual bleeding with sustained clinical benefits through 5 years of follow-up, a low incidence of surgical reintervention, high patient satisfaction, and a favorable safety profile with no device-related adverse events.

Other favorable outcomes include a short length of stay, rapid return to normal activity and work, and significant improvements in quality of life, symptom severity, and activity levels.

5 YEAR OUTCOMES

- 1, 2, 3, and 5-year long-term published clinical outcomes demonstrating durable and significant reduction in symptoms, with high patient satisfaction and low reintervention rates
- Multiple prospective, multicenter, controlled trials from various stakeholders, including an FDA IDE Pivotal Trial, all showing consistent, sustained, and significant symptom relief

14 STUDIES

- 14 clinical research trials, studies, and sub-studies, including 3 health economic outcomes research studies
- CHOICES Comparative Trial of TFA versus Myomectomy; peer-reviewed and published in the Journal of ClinicoEconomics and Outcomes Research; abstract published in Value in Health Journal by ISPOR, the leading global scientific and educational organization for health economics and outcomes research

25 PUBLICATIONS

- More than 25 peer-reviewed publications
- *"Ultrasound-Guided Transcervical Ablation of Uterine Leiomyomas"* (12-month results of the SONATA pivotal clinical trial), as published in Obstetrics and Gynecology (the Green Journal), was included among the article choices in 2019 by the American Board of Obstetrics & Gynecology for Maintenance of Certification

3 ECONOMIC STUDIES

- 3 health economic outcomes research studies demonstrate significant cost savings for payers and facilities when utilizing Sonata compared to hysterectomy and myomectomy
- SAGE global registry provides real-world data supporting the favorable safety profile established in other clinical research studies

TABLE OF CONTENTS

I: SONATA SYSTEM TECHNOLOGY OVERVIEW

THE BENEFITS

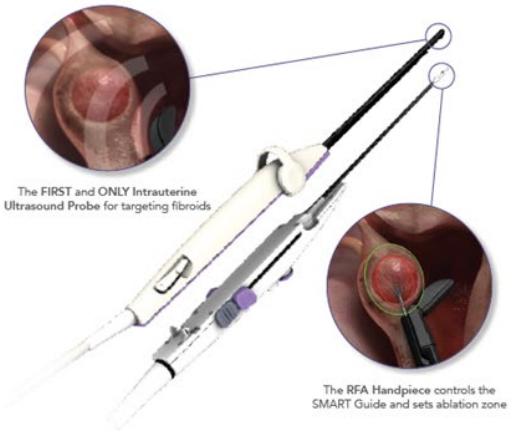
- Incision-free, uterus-preserving treatment, avoids the peritoneal cavity, an alternative to invasive surgical procedures
- Treats larger and deeper fibroids that are not accessible by hysteroscopy, expands transcervical fibroid treatment options
- Favorable safety profile, well tolerated, high patient satisfaction, no device-related adverse events
- Outpatient - does not require general anesthesia
- Rapid recovery, return to normal activities and work
- Significant and durable symptom relief
- Lower cost treatment alternative

THE TECHNOLOGY

- The Sonata System is intended for diagnostic intrauterine imaging and transcervical treatment of symptomatic uterine fibroids, including those associated with heavy menstrual bleeding. TFA (transcervical fibroid ablation) with the Sonata System is an incisionless, uterus-preserving procedure that does not require general anesthesia.
- The enabling platform technology that provides this breakthrough treatment is the first ever intrauterine ultrasound imaging probe. This probe, coupled to a radiofrequency (RF) energy delivery handpiece, creates a single treatment device on the sterile field.
- The treatment device is delivered transcervically to the uterine cavity. The novel imaging probe identifies the fibroids and utilizes a proprietary graphic user interface (SMART Guide) for fibroid targeting in real time. The delivery of RF energy ablates the targeted fibroid, while avoiding the peritoneal cavity to access the full range of fibroids contained within the myometrium (submucous, transmural, intramural, and subserosal).

THE PATIENT NEED

Women are not satisfied with the current treatment options for symptomatic fibroids. In a national survey, women waited an average of 3.6 years to seek treatment for this condition. Most women want to avoid invasive surgery and desire a uterus-preserving treatment irrespective of their desire for childbearing.[1]



[1] Borah, BJ, Nicholson WK, Bradley L, Stewart EA. The impact of uterine leiomyomas: a national survey of affected women. *Am J Obstet Gynecol.* 2013;209:219.e1-20

II: SUMMARIES OF PEER-REVIEWED CLINICAL AND HEALTH ECONOMIC PUBLICATIONS

The following publications in support of transcervical fibroid ablation with the Sonata System are summarized on the following pages.

SONATA Pivotal FDA IDE Clinical Trial: 12-month Results	Chudnoff S, Guido R, Roy K, Levine D, Mihalov L, Garza-Leal JG. Ultrasound-Guided Transcervical Ablation of Uterine Leiomyomas. *Obstet Gynecol*. 2019;133:13-22.
SONATA Pivotal FDA IDE Clinical Trial: 2-year Results	Miller CE, Osman KM. Transcervical Radiofrequency Ablation of Symptomatic Uterine Fibroids: 2-Year Results. *J Gynecol Surg.* 2019;35:345-349.
SONATA Pivotal FDA IDE Clinical Trial: 3-year Results	Lukes A, Green MA. Three-Year Results of the SONATA Pivotal Trial of Transcervical Fibroid Ablation for Symptomatic Uterine Myomata. *J Gynecol* Surg. 2020;36:5, 228-233.
CHOICES Comparative Trial: Sonata vs. Myomectomy	Brooks E, Singer A, Delvadia D et al. The CHOICES Study: Facility Level Comparative Cost, Resource Utilization, and Outcomes Analysis of Myomectomy Compared to Transcervical Fibroid Ablation. *ClinicoEconomics and Outcomes Research.* 2020;299-306.
FAST-EU Clinical Trial: 12-month Results	Brölmann H, Bongers M, Garza-Leal JG et al. The FAST-EU trial: 12-month clinical outcomes of women after intra-uterine sonography-guided transcervical radiofrequency ablation of uterine fibroids. *Gynecol Surg*. 2016;13:27-35.
VITALITY Clinical Study: 5-year Long-Term Clinical Outcomes	Garza-Leal JG. Long-Term Clinical Outcomes of Transcervical Radiofrequency Ablation of Uterine Fibroids: The VITALITY Study. *J Gynecol Surgery*. 2019;35:19-23.
Systematic Review of Non-Resective Treatments of Uterine and Fibroid Volume Reductions	Taheri M, Galo L, Potts C, Sakhel K, Quinn SD. Nonresective treatments for uterine fibroids: a systematic review of uterine and fibroid volume reductions. *Int J Hyperthermia*. 2019;36: 295-301.
Systematic Review and Meta-Analysis of Radiofrequency Ablation of Uterine Fibroids	Bradley LD, Pasic RP, Miller LE. Clinical Performance of Radiofrequency Ablation for Treatment of Uterine Fibroids: Systematic Review and Meta-Analysis of Prospective Studies. *J Laparoendosc Adv Surg Tech. 2019; 29:1507-1517.*
OPEN Clinical Trial: Evaluation of Uterine Patency following TFA with Sonata	Bongers M, Quinn SD, Mueller MD et al. Evaluation of uterine patency following transcervical uterine fibroid ablation with the Sonata system (the OPEN clinical trial). *Eur J Obstet Gynecol Reprod Biol*. 2019;242:122-125.
INSPIRE Health Economics Outcomes Research (HEOR) Payer Cost Study	Brooks E, Mihalov L, Delvadia D et al. The INSPIRE Comparative Cost Study: 12-Month Health Economic and Clinical Outcomes Associated with Hysterectomy, Myomectomy, and Treatment with the Sonata System. *ClinicoEconomics and Outcomes Research*. 2020;1-11.
COMPARE Health Economics Outcomes Research (HEOR) Facility Cost Study	Brooks E, Mihalov L, Delvadia D et al. The COMPARE Study: Facility Costs Associated with Hysterectomy, Myomectomy, and the Sonata Procedure for Treatment of Uterine Fibroids. *Managed Care*. 2019;40-45.
Health Utility After Radiofrequency Ablation	Huirne J, Brooks E. Improvement in health utility after transcervical radiofrequency ablation of uterine fibroids with the sonata system: Health utility after radiofrequency ablation. *Eur J Obstet Gynecol Reprod Biol.* 2018;224:175-180.

SONATA PIVOTAL FDA IDE CLINICAL TRIAL: 12-MONTH RESULTS

Chudnoff S, Guido R, Roy K, Levine D, Mihalov L, Garza-Leal JG. Ultrasound-Guided Transcervical Ablation of Uterine Leiomyomas. *Obstet Gynecol.* 2019; 133:13-22

OBJECTIVE	To evaluate the 12-month safety and effectiveness of transcervical fibroid ablation (TFA) with the Sonata System for the treatment of symptomatic uterine leiomyomas.
TRIAL DESIGN	Prospective, controlled, longitudinal, multicenter, single-arm interventional trial. Patients treated on an outpatient basis with follow-up of 3 years.
ENDPOINTS	• Surgical reintervention for heavy menstrual bleeding • Reduction in menstrual bleeding • Treatment satisfaction and symptom improvement • Quality of life and symptom severity measures • Reduction in work and activity impairment • Safety
N=	147 patients enrolled at 22 centers
RESULTS/ CONCLUSIONS	• 442 fibroids treated (mean 3.0 fibroids ablated per patient) • Mean Procedure Time (from device insertion to device removal) = 47 minutes • Mean Length of Stay (from device insertion to time of discharge) = 2.5 hours TFA with the Sonata System resulted in a significant reduction in leiomyoma symptoms with no device-related adverse events and a low surgical reintervention rate through 12 months, demonstrating its safety and effectiveness in treating all nonpedunculated fibroids through a uterus-conserving, incisionless approach.

Leiomyomas: *Original Research*

Ultrasound-Guided Transcervical Ablation of Uterine Leiomyomas

Scott Chudnoff, MD, MS, Richard Guido, MD, Kelly Roy, MD, David Levine, MD, Linda Mihalov, MD, and José Gerardo Garza-Leal, MD

OBJECTIVE: To evaluate the 12-month safety and effectiveness of transcervical ablation for the treatment of symptomatic uterine leiomyomas.

METHODS: In this prospective, multicenter, single-arm interventional trial, transcervical ablation was performed on 1–10 leiomyomas per patient with leiomyoma diameters ranging from 1 to 5 cm. Treated leiomyomas included all nonpedunculated types. Coprimary endpoints assessed at 12 months were reduction in menstrual blood loss and absence of surgical reintervention. Additional assessments included symptom severity, quality of life, patient satisfaction, reductions in uterine and leiomyoma volumes, and safety.

RESULTS: One hundred forty-seven patients were enrolled and treated in the United States and Mexico. The study met its coprimary endpoints at 12 months (N=143; full analysis set), because 64.8% of patients (95% CI 56.3–72.6%) experienced 50% or greater reduction in menstrual bleeding and 99.3% of patients (95% CI 95.1–99.9%) were free from surgical reintervention. The mean pictorial blood loss assessment chart score decreased by 38.9%, 48.4%, and 51.1% at 3, 6, and 12 months, respectively ($P<.001$), and 95.1% of patients experienced a reduction in menstrual bleeding at 12 months. There were significant mean improvements in symptom severity and health-related quality of life of 32.1 points and 43.7 points, respectively, at 12 months (all $P<.001$). Mean maximal leiomyoma volume reduction per patient was 62.4% ($P<.001$). More than half of patients returned to normal activity within 1 day, 96.3% of patients reported symptom improvement at 12 months, and 97% expressed satisfaction with the treatment at 12 months. There were no device-related adverse events.

CONCLUSION: Transcervical ablation was associated with a significant reduction in leiomyoma symptoms with no device-related adverse events and a low surgical reintervention rate through 12 months, demonstrating its potential to safely and effectively treat all nonpedunculated leiomyoma types through a uterus-conserving, incisionless approach.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT02228174.

Funding Source: Supported by Gynesonics, Inc.

(Obstet Gynecol 2019;00:1–10)

DOI: 10.1097/AOG.0000000000003032

Uterine leiomyomas are highly prevalent and, when symptomatic, may be treated with a variety of options such as hormonal manipulation, uterine artery embolization, myomectomy, or definitive hys-

From the Stanford Hospital, Stamford, Connecticut; Magee-Women's Hospital, Pittsburgh, Pennsylvania; Arizona Gynecology Consultants, Phoenix, Arizona; Mercy Hospital, St. Louis, Missouri; Virginia Mason Medical Center, Seattle, Washington; and Hospital Universitario "Dr. José Eleuterio González" de Universidad Autónoma de Nuevo León, Monterrey, NL, Mexico.

The institutions involved in this study received research support from Gynesonics, Inc.

The authors thank David Trad, MD, MBA, Medical Director of Gynesonics, Inc., and Taraneh G. Farazi, PhD, Vice-President of Clinical Affairs at Gynesonics, for contributing to the preparation and review of the manuscript. QST Consultations, LTD provided biostatistical analysis for this study.

Each author has confirmed compliance with the journal's requirements for authorship.

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Financial Disclosure

Scott Chudnoff, Richard Guido, Linda Mihalov, and José Gerardo Garza-Leal have served on the Gynesonics, Inc. advisory board. Scott Chudnoff received travel and lodging expenses for attendance at an investigator meeting and has received honoraria for speaking from Gynesonics, Inc. Kelly Roy has received royalties from CrossBay Medical, Inc. and stock options from Channel Medical, Inc. and has served as a consultant for Boston Scientific, Inc. David Levine has been a consultant for Gynesonics and a consultant for Aegea Medical. Linda Mihalov has also served on the advisory board for Abbvie. José Gerardo Garza-Leal has received a stock option grant from Gynesonics, Inc. Scott Chudnoff, Richard Guido, Kelly Roy, David Levine, and Linda Mihalov serve on the Sonography Guided Transcervical Ablation of Uterine Fibroids study steering committee.

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Highlights of patient outcomes at 12 months:

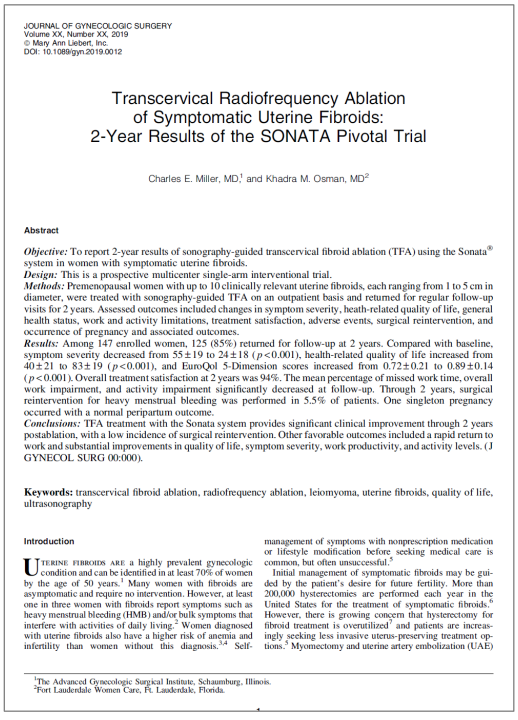
- 99% free from surgical reintervention *(0.7% surgical reintervention rate for heavy menstrual bleeding)*
- 95% experienced a reduction in their menstrual bleeding *(65% reported ≥50% reduction)*
- 97% of women were satisfied with their treatment
- 96% reported symptom improvement
- No device-related adverse events
- 50% of women returned to normal activity by the next day

NOTEWORTHY POINT: The trial included women with heavy menstrual bleeding whose most indenting fibroid was a type 3 fibroid. At 12 months, these patients had treatment effectiveness similar to the overall study population. This suggests a possible association of type 3 fibroids with heavy menstrual bleeding.

SONATA PIVOTAL FDA IDE CLINICAL TRIAL: 2-YEAR RESULTS

Miller CE, Osman KM. Transcervical Radiofrequency Ablation of Symptomatic Uterine Fibroids: 2-Year Results of the SONATA Pivotal Trial. *J Gynecol Surg.* 2019;35:345-349.

OBJECTIVE	To evaluate the 2-year safety and effectiveness of transcervical fibroid ablation (TFA) with the Sonata System for the treatment of symptomatic uterine leiomyomas.
TRIAL DESIGN	Prospective, controlled, longitudinal, multicenter, single-arm interventional trial. Patients treated on an outpatient basis with follow-up of 3 years.
2-YEAR ENDPOINTS	• Surgical reintervention for heavy menstrual bleeding • Treatment satisfaction and symptom improvement • Quality of life and symptom severity measures • Reduction in work and activity impairment • Safety
N=	125 of the enrolled 147 patients were accounted for in 2-year follow-up
CONCLUSIONS	TFA treatment with the Sonata System provides significant clinical improvement through 2 years post-ablation with a low incidence of surgical reintervention. Other favorable outcomes included substantial improvements in quality of life, symptom severity, work productivity, activity levels, and patient satisfaction.



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Transcervical Radiofrequency Ablation of Symptomatic Uterine Fibroids: 2-Year Results of the SONATA Pivotal Trial

Charles E. Miller, MD,[1] and Khadra M. Osman, MD[2]

Abstract

Objective: To report 2-year results of sonography-guided transcervical fibroid ablation (TFA) using the Sonata® system in women with symptomatic uterine fibroids.
Design: This is a prospective multicenter single-arm interventional trial.
Methods: Premenopausal women with up to 10 clinically relevant uterine fibroids, each ranging from 1 to 5 cm in diameter, were treated with sonography-guided TFA on an outpatient basis and returned for regular follow-up visits for 2 years. Assessed outcomes included changes in symptom severity, heath-related quality of life, general health status, work and activity limitations, treatment satisfaction, adverse events, surgical reintervention, and occurrence of pregnancy and associated outcomes.
Results: Among 147 enrolled women, 125 (85%) returned for follow-up at 2 years. Compared with baseline, symptom severity decreased from 55±19 to 24±18 ($p<0.001$), health-related quality of life increased from 40±21 to 83±19 ($p<0.001$), and EuroQol 5-Dimension scores increased from 0.72±0.21 to 0.89±0.14 ($p<0.001$). Overall treatment satisfaction at 2 years was 94%. The mean percentage of missed work time, overall work impairment, and activity impairment significantly decreased at follow-up. Through 2 years, surgical reintervention for heavy menstrual bleeding was performed in 5.5% of patients. One singleton pregnancy occurred with a normal peripartum outcome.
Conclusions: TFA treatment with the Sonata system provides significant clinical improvement through 2 years postablation, with a low incidence of surgical reintervention. Other favorable outcomes included a rapid return to work and substantial improvements in quality of life, symptom severity, work productivity, and activity levels. (J GYNECOL SURG 00:000).

Keywords: transcervical fibroid ablation, radiofrequency ablation, leiomyoma, uterine fibroids, quality of life, ultrasonography

Introduction

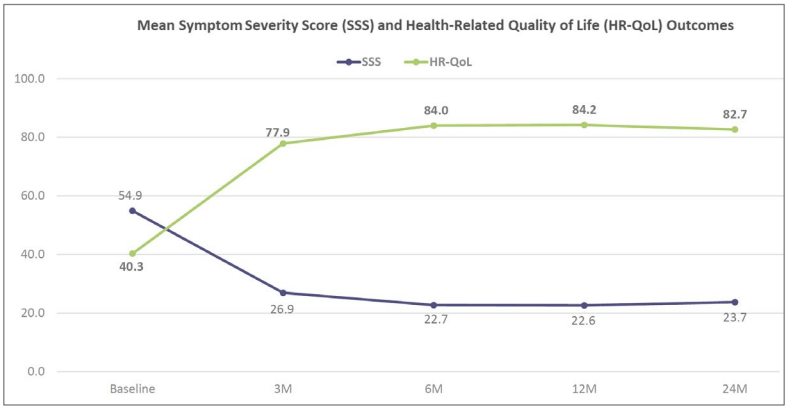
UTERINE FIBROIDS ARE a highly prevalent gynecologic condition and can be identified in at least 70% of women by the age of 50 years.[1] Many women with fibroids are asymptomatic and require no intervention. However, at least one in three women with fibroids report symptoms such as heavy menstrual bleeding (HMB) and/or bulk symptoms that interfere with activities of daily living.[2] Women diagnosed with uterine fibroids also have a higher risk of anemia and infertility than women without this diagnosis.[3,4] Self-management of symptoms with nonprescription medication or lifestyle modification before seeking medical care is common, but often unsuccessful.[5]

Initial management of symptomatic fibroids may be guided by the patient's desire for future fertility. More than 200,000 hysterectomies are performed each year in the United States for the treatment of symptomatic fibroids.[6] However, there is growing concern that hysterectomy for fibroid treatment is overutilized[7] and patients are increasingly seeking less invasive uterus-preserving treatment options.[8] Myomectomy and uterine artery embolization (UAE)

[1]The Advanced Gynecologic Surgical Institute, Schaumburg, Illinois.
[2]Fort Lauderdale Women Care, Ft. Lauderdale, Florida.

Highlights of patient outcomes at 2 years:

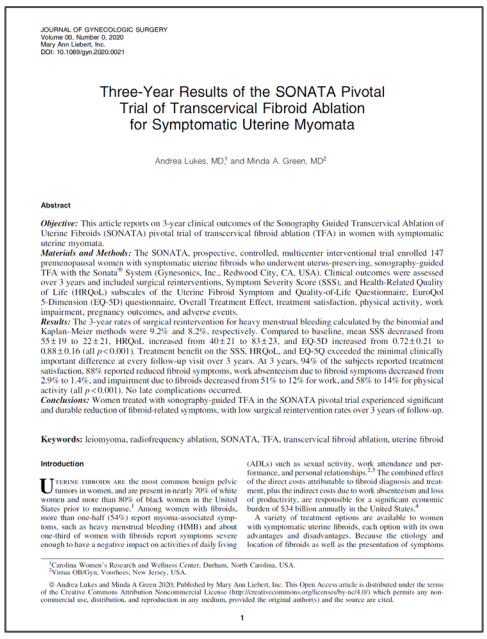
- 95% free from surgical reintervention *(5% surgical reintervention rate for heavy menstrual bleeding)*
- 94% of women were satisfied with their treatment
- Significant reduction in activity impairment due to fibroid symptoms; work productivity increased
- Improvements in Symptom Severity and Quality of Life scores realized at 3 months continued to increase and were sustained through 2 years



SONATA PIVOTAL FDA IDE CLINICAL TRIAL: 3-YEAR RESULTS

Lukes A, Green MA. Three-Year Results of the SONATA Pivotal Trial of Transcervical Fibroid Ablation for Symptomatic Uterine Myomata. J Gynecol Surg. 2020;36:5, 228-233.

OBJECTIVE	To evaluate the 3-year safety and effectiveness of transcervical fibroid ablation (TFA) with the Sonata System for the treatment of symptomatic uterine leiomyomas.
TRIAL DESIGN	Prospective, controlled, longitudinal, multicenter, single-arm interventional trial. Patients treated on an outpatient basis with follow-up of 3 years.
3-YEAR ENDPOINTS	• Surgical reintervention for heavy menstrual bleeding • Treatment satisfaction and symptom improvement • Quality of life and symptom severity measures • Reduction in work and activity impairment • Safety
N=	132 of the enrolled 147 patients (90%) were accounted for in 3-year follow-up
CONCLUSIONS	Women treated with TFA in the SONATA Pivotal Trial experienced significant and durable improvement in fibroid-related symptoms with low surgical reintervention rates over 3 years of follow-up.



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Three-Year Results of the SONATA Pivotal Trial of Transcervical Fibroid Ablation for Symptomatic Uterine Myomata

Andrea Lukes, MD,[1] and Minda A. Green, MD[2]

Abstract

Objective: This article reports on 3-year clinical outcomes of the Sonography Guided Transcervical Ablation of Uterine Fibroids (SONATA) pivotal trial of transcervical fibroid ablation (TFA) in women with symptomatic uterine myomata.
Materials and Methods: The SONATA, prospective, controlled, multicenter interventional trial enrolled 147 premenopausal women with symptomatic uterine fibroids who underwent uterus-preserving, sonography-guided TFA with the Sonata® System (Gynesonics, Inc., Redwood City, CA, USA). Clinical outcomes were assessed over 3 years and included surgical reinterventions, Symptom Severity Score (SSS), and Health-Related Quality of Life (HRQoL) subscales of the Uterine Fibroid Symptom and Quality-of-Life Questionnaire, EuroQol 5-Dimension (EQ-5D) questionnaire, Overall Treatment Effect, treatment satisfaction, physical activity, work impairment, pregnancy outcomes, and adverse events.
Results: The 3-year rates of surgical reintervention for heavy menstrual bleeding calculated by the binomial and Kaplan–Meier methods were 9.2% and 8.2%, respectively. Compared to baseline, mean SSS decreased from 55±19 to 22±21, HRQoL increased from 40±21 to 83±23, and EQ-5D increased from 0.72±0.21 to 0.88±0.16 (all $p<0.001$). Treatment benefit on the SSS, HRQoL, and EQ-5Q exceeded the minimal clinically important difference at every follow-up visit over 3 years. At 3 years, 94% of the subjects reported treatment satisfaction, 88% reported reduced fibroid symptoms, work absenteeism due to fibroid symptoms decreased from 2.9% to 1.4%, and impairment due to fibroids decreased from 51% to 12% for work, and 58% to 14% for physical activity (all $p<0.001$). No late complications occurred.
Conclusions: Women treated with sonography-guided TFA in the SONATA pivotal trial experienced significant and durable reduction of fibroid-related symptoms, with low surgical reintervention rates over 3 years of follow-up.

Keywords: leiomyoma, radiofrequency ablation, SONATA, TFA, transcervical fibroid ablation, uterine fibroid

Introduction

UTERINE FIBROIDS ARE the most common benign pelvic tumors in women, and are present in nearly 70% of white women and more than 80% of black women in the United States prior to menopause.[1] Among women with fibroids, more than one-half (54%) report myoma-associated symptoms, such as heavy menstrual bleeding (HMB) and about one-third of women with fibroids report symptoms severe enough to have a negative impact on activities of daily living (ADLs) such as sexual activity, work attendance and performance, and personal relationships.[2,3] The combined effect of the direct costs attributable to fibroid diagnosis and treatment, plus the indirect costs due to work absenteeism and loss of productivity, are responsible for a significant economic burden of $34 billion annually in the United States.[4]
A variety of treatment options are available to women with symptomatic uterine fibroids, each option with its own advantages and disadvantages. Because the etiology and location of fibroids as well as the presentation of symptoms

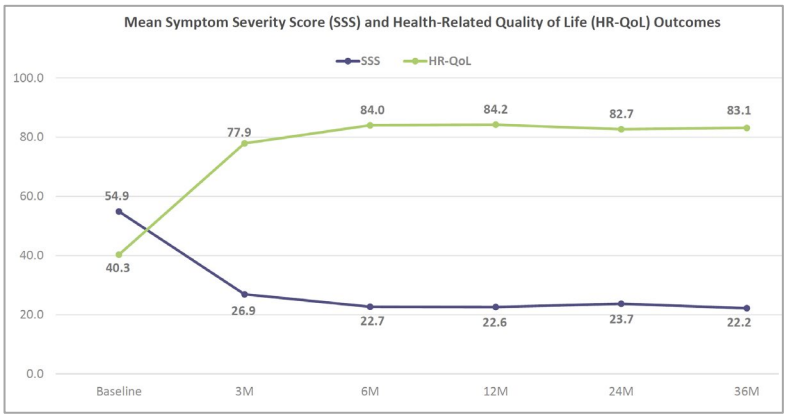
[1]Carolina Women's Research and Wellness Center, Durham, North Carolina, USA.
[2]Virtua OB/Gyn, Voorhees, New Jersey, USA.

1

Highlights of patient outcomes at 3 years:

- 92% free from surgical reintervention *(8% surgical reintervention rate for heavy menstrual bleeding)*
- 94% of women were satisfied with their treatment
- Significant improvements in Symptom Severity and Quality of Life scores realized at 3 months continued to increase and were sustained through 3 years ($p<0.001$)
- No device-related adverse events

Timepoint	Cumulative Surgical Reinterventions	Cumulative Surgical Reintervention Rate (Kaplan-Meier)
1 Year	1	0.7%
2 Year	7	5.0%
3 Year	11	8.2%



CHOICES COMPARATIVE TRIAL: SONATA VS MYOMECTOMY

Brooks E, Singer A, Delvadia D et al. The CHOICES Study: Facility Level Comparative Cost, Resource Utilization, and Outcomes Analysis of Myomectomy Compared to Transcervical Fibroid Ablation. *ClinicoEconomics and Outcomes Research.* 2020;299-306.

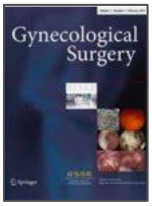
Abstract also accepted to ISPOR Journal *Value in Health* DOI: 2020.04.614
ISPOR is the leading global scientific and educational organization for health economics and outcomes research.

OBJECTIVE	To compare short-term resource utilization, facility costs, and perioperative patient outcomes between transcervical fibroid ablation (TFA) with the Sonata System and myomectomy for the treatment of symptomatic uterine fibroids.
TRIAL DESIGN	Retrospective, facility-level, case-matched comparator cost analysis using patients treated in the SONATA Pivotal IDE Trial compared to myomectomy patients at the same 4 centers. Facility costs were derived from the institution billing forms and healthcare provider billing forms contributed by the centers for each procedure.
ENDPOINTS	▪ Operating Room (OR) duration, defined as time entered to time left the OR ▪ Length of stay (LOS), defined as time of admission to time of discharge ▪ Facility costs including anesthesia, laboratory, pathology, pharmacy costs and any 30-day readmissions
N=	TFA=44; Myomectomy=44
CONCLUSIONS:	TFA with the Sonata System has a significantly shorter OR duration and LOS than myomectomy for the treatment of symptomatic uterine fibroids. All procedure, anesthesia, laboratory, pathology, and pharmacy costs were significantly higher for myomectomy as compared to treatment with the Sonata System. TFA was also associated with significantly lower facility procedure-related costs compared to inpatient, abdominal, or laparoscopic myomectomy.

Outcomes Measure	TFA (Sonata)	Myomectomy
Mean OR Duration	**90 min**	143 min
Mean LOS	**5 hours**	46 hours
Mean Facility Costs	**$7,563**	$11,425

Highlights:

- TFA has significantly shorter OR duration and LOS than myomectomy leading to a decrease in overall facility costs associated with the procedure
- All procedure, anesthesia, laboratory, pathology, and pharmacy costs were significantly higher for myomectomy compared to treatment with the Sonata System
- TFA with the Sonata System was associated with significantly lower facility procedure-related costs compared to inpatient, abdominal, or laparoscopic myomectomy



FAST-EU CLINICAL TRIAL: 12-MONTH RESULTS

Brölmann H, Bongers M, Garza-Leal J, Gupta J, et al. The FAST-EU trial: 12-month clinical outcomes of women after intrauterine sonography-guided transcervical radiofrequency ablation of uterine fibroids. *Gynecol Surg.* 2016; 13:27-35.

OBJECTIVE	To evaluate safety and effectiveness of sonography-guided transcervical fibroid ablation (TFA) with the Sonata System (formerly named VizAblate) in women with symptomatic uterine fibroids.
TRIAL DESIGN	Multicenter, prospective, single-arm trial with independent reviewers. Follow-up at 3, 6, and 12 months.
ENDPOINTS	• Surgical reintervention for heavy menstrual bleeding • Reduction in menstrual bleeding • Patient satisfaction • Reduction in fibroid volume • Safety
N=	50 patients at 7 sites in Europe and Mexico
CONCLUSIONS:	Patients realized significant reductions in perfused and total fibroid volume, menstrual bleeding, overall symptoms, and improvements in quality of life. In addition, results suggest that TFA with the Sonata System is safe and effective through 12 months in relief of abnormal bleeding associated with submucous, intramural, and transmural fibroids.

Gynecol Surg (2016) 13:27–35
DOI 10.1007/s10397-015-0915-3

ORIGINAL ARTICLE

The FAST-EU trial: 12-month clinical outcomes of women after intrauterine sonography-guided transcervical radiofrequency ablation of uterine fibroids

Hans Brölmann[1] · Marlies Bongers[2] · José Gerardo Garza-Leal[3] · Janesh Gupta[4] · Sebastiaan Veersema[5] · Rik Quartero[6] · David Toub[7,8]

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Abstract The FAST-EU Trial was designed to establish the effectiveness and confirm the safety of transcervical intrauterine sonography-guided radiofrequency ablation with the VizAblate™ System in the treatment of symptomatic uterine fibroids. This was a multicenter, prospective, single-arm trial involving academic and community hospitals in the United Kingdom, the Netherlands, and Mexico. Women with qualifying uterine fibroids and heavy menstrual bleeding underwent intrauterine sonography-guided transcervical radiofrequency ablation (RFA) with the VizAblate System; anesthesia was individualized. Patients were required to have up to five fibroids from 1 to 5 cm in diameter. The primary trial endpoint was the percentage change in perfused fibroid volume, as assessed by contrast-enhanced MRI at 3 months by an independent core laboratory. Secondary endpoints, evaluated at 6 and 12 months, included safety, percentage reductions in the Menstrual Pictogram (MP) score, and the Symptom Severity Score (SSS) subscale of the Uterine Fibroid Symptom-Quality of Life (UFS-QOL) questionnaire, along with the rate of surgical reintervention for abnormal uterine bleeding and the mean number of days to return to normal activity. Additional assessments included the Health-Related Quality of Life (HRQOL) subscale of the UFS-QOL, nonsurgical reintervention for abnormal uterine bleeding, anesthesia regimen, patient satisfaction, and pain during the recovery period. An additional MRI study was performed at 12 months on a subgroup of patients. Fifty patients (89 fibroids) underwent transcervical radiofrequency ablation with the VizAblate System. At 3 and 12 months, perfused fibroid volumes were reduced from baseline by an average of 68.1±28.6 and 67.4±31.9 %, respectively, while total fibroid volumes were reduced from baseline by an average of 54.7±37.4 and 66.6±32.1 %, respectively (all $P<.001$ compared with baseline; Wilcoxon signed-rank test). At 12 months, mean MP score and SSS decreased by 53.8± 50.5 and 55.1±41.0 %, respectively; the mean HRQOL score increased by 277±483 %. There were four surgical reinterventions (8 %) within 12 months. This is the first report of the 12-month follow-up for patients in the FAST-EU Trial. In concert with previously reported 3- and 6-month endpoint data, the 12-month results of the FAST-EU Trial suggest that in addition to substantially reducing the perfused and total volume of targeted uterine fibroids, the VizAblate System is safe and effective through 12 months in providing relief of abnormal uterine bleeding associated with submucous, intramural, and transmural fibroids.

Keywords Fibroids · Radiofrequency ablation · VizAblate · Intrauterine sonography · Ultrasound

Introduction

Uterine fibroids are highly prevalent and the primary indication for over 200,000 hysterectomies performed annually in

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2 Máxima Medisch Centrum, Veldhoven, Netherlands
3 Universidad Autónoma de Nuevo León, Monterey, Nuevo Leon, Mexico
4 Birmingham Women's Hospital, Birmingham, UK
5 Sint Antonius Ziekenhuis, Nieuwegein, Netherlands
6 Medisch Spectrum Twente, Enschede, Netherlands
7 Gynesonics, Inc., Redwood City, CA 94063, USA
8 Albert Einstein Medical Center, 5501 Old York Road, Philadelphia, PA 19141, USA

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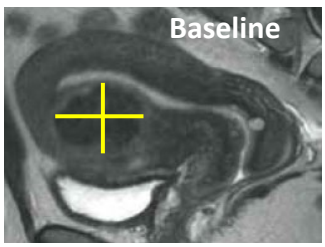
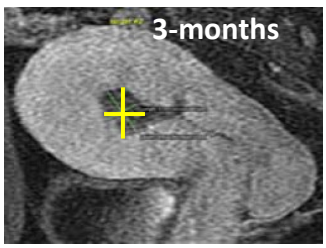
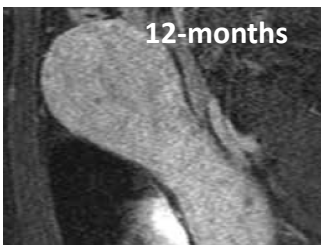
Highlights of patient outcomes at 12 months:

- 92% free from surgical reintervention *(8% surgical reintervention rate for heavy menstrual bleeding)*
- 90% experienced a reduction in menstrual bleeding as reflected by their MP scores at 3 months, with an average reduction of 54% at 12 months *(65% had >50 % reduction in MP scores at 12 months)*
- 88% overall patient satisfaction
- 67% mean reduction in fibroid volume *(73% median reduction)*; Significant reductions in both perfused and total fibroid volume
- Patients experienced a 55% reduction in symptom severity (SSS) at 12 months from baseline and had a 277% increase in quality of life (HR-QoL), all statistically significant at $p<0.001$)
- No device-related adverse events





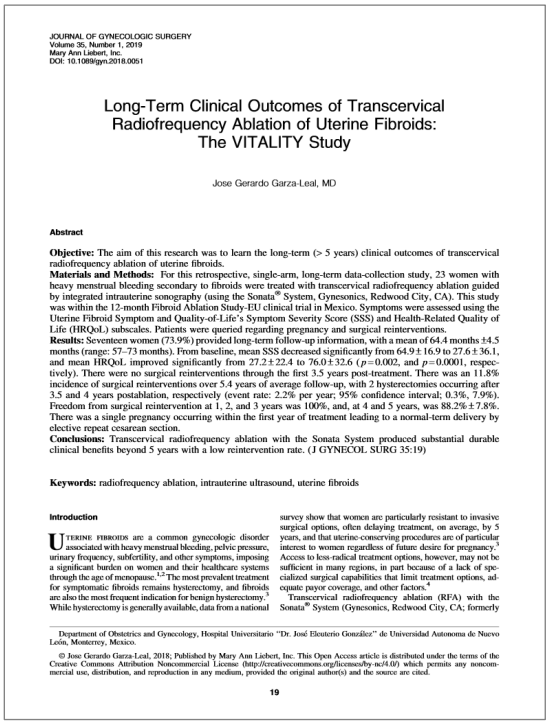


Time Course Series:
MRI demonstrating fibroid reduction over time.

VITALITY STUDY: 5-YEAR LONG-TERM CLINICAL OUTCOMES

Garza-Leal JG. Long-Term Clinical Outcomes of Transcervical Radiofrequency Ablation of Uterine Fibroids: The VITALITY Study. *Journal of Gynecologic Surg.* 2019; 35:19-23.

OBJECTIVE	To evaluate the long-term (>5-year) clinical outcomes of transcervical radiofrequency ablation of uterine fibroids (TFA) with the Sonata System.
STUDY DESIGN	Retrospective, single-site, single-arm clinical study using patient cohort from FAST-EU Trial.
ENDPOINTS	• Surgical reintervention for heavy menstrual bleeding • Quality of life measures
N=	17 patients
CONCLUSIONS	TFA with the Sonata System produced substantial durable clinical benefits beyond 5 years with a low surgical reintervention rate.



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Long-Term Clinical Outcomes of Transcervical Radiofrequency Ablation of Uterine Fibroids: The VITALITY Study

Jose Gerardo Garza-Leal, MD

Abstract

Objective: The aim of this research was to learn the long-term (> 5 years) clinical outcomes of transcervical radiofrequency ablation of uterine fibroids.
Materials and Methods: For this retrospective, single-arm, long-term data-collection study, 23 women with heavy menstrual bleeding secondary to fibroids were treated with transcervical radiofrequency ablation guided by integrated intrauterine sonography (using the Sonata® System, Gynesonics, Redwood City, CA). This study was within the 12-month Fibroid Ablation Study-EU clinical trial in Mexico. Symptoms were assessed using the Uterine Fibroid Symptom and Quality-of-Life's Symptom Severity Score (SSS) and Health-Related Quality of Life (HRQoL) subscales. Patients were queried regarding pregnancy and surgical reinterventions.
Results: Seventeen women (73.9%) provided long-term follow-up information, with a mean of 64.4 months ±4.5 months (range: 57–73 months). From baseline, mean SSS decreased significantly from 64.9 ± 16.9 to 27.6 ± 36.1, and mean HRQoL improved significantly from 27.2 ± 22.4 to 76.0 ± 32.6 ($p = 0.002$, and $p = 0.0001$, respectively). There were no surgical reinterventions through the first 3.5 years post-treatment. There was an 11.8% incidence of surgical reinterventions over 5.4 years of average follow-up, with 2 hysterectomies occurring after 3.5 and 4 years postablation, respectively (event rate: 2.2% per year; 95% confidence interval; 0.3%, 7.9%). Freedom from surgical reintervention at 1, 2, and 3 years was 100%, and, at 4 and 5 years, was 88.2% ± 7.8%. There was a single pregnancy occurring within the first year of treatment leading to a normal-term delivery by elective repeat cesarean section.
Conclusions: Transcervical radiofrequency ablation with the Sonata System produced substantial durable clinical benefits beyond 5 years with a low reintervention rate. (J GYNECOL SURG 35:19)

Keywords: radiofrequency ablation, intrauterine ultrasound, uterine fibroids

Introduction

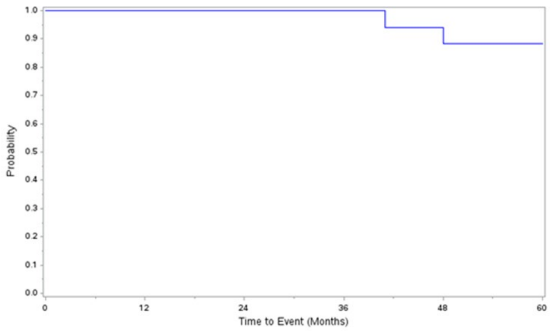
Uterine fibroids are a common gynecologic disorder associated with heavy menstrual bleeding, pelvic pressure, urinary frequency, subfertility, and other symptoms, imposing a significant burden on women and their healthcare systems through the age of menopause.[1,2] The most prevalent treatment for symptomatic fibroids remains hysterectomy, and fibroids are also the most frequent indication for benign hysterectomy.[3] While hysterectomy is generally available, data from a national survey show that women are particularly resistant to invasive surgical options, often delaying treatment, on average, by 5 years, and that uterine-conserving procedures are of particular interest to women regardless of future desire for pregnancy.[4] Access to less-radical treatment options, however, may not be sufficient in many regions, in part because of a lack of specialized surgical capabilities that limit treatment options, adequate payor coverage, and other factors.[4]

Transcervical radiofrequency ablation (RFA) with the Sonata® System (Gynesonics, Redwood City, CA; formerly

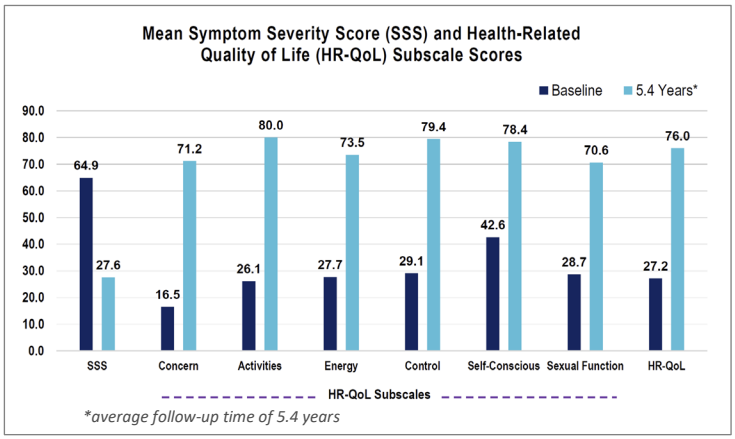
Department of Obstetrics and Gynecology, Hospital Universitario "Dr. José Eleuterio González" de Universidad Autonoma de Nuevo León, Monterrey, Mexico.

Highlights:

- 0% surgical reintervention for heavy menstrual bleeding in the first 3.5 years
- 11.8% cumulative reintervention rate over a mean 5.4 years of follow-up
- Significant improvements in mean Symptom Severity Scores (SSS) and Health-Related Quality of Life (HR-QoL) measures beyond 5 years



Kaplan–Meier survival curve for surgical reintervention after treatment with the Sonata System.



*average follow-up time of 5.4 years

SYSTEMATIC REVIEW OF NON-RESECTIVE TREATMENTS OF UTERINE AND FIBROID VOLUME REDUCTIONS

Taheri M, Galo L, Potts C, Sakhel K, Quinn SD. Nonresective treatments for uterine fibroids: a systematic review of uterine and fibroid volume reductions. *Int J Hyperthermia*. 2019;36(1):295-301.

OBJECTIVE	Compare and contrast the existing literature on fibroid and uterine volume changes among current non-resective uterus-sparing treatment modalities: radiofrequency ablation (RFA), uterine artery embolization (UAE), and focused ultrasound (FUS).
STUDY DESIGN	PubMed and MedlinePlus databases were searched from October 1956 to September 2016. Publications with >20 patients were included. Measurements by ultrasound scan, MRI, or CT scan were analyzed together to gather the uterine volume and fibroid volume changes seen in these studies up to 36 months.
OUTCOMES FOR ANALYSIS	• Changes in uterine volume • Changes in fibroid volume
N=	81 total articles: 11 related to RFA, 52 to UAE and 17 to FUS
CONCLUSIONS	All three types of non-resective treatment result in fibroid volume reduction. Fibroid volume reduction is most marked with RFA .

INTERNATIONAL JOURNAL OF HYPERTHERMIA

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Nonresective treatments for uterine fibroids: a systematic review of uterine and fibroid volume reductions

Melody Taheri[a], Laura Galo[b], Callum Potts[b], Khaled Sakhel[b] and Stephen Derek Quinn[a]

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ABSTRACT

Patients are increasingly seeking uterus-preserving, minimally invasive treatments for symptomatic uterine fibroids. This has led to a greater use of nonresective treatments such as uterine artery embolization (UAE), focused ultrasound (FUS) and more recently, radiofrequency ablation (RFA) of fibroids. This systematic review, following PRISMA guidelines, examines the change in uterine and fibroid volumes associated with UAE, FUS, and RFA. Pubmed and MedlinePlus databases were searched from 1956 to 2016. The keywords used were 'radiofrequency ablation,' 'magnetic resonance guided focused ultrasound,' 'ultrasound guided focused ultrasound', 'uterine artery embolization,' 'uterine fibroid embolization,' and 'leiomyoma' or 'fibroid'. Publications with at least 20 patients were included. Data were collected and analyzed using Microsoft Excel® (Microsoft Corporation, Redmond, WA) software. Eighty-one relevant papers were identified: 52 related to UAE, 11 to RFA, 17 to FUS, 1 compared UAE and FUS. We report the published uterine volume and fibroid volume changes seen in these studies at 1 to 36-months. The pooled fibroid volume reductions at six months seen with RFA were 70%, UAE 54% and FUS 32%. All three types of nonresective treatment result in fibroid volume reduction. However, fibroid volume reduction is most marked with RFA, with UAE resulting in the next most volume reduction. Additional larger cohort studies, including those that are randomized and/or comparative, would enable definitive conclusions. This is the first systematic review comparing uterine and fibroid volume reduction after RFA, UAE and MRgFUS.

ARTICLE HISTORY
Received 7 October 2018
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KEYWORDS
Radiofrequency ablation; magnetic resonance-guided focused ultrasound; ultrasound-guided focused ultrasound; uterine artery embolization; uterine fibroid embolization; leiomyoma; fibroid; volume

Introduction

Uterine fibroids may be present in over 70% of the premenopausal population [1,2], with a prevalence that increases with age [3]. It is estimated that as many as 50% of leiomyomas are symptomatic [4] and represent the most common indication for hysterectomy in many countries. Fibroids account for approximately 240 000 cases, or 40% of all hysterectomies performed annually in the United States [5] and nearly 20 000 inpatient admissions in the United Kingdom [6]. Uterus-sparing treatment options have been increasing in usage because of many women's desire to preserve fertility and/or their uteri, as well as to avoid major surgery, income, education and insurance type also may play a role in the choice of fibroid treatment [7]. In a prospective study on management options chosen by 933 women with symptomatic leiomyomas, only 16% had hysterectomy, 27% had at least one uterus-sparing procedure, and 57% chose nonprocedural interventions [8].

Uterus-sparing procedures include myomectomy (transabdominal, laparoscopic or hysteroscopic routes), radiofrequency ablation (RFA), uterine artery embolization (UAE), and focused ultrasound (FUS), which can be performed under magnetic resonance guidance (MRgFUS) or ultrasound guidance (USgHIFU). Of note, alternatives to hysterectomy that leave treated fibroids in-situ (e.g., RFA, UAE and FUS) are effective with regard to durable symptom relief if and only if there is some degree of reduction in total fibroid volume [9]. While data from studies involving MRgFUS have suggested that nonperfused volumes >20% are associated with sustained symptom relief at 24 months, it is also expected that higher percentages of fibroid ablation are more likely to result in improved clinical outcomes [10–12]. Similarly, the percentage of fibroid tissue that is infarcted during UAE is also predictive of clinical outcome [13]. With this understanding that greater ablation is associated with higher treatment success, the aim of this systematic review is to compare and contrast the existing literature on fibroid and uterine volume changes among current nonresective uterus-sparing treatment modalities: RFA, UAE and FUS. This is the first systematic review of its kind. There has not previously been a study that collates data from primary studies on fibroid or uterine volume changes with these three uterine sparing, nonresective treatments nor have these modalities been compared to

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Supplemental data for this article can be accessed here.

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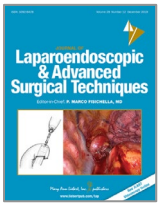
Highlights:

- Transcervical Fibroid Ablation (TFA) with the Sonata System uses radiofrequency ablation (RFA) to treat uterine fibroids
- RFA demonstrates the greatest reduction in fibroid volume compared to UAE and FUS and this pattern was seen consistently at all time points

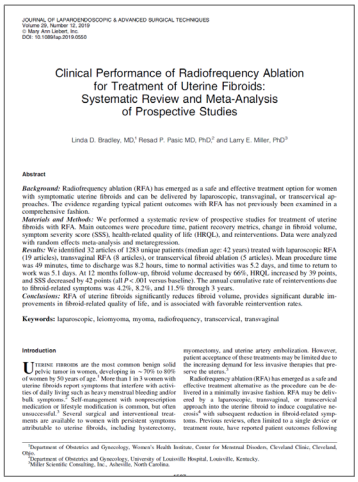
% Pooled Mean Fibroid Volume Reduction	6 months	12 months	24 months	36 months
RFA	**70%**	**75%**	**83%**	**84%**
UAE	54%	66%	70%	--
FUS	32%	28%	34%	32%



SYSTEMATIC REVIEW AND META-ANALYSIS OF RFA FOR UTERINE FIBROIDS

Bradley LD, Pasic RP, Miller LE. Clinical Performance of Radiofrequency Ablation for Treatment of Uterine Fibroids: Systematic Review and Meta-Analysis of Prospective Studies. *J Laparoendosc Adv Surg Tech. 2019; 29:1507-1517.*

OBJECTIVE	To examine the evidence regarding typical patient outcomes with radiofrequency ablation (RFA) including percutaneous laparoscopic, transvaginal, and transcervical (Sonata System) approaches.
STUDY DESIGN	Systematic review of prospective studies for treatment of uterine fibroids with RFA.
OUTCOMES FOR ANALYSIS	• Procedure time • Patient recovery metrics • Change in fibroid volume • Symptom Severity Score (SSS) and Health-Related Quality of Life (HRQL) • Reinterventions
N=	32 articles 1283 unique patients
CONCLUSIONS	Radiofrequency ablation (RFA) of uterine fibroids significantly reduces fibroid volume, provides significant durable improvements in fibroid-related quality of life, and is associated with favorable reintervention rates.



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Clinical Performance of Radiofrequency Ablation for Treatment of Uterine Fibroids: Systematic Review and Meta-Analysis of Prospective Studies

Linda D. Bradley, MD,[1] Resad P. Pasic MD, PhD,[2] and Larry E. Miller, PhD[3]

Abstract

Background: Radiofrequency ablation (RFA) has emerged as a safe and effective treatment option for women with symptomatic uterine fibroids and can be delivered by laparoscopic, transvaginal, or transcervical approaches. The evidence regarding typical patient outcomes with RFA has not previously been examined in a comprehensive fashion.

Materials and Methods: We performed a systematic review of prospective studies for treatment of uterine fibroids with RFA. Main outcomes were procedure time, patient recovery metrics, change in fibroid volume, symptom severity score (SSS), health-related quality of life (HRQL), and reinterventions. Data were analyzed with random effects meta-analysis and metaregression.

Results: We identified 32 articles of 1283 unique patients (median age: 42 years) treated with laparoscopic RFA (19 articles), transvaginal RFA (8 articles), or transcervical fibroid ablation (5 articles). Mean procedure time was 49 minutes, time to discharge was 8.2 hours, time to normal activities was 5.2 days, and time to return to work was 5.1 days. At 12 months follow-up, fibroid volume decreased by 66%, HRQL increased by 39 points, and SSS decreased by 42 points (all $P < .001$ versus baseline). The annual cumulative rate of reinterventions due to fibroid-related symptoms was 4.2%, 8.2%, and 11.5% through 3 years.

Conclusions: RFA of uterine fibroids significantly reduces fibroid volume, provides significant durable improvements in fibroid-related quality of life, and is associated with favorable reintervention rates.

Keywords: laparoscopic, leiomyoma, myoma, radiofrequency, transcervical, transvaginal

Introduction

Uterine fibroids are the most common benign solid pelvic tumor in women, developing in ~70% to 80% of women by 50 years of age.[1] More than 1 in 3 women with uterine fibroids report symptoms that interfere with activities of daily living such as heavy menstrual bleeding and/or bulk symptoms.[2] Self-management with nonprescription medication or lifestyle modification is common, but often unsuccessful.[3] Several surgical and interventional treatments are available to women with persistent symptoms attributable to uterine fibroids, including hysterectomy, myomectomy, and uterine artery embolization. However, patient acceptance of these treatments may be limited due to the increasing demand for less invasive therapies that preserve the uterus.[4]

Radiofrequency ablation (RFA) has emerged as a safe and effective treatment alternative as the procedure can be delivered in a minimally invasive fashion. RFA may be delivered by a laparoscopic, transvaginal, or transcervical approach into the uterine fibroid to induce coagulative necrosis[4] with subsequent reduction in fibroid-related symptoms. Previous reviews, often limited to a single device or treatment route, have reported patient outcomes following

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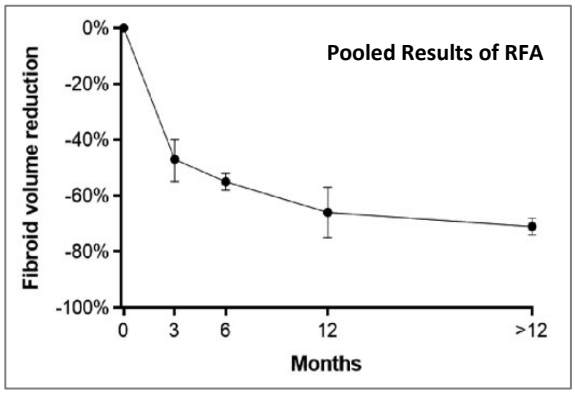
Highlights:

- Regardless of approach, RFA significantly reduces fibroid volume and provides durable improvements in SSS and HRQoL
- RFA is associated with favorable reintervention rates
- Transcervical fibroid ablation with Sonata compares favorably to laparoscopic fibroid ablation

Reported Outcomes	Transcervical approach (Sonata)	Laparoscopic approach
Mean procedure time	**44 min**	73 min
Mean time to discharge	**2.5 hours**	10.7 hours
Mean return to normal activities	**3.3 days**	9.0 days
Mean time to return to work	**3.6 days**	6.5 days



OPEN CLINICAL TRIAL: EVALUATION OF CLINICAL PATENCY FOLLOWING TFA WITH THE SONATA SYSTEM

Bongers M, Quinn S, Mueller M, Bernhard K, et al. Evaluation of Uterine Patency following Transcervical Uterine Fibroid Ablation with the Sonata System (the OPEN Clinical Trial). *Eur J Obstet Gynecol Reprod Biol.* 2019;242:122-125.

OBJECTIVE	To characterize the incidence of new intrauterine adhesions following transcervical fibroid ablation (TFA) with the Sonata System.
TRIAL DESIGN	Post-market, multicenter, prospective, single-arm interventional trial. Baseline and 6-week second-look hysteroscopy videos assessed by independent reviewers.
ENDPOINTS	• Incidence of new adhesions at 6 weeks per European Society of Hysteroscopy adhesion scoring by independent reviewers • Safety
N=	37 patients treated 34 had evaluable baseline and second-look hysteroscopy videos* 50 fibroids treated (including 6 pairs of apposing fibroids at significantly higher risk of adhesiogenesis based on the hysteroscopic myomectomy literature)
CONCLUSIONS:	Intrauterine adhesiogenesis was not seen post-TFA with the Sonata System suggesting that adhesiogenesis after TFA, including in women with apposing submucous and/or transmural myomata, may be minimal.

* 2 patients lost to follow-up and 1 patient with unevaluable hysteroscopy video

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Full length article

Evaluation of uterine patency following transcervical uterine fibroid ablation with the Sonata system (the OPEN clinical trial)

Marlies Bongers[a,b,*], Stephen D. Quinn[c,d], Michael D. Mueller[e], Bernhard Krämer[f], Benjamin Tuschy[g], Marc Sütterlin[h], Ricardo Bassil Lasmar[b], Scott Chudnoff[i], Andreas Thurkow[j], Rudy Leon De Wilde[k,l]

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ABSTRACT

Objective: Standard transcervical fibroid treatment via hysteroscopic myomectomy can result in a significant rate of intrauterine adhesiogenesis. The primary objective of this study was to document the incidence of de novo uterine adhesions after transcervical fibroid ablation (TFA) of symptomatic uterine fibroids with the Sonata® system.
Study design: In this European postmarket prospective, multicenter, single-arm interventional trial, patients were eligible for inclusion if they chose TFA with the Sonata System for symptomatic fibroids and had at least 1 type 1, type 2 or type 2–5 myoma. The presence or absence of intrauterine adhesions was assessed by diagnostic hysteroscopy at baseline and at 6 weeks post-ablation. The hysteroscopy videos were scored by a committee of 3 independent readers.
Results: A total of 6 sites enrolled 37 patients. Fifty fibroids with a mean diameter of 3.4 ± 1.8 cm (range 1–8 cm) were ablated. Of the 37 enrolled subjects, 35 completed the study follow-up and 2 electively withdrew from the study prior to the completion of study follow-up. Thirty-four out of 35 pairs of baseline and 6-week hysteroscopies were evaluated by the independent readers with none having de novo adhesions at 6 weeks after treatment with Sonata, including 6 patients with apposing myomata. One patient was excluded from the analysis due to an unevaluable hysteroscopy video.
Conclusion: Intrauterine adhesiogenesis was not seen post-TFA with the Sonata system. These results suggest the potential for adhesiogenesis after TFA, including in women with apposing submucous and/or transmural myomata, may be minimal.

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Introduction

Uterine fibroids are the most common benign tumors in women, occurring in approximately 20–50% of premenopausal women, and the prevalence increases with age [1]. In White women, the lifetime risk of developing fibroids is as high as 70% and in black women as high as 80% [2]. Based on a 2010 population estimate, approximately 588,164 women seek treatment for symptomatic uterine fibroids annually in the United States [3]. Although often asymptomatic, uterine fibroids may cause a number of symptoms such as heavy menstrual bleeding, dyspareunia, dysmenorrhea, pelvic/abdominal pressure and subfertility. Uterine fibroids can negatively impact quality of life and are commonly associated with invasive and expensive treatments [4].

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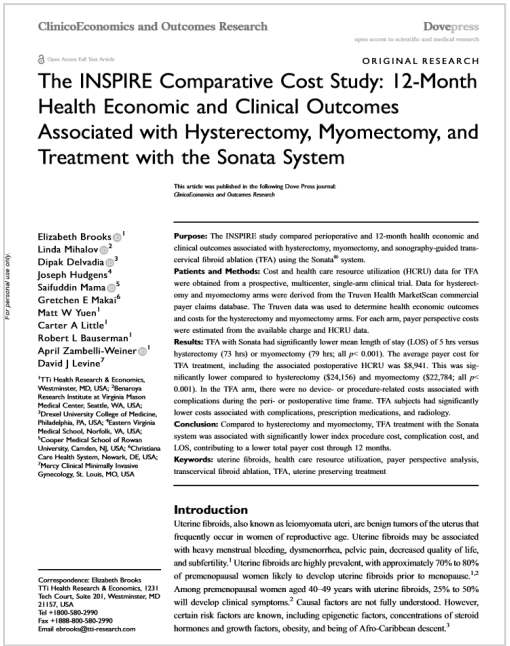
Highlights:

- Diagnostic hysteroscopy at baseline and at 6 weeks post-ablation was assessed by independent reviewers
- Study included 6 patients with apposing fibroids at high risk for adhesiogenesis
- No new adhesions were found post-TFA with the Sonata System
- No device-related adverse events

INSPIRE HEALTH ECONOMICS OUTCOMES RESEARCH (HEOR) PAYER COST STUDY

Brooks E, Mihalov L, Delvadia D et al. The INSPIRE Comparative Cost Study: 12-Month Health Economic and Clinical Outcomes Associated with Hysterectomy, Myomectomy, and Treatment with the Sonata System. *ClinicoEconomics and Outcomes Research.* 2020;1-11

OBJECTIVE	To examine payer costs and compare health economic outcomes of transcervical fibroid ablation (TFA) with the Sonata System versus the most common fibroid treatments: hysterectomy and myomectomy.
STUDY DESIGN	Retrospective, multicenter comparative payer cost study using SONATA Trial data and Truven database analysis for hysterectomy and myomectomy.
ENDPOINTS	• Total procedure payments through 12-months post procedure. • Length of stay (from admission to discharge)
N=	TFA=51; Hysterectomy=35,463; Myomectomy=8,548
CONCLUSIONS:	Compared to hysterectomy and myomectomy, TFA was associated with significantly lower index procedure cost, complication cost, and length of stay, contributing to a significantly lower total payer cost through 12 months.



ClinicoEconomics and Outcomes Research — Dovepress

ORIGINAL RESEARCH

The INSPIRE Comparative Cost Study: 12-Month Health Economic and Clinical Outcomes Associated with Hysterectomy, Myomectomy, and Treatment with the Sonata System

Elizabeth Brooks[1], Linda Mihalov[2], Dipak Delvadia[3], Joseph Hudgens[4], Saifuddin Mama[5], Gretchen E Makai[6], Matt W Yuen[1], Carter A Little[1], Robert L Bauserman[1], April Zambelli-Weiner[1], David J Levine[7]

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Purpose: The INSPIRE study compared perioperative and 12-month health economic and clinical outcomes associated with hysterectomy, myomectomy, and sonography-guided transcervical fibroid ablation (TFA) using the Sonata® system.

Patients and Methods: Cost and health care resource utilization (HCRU) data for TFA were obtained from a prospective, multicenter, single-arm clinical trial. Data for hysterectomy and myomectomy arms were derived from the Truven Health MarketScan commercial payer claims database. The Truven data was used to determine health economic outcomes and costs for the hysterectomy and myomectomy arms. For each arm, payer perspective costs were estimated from the available charge and HCRU data.

Results: TFA with Sonata had significantly lower mean length of stay (LOS) of 5 hrs versus hysterectomy (73 hrs) or myomectomy (79 hrs; all $p<0.001$). The average payer cost for TFA treatment, including the associated postoperative HCRU was $8,941. This was significantly lower compared to hysterectomy ($24,156) and myomectomy ($22,784; all $p<0.001$). In the TFA arm, there were no device- or procedure-related costs associated with complications during the peri- or postoperative time frame. TFA subjects had significantly lower costs associated with complications, prescription medications, and radiology.

Conclusion: Compared to hysterectomy and myomectomy, TFA treatment with the Sonata system was associated with significantly lower index procedure cost, complication cost, and LOS, contributing to a lower total payer cost through 12 months.

Keywords: uterine fibroids, health care resource utilization, payer perspective analysis, transcervical fibroid ablation, TFA, uterine preserving treatment

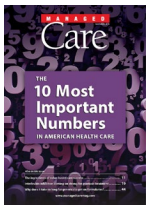
Introduction

Uterine fibroids, also known as leiomyomata uteri, are benign tumors of the uterus that frequently occur in women of reproductive age. Uterine fibroids may be associated with heavy menstrual bleeding, dysmenorrhea, pelvic pain, decreased quality of life, and subfertility.[1] Uterine fibroids are highly prevalent, with approximately 70% to 80% of premenopausal women likely to develop uterine fibroids prior to menopause.[1,2] Among premenopausal women aged 40–49 years with uterine fibroids, 25% to 50% will develop clinical symptoms.[2] Causal factors are not fully understood. However, certain risk factors are known, including epigenetic factors, concentrations of steroid hormones and growth factors, obesity, and being of Afro-Caribbean descent.[3]

Highlights:

- Transcervical Fibroid Ablation (TFA) with the Sonata System was associated with significantly lower index procedure cost and complication cost compared to hysterectomy and myomectomy
- TFA with the Sonata System had a significantly lower mean length of stay versus hysterectomy or myomectomy, $p<0.001$
- Mean total payments were ≥155% higher for both hysterectomy and myomectomy vs. Sonata, $p<0.001$

Measure	TFA (Sonata)	Hysterectomy	Myomectomy
Mean cost to payer	**$8,941**	$24,156	$22,784
Mean length of stay	**5 hours**	73 hours	79 hours



COMPARE HEALTH ECONOMICS OUTCOMES RESEARCH (HEOR) FACILITY COST STUDY

Brooks E, Mihalov L, Delvadia D et al. The COMPARE Study: Facility Costs Associated with Hysterectomy, Myomectomy, and the Sonata Procedure for Treatment of Uterine Fibroids. *Managed Care*. 2019;40-45.

OBJECTIVE	To examine facility costs of sonography-guided transcervical fibroid ablation (TFA) with the Sonata System, hysterectomy, and myomectomy for the treatment of symptomatic uterine fibroids.
STUDY DESIGN	Retrospective, multicenter facility perspective cost analysis using treatments in the SONATA Pivotal IDE Trial compared to Truven database analysis of hysterectomy and myomectomy (open and laparoscopic).
ENDPOINTS	• Index procedure and hospitalization costs to include related readmissions through 30-day post-discharge. • Length of stay (from admission to discharge)
N=	TFA=45; Hysterectomy=35,463; Myomectomy=5,228
CONCLUSIONS:	TFA using the Sonata System had a shorter length of stay than either comparator arms. TFA was also associated with considerably lower facility costs compared with either hysterectomy or myomectomy regardless of procedure route, site of service, or use of robotic assistance.

ORIGINAL RESEARCH

The COMPARE Study: Facility Costs Associated With Hysterectomy, Myomectomy, and the Sonata Procedure for Treatment of Uterine Fibroids

Elizabeth Brooks, PhD,[1] Linda Mihalov, MD,[2] Dipak Delvadia, DO,[3] Saifuddin Mama, MD,[4] Gretchen E. Makai, MD,[5] Matt Yuen, PhD,[1] Carter Little,[1] April Zambelli-Weiner, PhD,[1] David J. Levine, MD[6]

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INTRODUCTION

Uterine fibroids are benign smooth muscle tumors that are seen in more than 70% of women of childbearing age. While many women with uterine fibroids are asymptomatic, between 20% and 50% of women with uterine fibroids experience symptoms such as abnormal uterine bleeding, pelvic pressure, and subfertility (Wallach 1981, Evans 2007, Pritts 2001). Uterine fibroids place a substantial burden on the U.S. health care system and society — an estimated $4.1 billion to $9.4 billion annually in direct medical costs (2010 dollars) and further losses in work productivity (Cardozo 2012, Côté 2002).

The most common treatments for symptomatic uterine fibroids involve major surgical approaches. Hysterectomy is the most common. It is curative but involves the removal of the uterus and therefore childbearing potential. Myomectomy, the surgical removal of individual uterine fibroids, preserves the uterus (Lethaby 2001).

The adoption of new treatments no longer depends just on safety and effectiveness data. The net impact on health care resource utilization is becoming a large factor and is being scrutinized by payers and providers.

A new treatment alternative for symptomatic uterine fibroids is the Sonata procedure (Sonata System, Gynesonics Inc., Redwood City, Calif.), a minimally invasive, incisionless, transcervical fibroid ablation (TFA) treatment that preserves the uterus. The heat-induced coagulative necrosis that results from the targeted ablation causes fibroids to shrink over time and is associated with symptom relief (Garza-Leal 2011, Bongers 2015). The pivotal SONATA investigational device exemption (IDE) trial demonstrated statistically significant symptom relief, improved quality of health outcomes, zero device-related adverse events, and high patient satisfaction with a low rate of surgical re-intervention (Chudnoff 2019).

The FDA granted the Sonata

ABSTRACT

Purpose: The COMPARE study examined facility costs of sonography-guided transcervical fibroid ablation (TFA) using the Sonata System, hysterectomy, and myomectomy for the treatment of symptomatic uterine fibroids.

Design and methodology: A facility-perspective cost analysis of hospital charge data in the perioperative and the 30-day postoperative period was conducted. Length of stay (LOS) and charge data for the TFA arm were collected in the SONATA trial. Hospital-specific cost-to-charge ratios (CCRs) were used to convert charges to facility costs. Charge data and LOS for comparator arms were collected retrospectively from the IBM MarketScan Commercial Database and converted to costs using Medicare national average CCRs.

Results: TFA patients had a statistically significant shorter mean LOS (5.1 hours) compared with hysterectomy (73 hours) or myomectomy (80 hours; all $P<.001$) patients. The mean facility cost of TFA was $7,701, lower than the $10,353 for hysterectomy and the $12,003 for myomectomy (all $P<.001$). TFA facility costs were also statistically significantly lower across all stratifications ($P<.01$) compared with hysterectomy and myomectomy subgroups for site of service (inpatient or outpatient), and/or use of robotic assistance. The lower facility costs were preserved in follow-up analyses that included route subtypes (e.g., laparoscopic, open, vaginal) and removal of high-cost outliers from comparator arms.

Conclusion: TFA using the Sonata System had a shorter LOS than either comparator arms regardless of the procedure route. Sonata was also associated with considerably lower facility costs compared with either hysterectomy or myomectomy regardless of procedure route, site of service, or use of robotic assistance.

Keywords: Uterine fibroids; Sonata; health care resource utilization; facility perspective; database analysis; transcervical fibroid ablation; TFA, uterine preserving; cost analysis; radiofrequency ablation.

Highlights:

- TFA with the Sonata System was associated with significantly lower facility costs compared with either hysterectomy or myomectomy regardless of procedure route
- Mean total costs were higher for both hysterectomy (56%) and myomectomy (34%) compared to Sonata treatment (p<0.001)
- Statistically significant cost savings for Sonata treatment remained after removal of robotic-assisted and high-cost outliers from the comparator arms

Measure	TFA (Sonata)	Hysterectomy	Myomectomy
Mean costs to facility	**$7,701**	$10,353	$12,003
Mean length of stay	**5 hours**	73 hours	80 hours

IMPROVEMENT IN HEALTH UTILITY AFTER RF ABLATION WITH SONATA

Huirne J, Brooks E. Improvement in health utility after transcervical radiofrequency ablation of uterine fibroids with the Sonata system: Health utility after radiofrequency ablation. *Eur J Obstet Gynecol Reprod Biol.* 2018;224:175-180.

OBJECTIVE	To establish the improvement in patient health utilities following treatment of symptomatic uterine fibroids with the Sonata System.
TRIAL DESIGN	Prospective, single-arm trial. The EQ-5D-3L system was utilized in the FAST-EU Trial to collect patient health status at baseline, 3, 6, and, 12 months post-procedure. Patient-reported health states at each time point were converted into a health utility value using time-trade off methodology.
ENDPOINTS	• Patient Health Utility Measures • Quality-Adjusted Life Years (QALYs)
N=	49 patients enrolled in the FAST-EU Trial
CONCLUSIONS	Transcervical radiofrequency ablation of uterine fibroids with the Sonata System (TFA) resulted in statistically significant 12-month improvements in health utility. After translating health utility values into quality-adjusted life years (QALYs) and including only those patients with complete utility measurements, the average 12-month QALYs experienced was 0.87. This is consistent with the other patient reported outcomes from the FAST-EU trial, including patient satisfaction, symptom severity, and health related quality of life measure

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Full length article

Improvement in health utility after transcervical radiofrequency ablation of uterine fibroids with the sonata system: Health utility after radiofrequency ablation

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ABSTRACT

Objectives: To establish the improvement in patient health utilities following treatment of symptomatic uterine fibroids with the Sonata™ System.
Study design: A prospective, single-arm trial was conducted in which 49 women in the United Kingdom, Netherlands and Mexico with fibroids were treated with transcervical, intrauterine ultrasound- guided radiofrequency ablation. The EQ-5D-3L system was utilized to collect patient health states at baseline, 3, 6, and, 12 months post-procedure. Patient-reported health states at each time point were converted into a health utility value using time-trade off methodology.
Results: In the overall cohort, patient health utility increased from a mean of 0.745 at baseline, to means of 0.838, 0.852, and 0.914 at 3 months, 6 months, and 12 months, respectively. The change from baseline at 12 months was significant. When stratified by country, the 12-month improvement in health utility remained significant for both the Mexican and Dutch cohorts.
Conclusions: Transcervical radiofrequency ablation of uterine fibroids with the Sonata System resulted in statistically significant 12-month improvements in health utility for the overall patient cohort and for the Mexican and Dutch sub-populations.

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Introduction

Uterine fibroids, also known as leiomyomata, are noncancerous growths of the uterus. They can vary in size and number and often appear during childbearing years. Uterine fibroids are common; one study of women undergoing pelvic sonography found that over 80% of African-American and almost 70% of Caucasian women will have fibroids by the age of 50 [1]. Whilst the majority of uterine fibroids are asymptomatic [2], 20–50% may produce symptoms [3]; the most common symptom being abnormal uterine bleeding [4]. Fibroids may also cause pelvic pressure and pain [3]. A study of 21,746 women with symptomatic fibroids [5] found that more than half of the patients' symptoms had a negative impact on their lives. Another study found that almost a third of women with symptomatic uterine fibroids reported work absenteeism and over a third reported presenteeism (i.e., reduced work productivity) and impaired general activity [6].

Definitive treatment for uterine fibroids is hysterectomy, with or without removal of the ovaries. However, there are several treatment options for women suffering from fibroids that do not involve surgical removal of the uterus, and these include surgical removal of myomata (myomectomy); uterine artery embolization (UAE); and magnetic resonance-guided focused ultrasound (MRgFUS). With effective treatment, women who had been living with fibroid symptoms can realize improvements in health-related quality of life (HRQOL) [7].

The availability of a variety of treatment options allows women the opportunity to choose an appropriate treatment based on symptom severity, past medical history, and values and preferences (desire for fertility and for uterine preservation). A recent US study found that almost 75% of women would prefer less invasive treatments, with 51% choosing to preserve their uteri, and 43% of women under age 40 desiring fertility preservation [8].

With the goal of providing an incisionless, uterus-preserving alternative to hysterectomy and other treatment options, the Sonata® System (which received CE Mark approval) takes a transcervical approach to treating symptomatic fibroids with

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[1] Locations of study sites: Birmingham, United Kingdom; Haywards Heath, United Kingdom; Amsterdam, Netherlands; Eindhoven, Netherlands; Nieuwegein, Netherlands; Enschede, Netherlands; Monterrey, Mexico.

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Highlights:

- Health utility index is a measure of how a patient perceives her health status, with a health utility index of 1.0 considered to be perfect health
- The study utilized a validated, widely accepted and standardized instrument, the EQ-5D-3L, for measuring general health status providing the health utility index
- A change in health utility index of 0.1 or more, is considered significant by healthcare economists
- Health utility index following treatment with TFA significantly increased from a mean of 0.745 to 0.914 at 12 months (p<0.001)
- A mean healthy utility index increase of 0.17 is more than 1.5 times what is considered clinically significant, demonstrating substantial improvement in patients' health post treatment with the Sonata System
- Transcervical radiofrequency ablation of symptomatic uterine fibroids with the Sonata System resulted in a statistically significant improvement in healthy utility index as early as 3 months post treatment with sustained improvement through 12 months resulting in values that approached perfect health (p<0.001)

III: SELECTED BIBLIOGRAPHY

As of March 2022

This bibliography is intended for distribution to Health Care Providers and includes publications and case studies that are consistent with distributed labeling of Gynesonics' products. Additional publications are available from our Medical Director through a submission on the company website at: gynesonics.com/request-for-medical-information.

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IV: INDICATIONS AND SAFETY INFORMATION

INTENDED USE

The Sonata System is intended for diagnostic intrauterine imaging and transcervical treatment of symptomatic uterine fibroids, including those associated with heavy menstrual bleeding.

CONTRAINDICATIONS

The Sonata System is contraindicated in the following conditions:

- Current pregnancy
- Active pelvic infection
- Known or suspected gynecologic malignancy or premalignant disorders such as atypical endometrial hyperplasia
- Presence of one or more intratubal implants for sterilization
- Presence of an intrauterine device (IUD), unless removed prior to the introduction of the Sonata Treatment Device

OTHER CONSIDERATIONS

- Safety and effectiveness with regard to fertility and fecundity after the use of the Sonata System have not been established. As a uterus-conserving alternative to hysterectomy, treatment with the Sonata System does not eliminate the possibility of pregnancy.
- Effectiveness in women with clinically significant adenomyosis has not been established
- Transcervical radiofrequency ablation with the Sonata System should not be performed in patients with known hip implants or other metal implants near the ablation site or along the RF return path to Dispersive Electrodes
- The Sonata System should be used with caution in patients with a known nickel allergy
- Other considerations as stated in the Sonata System Operator's Manual

PATIENT COUNSELING, POTENTIAL POST-OPERATIVE EVENTS, AND RISKS

As with any procedure, the clinician should discuss the potential risks and expected outcomes related to the Sonata procedure with patients. The Sonata System is intended for the transcervical ablation of symptomatic uterine fibroids, including those associated with heavy menstrual bleeding. Full benefits may not be realized for several months, as the ablated fibroids shrink over time.

- **Anticipated postoperative events** include: abdominopelvic pain/cramping; back pain; constipation; dizziness/fatigue; headache; fever; malaise; post-ablation inflammatory symptoms; nausea/vomiting; sloughing and, less commonly, intact expulsion of ablated fibroid tissue *per vaginam* (particularly after ablation of submucous fibroids), and vaginal spotting/bleeding/dysmenorrhea

PATIENT COUNSELING, POTENTIAL POST-OPERATIVE EVENTS, AND RISKS (continued)

- **Potential risks associated with fibroid ablation using the Sonata System** include: allergic reactions (including rash) to device materials; bowel or bladder perforation; cervical/vaginal laceration or tear; dysmenorrhea; electrical shock; hematometrium; hemorrhage; infections: major and minor local and systemic infections, including intrauterine infection; retention of device fragment; skin burn from the dispersion of RF energy; thrombotic events; unintended injury to the uterus, cervix or vaginal vault, adjacent organs or tissue; unknown risk to future pregnancies; and complications including death
- Additionally, the clinician should include in their discussion the risks associated with the anesthesia regimen selected for performing the Sonata procedure.

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Ultrasound-Guided Transcervical Ablation of Uterine Leiomyomas

Scott Chudnoff, MD, MSc, *Richard Guido,* MD, *Kelly Roy,* MD, *David Levine,* MD, *Linda Mihalov,* MD, *and José Gerardo Garza-Leal,* MD

OBJECTIVE: To evaluate the 12-month safety and effectiveness of transcervical ablation for the treatment of symptomatic uterine leiomyomas.

METHODS: In this prospective, multicenter, single-arm interventional trial, transcervical ablation was performed on 1–10 leiomyomas per patient with leiomyoma diameters ranging from 1 to 5 cm. Treated leiomyomas included all nonpedunculated types. Coprimary endpoints assessed at 12 months were reduction in menstrual blood loss and absence of surgical reintervention. Additional assessments included symptom severity, quality of life, patient satisfaction, reductions in uterine and leiomyoma volumes, and safety.

RESULTS: One hundred forty-seven patients were enrolled and treated in the United States and Mexico. The study met its coprimary endpoints at 12 months (N=143; full analysis set), because 64.8% of patients (95% CI 56.3–72.6%) experienced 50% or greater reduction in menstrual bleeding and 99.3% of patients (95% CI 95.1–99.9%) were free from surgical reintervention. The mean pictorial blood loss assessment chart score decreased by 38.9%, 48.4%, and 51.1% at 3, 6, and 12 months, respectively ($P<.001$), and 95.1% of patients experienced a reduction in menstrual bleeding at 12 months. There were significant mean improvements in symptom severity and health-related quality of life of 32.1 points and 43.7 points, respectively, at 12 months (all $P<.001$). Mean maximal leiomyoma volume reduction per patient was 62.4% ($P<.001$). More than half of patients returned to normal activity within 1 day, 96.3% of patients reported symptom improvement at 12 months, and 97% expressed satisfaction with the treatment at 12 months. There were no device-related adverse events.

CONCLUSION: Transcervical ablation was associated with a significant reduction in leiomyoma symptoms with no device-related adverse events and a low surgical reintervention rate through 12 months, demonstrating its potential to safely and effectively treat all nonpedunculated leiomyoma types through a uterus-conserving, incisionless approach.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT02228174.

Funding Source: Supported by Gynesonics, Inc.

(Obstet Gynecol 2019;00:1–10)

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Uterine leiomyomas are highly prevalent and, when symptomatic, may be treated with a variety of options such as hormonal manipulation, uterine artery embolization, myomectomy, or definitive hys-

From the Stamford Hospital, Stamford, Connecticut; Magee-Women's Hospital, Pittsburgh, Pennsylvania; Arizona Gynecology Consultants, Phoenix, Arizona; Mercy Hospital, St. Louis, Missouri; Virginia Mason Medical Center, Seattle, Washington; and Hospital Universitario "Dr. José Eleuterio González" de Universidad Autónoma de Nuevo León, Monterrey, NL, Mexico.

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Each author has confirmed compliance with the journal's requirements for authorship.

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Financial Disclosure
Scott Chudnoff, Richard Guido, Linda Mihalov, and José Gerardo Garza-Leal have served on the Gynesonics, Inc, advisory board. Scott Chudnoff received travel and lodging expenses for attendance at an investigator meeting and has received honoraria for speaking from Gynesonics, Inc. Kelly Roy has received royalties from CrossBay Medical, Inc. and stock options from Channel Medical, Inc, and has served as a consultant for Boston Scientific, Inc. David Levine has been a consultant for Gynesonics and a consultant for Aegea Medical. Linda Mihalov has also served on the advisory board for Abbvie. José Gerardo Garza-Leal has received a stock option grant from Gynesonics, Inc. Scott Chudnoff, Richard Guido, Kelly Roy, David Levine, and Linda Mihalov serve on the Sonography Guided Transcervical Ablation of Uterine Fibroids study steering committee.

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terectomy.[1] Medical management has largely focused on treatment of leiomyoma symptoms and not the underlying problem. Even with recent advances, medical treatment requires continued hormonal manipulation with resulting side effects until menopause to maintain the effect. Symptomatic women with leiomyomas wish to avoid invasive surgery, and one fourth delay treatment for up to 5 years.[2] All alternatives to hysterectomy may result in a need for surgical reintervention, and lower rates are desirable from the patient and health system perspective. Hirst et al[3] reported a 23% cumulative probability of undergoing hysterectomy within 4.6 years of uterine artery embolization.

In response to a perceived need for additional, less invasive treatment options, a significant literature base has emerged demonstrating the efficacy of radiofrequency and other hyperthermal ablation methods in the management of uterine leiomyomas and other solid tumors.[4–14] The Sonata System (previously called VizAblate) provides transcervical radiofrequency ablation and has been shown, through the results of the FAST-EU Trial, to reduce leiomyoma volume, decrease heavy menstrual bleeding, and improve health utility scores in women with symptomatic leiomyomas.[15–17]

This article describes results through 12 months of the Sonography Guided Transcervical Ablation of Uterine Fibroids pivotal trial. The aims of this trial were to assess the treatment efficacy, including freedom from surgical reintervention, and safety of the Sonata System in a cohort of patients with heavy menstrual bleeding and uterine leiomyomas.

ROLE OF THE FUNDING SOURCE

Gynesonics, Inc funded this study and participated in the study design, research, analysis, interpretation of data, review and approval of the publication.

METHODS

Sonography Guided Transcervical Ablation of Uterine Fibroids is a prospective, interventional, multicenter, single-arm trial involving patients with symptomatic uterine leiomyomas who elected transcervical leiomyoma ablation as treatment. The Sonography Guided Transcervical Ablation of Uterine Fibroids trial was performed under an investigational device exemption from the U.S. Food and Drug Administration (FDA). The investigational device exemption application (IDE G140114) received FDA approval without conditions on October 3, 2014. Study enrollment began in April 2015 and ended in October 2016. The coprimary endpoints, both assessed at 12 months postablation, consisted of 1) reduction in menstrual blood loss as assessed by pictorial blood loss assessment chart and 2) the rate of surgical reintervention for heavy menstrual bleeding resulting from treatment failure. The pictorial blood loss assessment chart is a validated assessment tool to estimate menstrual blood loss using icons representing various degrees of saturation of sanitary products.[18] Scores 100 or less have been reported to represent eumenorrhea.[18–20] Secondary endpoints included safety, reduction in total and perfused leiomyoma volume as measured by contrast-enhanced magnetic resonance imaging, change in the symptom severity score and health-related quality-of-life subscales of the Uterine Fibroid Symptom and Quality-of-Life Questionnaire, overall patient treatment outcome using the Overall Treatment Effect Scale, time to return to normal activity, satisfaction, change in general health outcome as determined by the EuroQoL questionnaire, pain and tolerance of the procedure, length of stay, and occurrence of pregnancy with pregnancy outcome. Self-reported scores on the Euro-QoL questionnaire are translated to health utility scores ranging from values of less than 0, representing health states worse than "death," to a maximum score of 1.0, representing "perfect health." An increase of 0.04 is considered by health economists to represent a minimally important difference.[21] Enrolled patients were followed at 10 days, 30 days, 3 months, 6 months, and at 12 months, with longer term follow-up planned for 24 and 36 months.

Premenopausal women between the ages of 25 and 50 years were enrolled if they met specific inclusion criteria. These included the presence of up to 10 leiomyomas of International Federation of Gynecology and Obstetrics types 1, 2, 3, 4, 2–5 (transmural), or all of these with diameters between 1.0 and 5.0 cm (Fig. 1). Patients were also required to have at least one leiomyoma that indented or impinged on the endometrial cavity (eg, International Federation of Gynecology and Obstetrics type 1, type 2, type 3, or type 2–5). A minimum pictorial blood loss assessment chart score 150 or greater and 500 or less was required at baseline along with consistent menstrual cycles that were within normal limits. Exclusion criteria included a desire for future pregnancy, the presence of type 0 myomata 1.0 cm or greater, endometrial polyps 1.5 cm or greater or multiple polyps, bulk symptoms attributable to subserous leiomyomas, prior endometrial ablation or uterine artery embolization or uterine artery occlusion or hyperthermic ablation of leiomyomas, uterine volume 1,000 cm^3 or greater, the presence of tubal implants for sterilization, and clinically significant

adenomyosis. Although from a technical perspective, transcervical leiomyoma ablation could be used to treat type 0 myomata, considering the relative availability and ease of treatment of type 0 leiomyomas through existing modalities, patients with such leiomyomas were excluded. Washout periods were required for medicated intrauterine systems, long-acting progestins, and medical therapy for heavy menstrual bleeding. Women taking hormonal contraceptive pills were required to remain on their current regimen without interruption or brand change for 6 months before enrollment through 12 months of follow-up and the introduction of medical therapy for heavy menstrual bleeding during the 12-month posttreatment period was not permitted.

Baseline investigations included transvaginal ultrasonography, contrast-enhanced magnetic resonance imaging (for subsequent volume and perfusion calculations as well as to exclude significant adenomyosis and hypercalcified leiomyomas), sexually transmitted infection screening along with the pictorial blood loss assessment chart, Uterine Fibroid Symptom and Quality-of-Life, and EuroQoL assessments. Patients were required to have had standard cervical cancer screening per national guidelines along with negative endometrial sampling within the previous 12 months and a negative pregnancy test before the procedure. Additional imaging of the endometrial cavity such as diagnostic hysteroscopy or saline infusion ultrasonography was at the discretion of the investigator. Treated patients also underwent a second contrast-enhanced magnetic resonance study at 12 months postablation; this enabled the measurements of changes in total and perfused leiomyoma volume (using voxel volume determination) and total uterine volume. All baseline and 12-month magnetic resonance studies were submitted to an independent core imaging laboratory to ensure quality control and consistency regarding measurements and determination of eligibility. The core imaging laboratory also credentialed magnetic resonance facilities used by each clinical site and provided protocol training to each site's associated magnetic resonance technologists. For each patient at 12 months, the treatable leiomyoma with the greatest percentage reduction in total leiomyoma volume from baseline was identified on magnetic resonance imaging. This was used to calculate mean maximal total and perfused leiomyoma volume reductions per patient at 12 months.

Each patient provided her informed consent to participate in the trial, and every clinical site obtained local institutional review board or ethics committee approval before commencing patient enrollment. The FDA and the Federal Commission for Protection against Health Risks in Mexico approved the Sonography Guided Transcervical Ablation of Uterine Fibroids trial. All studies and records had protected health information removed to deidentify each patient's data in the clinical database. All magnetic resonance studies were similarly anonymized before being sent to the core imaging laboratory.

Treatment was provided using the Sonata System, which integrates intrauterine ultrasound imaging with

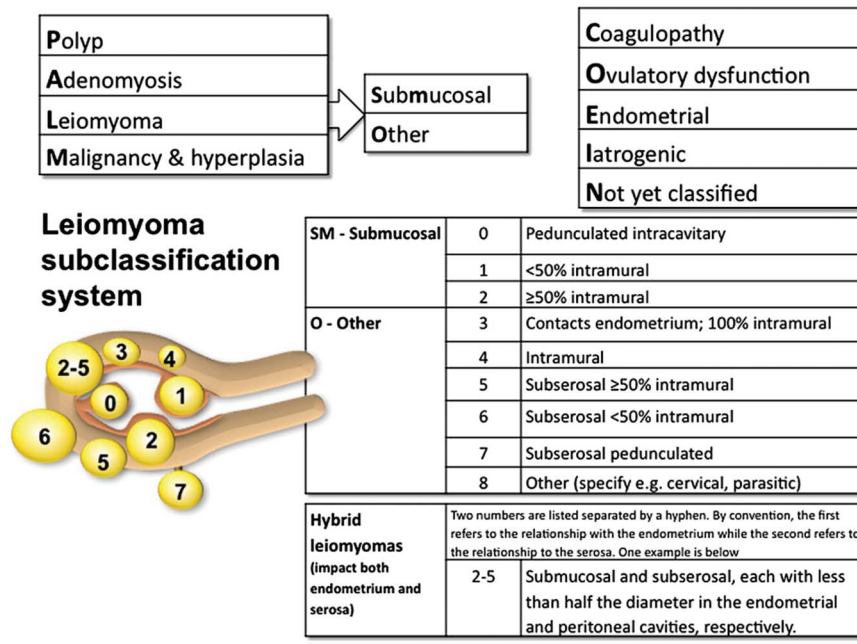

Fig. 1. The FIGO classification system (PALM-COEIN) of causes of abnormal uterine bleeding in the reproductive years, including the fibroid categorization system. Reprinted, with permission, from Munro MG, Critchley HOD, Broder MS, Fraser IS; FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet 2011;113:3–13. © 2011 International Federation of Gynecology and Obstetrics, with permission from Elsevier. Adapted from Munro MG. Abnormal uterine bleeding. Cambridge (UK): Cambridge University Press; 2010.

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a radiofrequency treatment device to provide a uterus-conserving, transcervical incisionless treatment for a range of leiomyoma types and sizes (Figs. 2 and 3). Sonata has received clearance by the FDA and has CE marking in the European Union. Transcervical radiofrequency ablation with the Sonata System has been described previously.[15,16,22] Gynecologist training entails didactic instruction and practice on physical uterine models with various leiomyoma configurations. This training is supervised and guided by industry-provided clinical specialists, experienced users of Sonata, or both.

A leiomyoma may require a single ablation but could also require more than one, depending on its size, location, and geometry. A treating physician can visualize the formation and distribution of hyperechoic water vapor (outgassing) within the leiomyoma that is associated with the thermal necrosis generated by radiofrequency energy within the targeted leiomyoma. This is normally visible both during and for several minutes after ablation. This guides individual physician judgment regarding any need for additional ablation within a given targeted leiomyoma.

Device insertion required cervical dilatation to 27 Fr (9 mm), and this could be accomplished with mechanical, osmotic, or pharmacologic dilators. The use of prophylactic antibiotics was at physician discretion.

Objective performance criteria were set for both coprimary endpoints. For the menstrual bleeding reduction coprimary endpoint, success required both a 50% or greater reduction in pictorial blood loss assessment chart score that was also 250 or less with a 95% lower confidence limit 45% or greater of patients (ie, at least 45% of patients must have achieved both a pictorial blood loss assessment chart reduction of at least 50% and a score 250 or less).

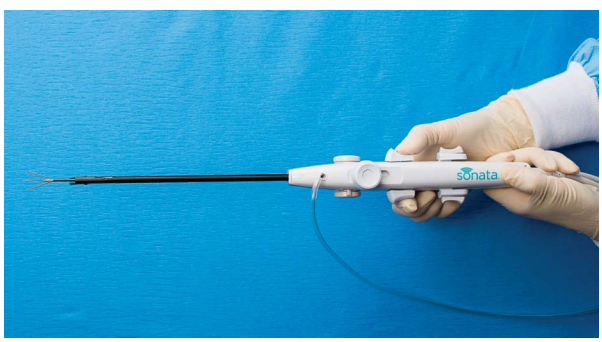

Fig. 2. The Sonata treatment device, which combines an intrauterine ultrasonography probe with a radiofrequency ablation handpiece.

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Success for the surgical reintervention endpoint was defined as the proportion of patients who did not require surgical reintervention for heavy menstrual bleeding with the 95% lower confidence limit of the percentage of patient success 75% or greater. Trial success required achieving or surpassing the objective performance criteria of both coprimary endpoints.

The sample size for this study was 125 or greater treated patients to achieve 90% power with an α level equal to 0.05 and an assumed success rate of 60%. Including a conservative estimate for "lost to follow-up" of 15%, the number of patients needed to treat was calculated to be 147. Patient success was calculated separately for the two coprimary endpoints such that it was possible for a patient to have experienced treatment success for one coprimary endpoint and not for the other. Study success was achieved if both coprimary endpoint success criteria were met. All statistical analyses were performed with SAS 9.3. Changes from baseline were analyzed with the Wilcoxon signed-rank test. Values were considered significant at the level of $\alpha=0.05$. The rate of surgical reintervention during 12 months, along with 95% CI, was determined using the life-table methods.

RESULTS

One hundred forty-seven patients were enrolled and treated at 22 investigational centers located in the United States (21) and Mexico (one). The median age was 43 years (range 31–50 years), and median body mass index (calculated as weight (kg)/[height (m)]^2) was 28 (range 18–50). Table 1 summarizes menstrual bleeding and leiomyoma characteristics at baseline.

All 147 patients were treated in an outpatient setting, including hospital-based operating rooms, ambulatory care centers, and procedure rooms within physician offices. Of these settings, 87 patients (59.2%) received treatment in a hospital-based operating room, 37 (25.2%) in an ambulatory care center, and 23 (15.6%) in a physician office. Seventy-four patients (50.3%) received general anesthesia, and 73 (49.7%) were treated under conscious sedation, both deep and mild sedation. Paracervical blockade was coadministered as an ancillary local anesthetic modality in 48.3% of patients. Mean length of stay (measured from procedure start to discharge, including procedure time) was 2.5 ± 1.2 hours with 109 of 147 patients (74.1%) having a length of stay 3 hours or less. Discretionary use of prophylactic antibiotics was provided for 57 (38.8%) patients.

Four patients were excluded from the full analysis set population as a result of having reached menopause with a resultant inability to provide a pictorial

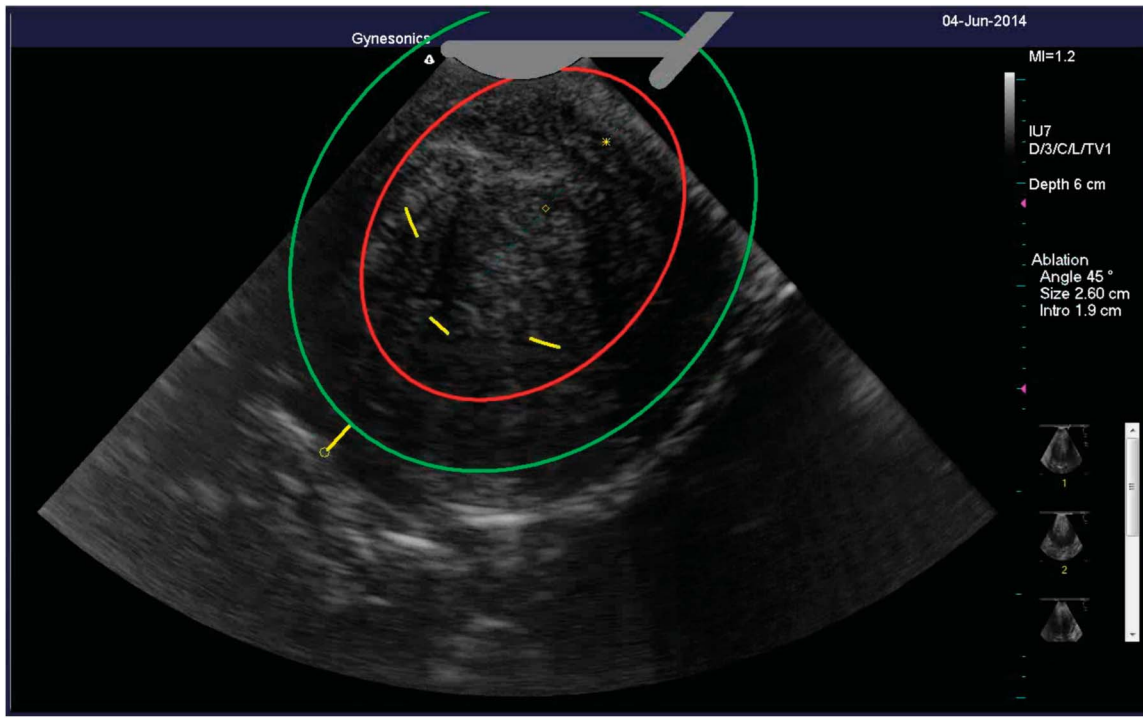

Fig. 3. The Sonata System Setting Margins of Ablation in Real Time (SMART) Guide, which is a graphic overlay displaying required information for targeting and deployment of the treatment device components used to deliver radiofrequency ablation. The SMART Guide includes the ablation zone (*red*), which denotes the area that is ablated, and the thermal safety border (*green*), indicating the distance from the ablation at which tissue is safe from potential thermal injury.
Chudnoff. Ultrasound-Guided Transcervical Ablation of Uterine Leiomyomas. Obstet Gynecol 2019.

blood loss assessment chart diary at their 12-month visits. Thus, the full analysis set consists of 143 patients. For the menstrual bleeding reduction endpoint evaluation in the full analysis set population, 142 of the 143 patients were included in this analysis, because the one patient who underwent surgical reintervention before her 12-month visit was excluded from the analysis of this endpoint per the prespecified study statistical analysis plan. Of these 142 patients, 135 provided a pictorial blood loss assessment chart questionnaire at their 12-month visits; the 12-month pictorial blood loss assessment chart was missing for the remaining seven patients: three patients completed the 12-month visit but did not provide a pictorial blood loss assessment chart diary, three patients were withdrawn before the 12-month visit, and one patient missed her 12-month visit. Missing pictorial blood loss assessment chart values for these seven patients were imputed using the last observation carried forward.

Detailed menstrual bleeding reduction results are provided in Table 2. The mean pictorial blood loss assessment chart score decreased by 38.9%, 48.4%, and 51.1% at 3, 6, and 12 months, respectively ($P<.001$), and 95.1% of patients experienced reduced menstrual bleeding at 12 months. At 12 months postablation, 99.3% of patients (95% CI 95.1–99.9%) did not undergo surgical reintervention for heavy menstrual bleeding (coprimary endpoint). One patient underwent elective hysterectomy for bleeding just before her 12-month visit.

Transcervical radiofrequency ablation of uterine leiomyomas with the Sonata System resulted in significant improvements in patient-reported outcomes, beginning with the 3-month visit (the first posttreatment visit that included these questionnaires). Detailed Uterine Fibroid Symptom and Quality-of-Life results are summarized in Tables 3 and 4. Regarding the Overall Treatment Effect Scale questionnaire, 96.3% of patients (130/135) at 12 months noted improvement in their leiomyoma symptoms, 3.0% (4/135) reported no change in symptoms, and 0.7% (1/135) noted a worsening of symptoms.

Patients reported significantly improved health status on the Euro-QoL questionnaire at 12 months postprocedure. At baseline, patients in the Sonography Guided Transcervical Ablation of Uterine Fibroids trial had a mean overall score of 0.72 (N=143).

Table 1. Baseline Menstrual Bleeding and Leiomyoma Characteristics

Characteristic	Value
PBAC	147
Mean±SD	300.6±98.5
Median	284.5
Minimum, maximum	150.2, 499.0
Total leiomyoma volume*	142
Mean±SD	71.1±84.7
Median	42.5
Minimum, maximum	0.8, 522.9
Total uterine volume*	147
Mean±SD	267.7±148.4
Median	236.8
Minimum, maximum	48.4, 868.1

* Volumes in cm^3.
Data are n unless otherwise specified.

At 12 months (n=133), their mean health utility scores rose 0.17 points to 0.89 ($P<.001$).

Most patients (97%) at 12 months reported satisfaction with the treatment and the same percentage (97%) would also recommend Sonata to a friend or family member. Specifically, 70.4% of reporting patients (n=135) indicated that they were "very satisfied" with treatment, 17.8% were "moderately satisfied," 8.9% were "somewhat satisfied," 2.2% were "somewhat dissatisfied," and 0.7% were "moderately dissatisfied" at 12 months. Similarly, 81.5% would "definitely recommend" treatment with Sonata, 15.6% would "probably recommend" it, and 3.0% would "probably not recommend" treatment with Sonata at 12 months. No patient indicated dissatisfaction with the treatment or that she would "definitely not recommend" the treatment.

Overall, 98% (144/147) of patients found the transcervical ablation treatment to have been tolerable: 64.6% (n=95) of patients reported the procedure to have been "very tolerable," 30.6% (n=45) found the procedure "moderately tolerable," 2.7% (n=4) characterized it as "minimally tolerable," and 2% (n=3) said it was "intolerable." Overall mean pain scores (0–10 scale) were 0.2±1.0 (range 0.0–7.0) during the procedure and 2.6±2.8 (range 0.0–10.0) during recovery (reported for the time between procedure completion and discharge and recorded before discharge). Mean procedural pain scores were 0.01±0.1 for procedures under general anesthesia and 0.5±1.3 for procedures under conscious sedation. Mean recovery pain scores were 3.4±2.9 for patients receiving general anesthesia and 1.9±2.4 for those who were treated under conscious sedation. During

Table 2. Change in Pictorial Blood Loss Assessment Chart Score by Visit

Visit	PBAC Score	Change	Percent Change
Baseline	142		
Mean±SD	303.6±98.6		
Median	285.9		
Minimum, maximum	150.2, 499.0		
3-mo*	117	117	117
Mean±SD	175.9±110.3	−119.3±116.0	−38.9±39.1
Median	153.4	−113.0	−44.4
Minimum, maximum	11.7, 647.8	−395.2, 445.1	−96.5, 219.6
$P^{\dagger}$		<.001	<.001
6-mo	142	142	142
Mean±SD	159.5±188.7	−144.1±180.0	−48.4±42.9
Median	119.1	−143.4	−56.5
Minimum, maximum	11.7, 2,043.5	−469.5, 1,549.2	−95.7, 313.4
P		<.001	<.001
12-mo	142	142	142
Mean±SD	143.8±111.4	−159.7±127.7	−51.1±40.9
Median	125.9	−147.8	−58.3
Minimum, maximum	0.0, 902.2	−494.3, 679.4	−100.0, 304.9
P		<.001	<.001

PBAC, pictorial blood loss assessment chart.
Data are n unless otherwise specified.
One patient was excluded from analysis as a result of surgical reintervention.
Missing values imputed using last observation carried forward.
* Patients who provided informed consent under the initial protocol were not scheduled to have a PBAC assessment at 3 months and are not included in the 3-month summary.
† *P* value from a Wilcoxon signed-rank test at each time point.

Table 3. Change in Symptom Severity Score by Visit

Visit	SSS	Change*
Baseline	143	
Mean±SD	54.9±18.65	
3-mo	141	141
Mean±SD	26.9±19.00	−27.9±22.85
P†		<.001
6-mo	138	138
Mean±SD	22.7±17.47	−31.9±20.98
P		<.001
12-mo	135	135
Mean±SD	22.6±17.75	−32.1±21.03
P		<.001

SSS, symptom severity score.
Data are n unless otherwise specified.
* Change calculated for those with baseline and the visit-level follow-up data.
† *P* value from a Wilcoxon signed-rank test at each time point.

recovery, 49 patients (33.3%) were managed with nonsteroidal antiinflammatory drugs and 39 patients (26.5%) received narcotics.

On average, patients reported returning to normal daily activities in 2.2±2.2 days, with more than half of the patients returning to normal activity within 1 day of the procedure. Employed patients returned to work in a mean 3.6±2.6 days postprocedure. Patients resumed a normal diet at 0.8±1.3 days, normal sleep at 0.7±1.6 days, and normal urinary and bowel functions at 0.2±0.8 days and 1.4±1.9 days, respectively.

Table 5 summarizes characteristics of ablated leiomyomas. Although patients were excluded for having one or more leiomyomas with diameters greater than 5.0 cm on transvaginal ultrasonogram, intrauterine ultrasonography from the Sonata System was used to provide the data in Table 5 regarding baseline leiomyoma size (for consistency, magnetic resonance measurements by the independent core imaging laboratory at baseline and 12 months were used to provide final comparative data regarding leiomyoma size and volume). On average, leiomyomas received 1.1±0.4 ablations; 64 leiomyomas (14.5%) were treated with two or more ablations. Most (80.8%) ablated leiomyomas ranged from 1 to 4 cm in diameter.

Table 4. Change in Health-Related Quality of Life by Visit

Visit	HRQoL	Change*
Baseline	142	
	40.3±20.51	
3 mo	140	139
Mean±SD	77.9±21.90	37.3±24.30
P†		<.001
6 mo	137	136
Mean±SD	84.0±17.63	43.3±25.07
P		<.001
12 mo	135	134
Mean±SD	84.2±18.96	43.7±24.25
P		<.001

HRQoL, health-related quality of life.
Data are n unless otherwise specified.
* Change calculated for those with baseline and the visit-level follow-up data.
† *P* value from a Wilcoxon signed-rank test at each time point.

Among the patients whose qualifying leiomyoma (ta) indented the endometrial cavity (types 1, 2, or 2–5), the success rates for achieving 50% or greater reduction in pictorial blood loss assessment chart at 12 months were similar (64.3%, 68.0%, 61.9%; *P*=.94). For the 25.4% (36/142) of patients included in the analysis of the bleeding reduction coprimary endpoint whose only qualifying leiomyoma was a type 3 myoma, 63.9% (23/36) realized at least a 50% reduction in pictorial blood loss assessment chart score at 12 months. There were no significant differences in study success for either coprimary endpoint regarding the inclusion qualifying leiomyoma type, including patients whose sole qualifying leiomyoma was a type 3 myoma.

At 12 months postprocedure, the mean reduction in total uterine volume was 12.9% (n=133), from 267.3 cm^3 at baseline to 232.6 cm^3 at 12 months (*P*<.001). The mean maximal reductions in total and perfused leiomyoma volumes per patient from baseline to 12 months was 62.4% (n=129) and 63.9% (n=128), respectively (*P*<.001 for both).

There were no occurrences of device-related adverse events, serious or otherwise. There were two procedure-related serious adverse events reported in two patients (1.4%). One involved a deep venous lower extremity thrombus diagnosed 15 days postprocedure, managed as an outpatient without sequelae. The other event involved a patient who had received prophylactic antibiotics at the time of her treatment, but presented with a chief complaint of leukorrhea, pelvic pain, and unconfirmed low-grade fever 28 days postprocedure and was managed with overnight admission and broad-spectrum antibiotics. An independent medical advisory committee concluded that the event was related to leiomyoma sloughing and leukorrhea with no evidence of infection.

Nonserious procedure-related adverse events were reported in 74 patients (50.3%). These included leiomyoma sloughing (30.6%), cramping or pain

Table 5. Characteristics of Ablated Leiomyomas

Procedure Parameter	Value
Treated leiomyoma diameter (cm)	442
Less than 1	24 (5.4)
1–2	162 (36.7)
Greater than 2–3	117 (26.5)
Greater than 3–4	78 (17.6)
Greater than 4	61 (13.8)
Treated leiomyoma type	442
1	15 (3.4)
2	77 (17.4)
2–5	91 (20.6)
3	116 (26.2)
4	100 (22.6)
5	39 (8.8)
6	4 (0.9)
No. of leiomyomas/patient	147
Mean±SD	3.5±2.2
Median	3.0
Minimum, maximum	1.0, 10.0
No. of treated leiomyomas/patient	147
Mean±SD	3.0±2.1
Median	2.0
Minimum, maximum	1.0, 9.0
Treated leiomyoma diameter (cm)	442
Mean±SD	2.5±1.2
Median	2.3
Minimum, maximum	0.3, 6.5

Data are n or n (%) unless otherwise specified.

(7.5%), leukorrhea (6.1%), uncomplicated genitourinary infections (4.8%), nonspecific (constitutional) symptoms (3.4%), expelled leiomyoma (1.4%), flu-like symptoms (1.4%), nausea or vomiting (0.7%), and other nongynecologic events (constipation, sore throat, atelectasis, high blood pressure; 5.4%).

DISCUSSION

Several studies have advocated for more effective and better tolerated leiomyoma management, because women with uterine leiomyomas often delay or avoid treatment as a result of a lack of acceptable options.[2,23] The transcervical route may provide benefits to women with symptomatic leiomyomas compared with open or laparoscopic treatment options, including avoidance of the peritoneal cavity and no requirement for general anesthesia except when necessary on clinical grounds (eg, morbid obesity) or based on anesthesiologist or patient preference.

The leiomyoma ablation system described here could expand access to transcervical leiomyoma treatment beyond the smaller intracavitary or indenting leiomyomas treatable with operative hysteroscopy. In the Sonography Guided Transcervical Ablation of Uterine Fibroids trial, 79% of treated leiomyomas were intramural (types 3 and 4), transmural (type 2–5), and subserosal (types 5 and 6) myomata.

It is noteworthy that the trial included women with heavy menstrual bleeding who had type 3 myomata without leiomyomas that indented the endometrial cavity. At 12 months, these patients had treatment effectiveness similar to that of the overall study population. This suggests a possible association of type 3 leiomyomas with heavy menstrual bleeding. Previous work indicates that type 4 leiomyomas may also be associated with heavy menstrual bleeding.[24]

There were 24 treating investigators at 22 sites, including academic centers, community hospitals, and several private physician offices. This represents a wide variety of practicing obstetrician–gynecologists, none of whom had prior experience with transcervical leiomyoma ablation. Each investigator received the same training and support, consisting of didactic training followed by procedure simulation with a phantom model of a leiomyoma uterus. The Sonography Guided Transcervical Ablation of Uterine Fibroids trial results suggest that with appropriate training and support, transcervical radiofrequency ablation may be safely and effectively provided by obstetrician–gynecologists.

Limitations of the Sonography Guided Transcervical Ablation of Uterine Fibroids trial include a nonrandomized design, a limit of 5 cm, and the exclusion of patients who desired fertility. Although not randomized, Sonography Guided Transcervical Ablation of Uterine Fibroids is a multicenter interventional trial with prospectively defined endpoints having set objective performance criteria. Well-designed interventional trials can provide compelling evidence for the effectiveness of a treatment.[25,26] The Sonography Guided Transcervical Ablation of Uterine Fibroids trial included a robust patient selection process to minimize confounding factors, excluding patients with other etiologies of abnormal uterine bleeding such as anovulation, adenomyosis, and bleeding disorders. Furthermore, the study included a mix of patient-reported outcomes to complement the objective reintervention and bleeding primary endpoints.

Maximum leiomyoma diameter was limited to 5 cm in Sonography Guided Transcervical Ablation of Uterine Fibroids. For purposes of this pivotal trial, leiomyomas were selected that could normally be treated with a single ablation. However, larger leiomyomas could be treated with multiple ablations. In the Sonography Guided Transcervical Ablation of

Uterine Fibroids trial, 64 leiomyomas (14.5%) were treated with at least two ablations.

Patients who desired fertility were excluded as a result of ethical reasons because Sonography Guided Transcervical Ablation of Uterine Fibroids was a pivotal safety and effectiveness study. This enriched the eligible population for older patients and minimized the ability to track perinatal and postpartum outcomes. However, the study includes 3-year follow-up of patients and the reporting of any pregnancy outcomes should they occur. In addition, a worldwide clinical registry characterizing the long-term outcomes with transcervical leiomyoma ablation out to 5 years is ongoing (SAGE Global Registry, NCT # 03118037).

The 12-month results from the Sonography Guided Transcervical Ablation of Uterine Fibroids trial compare favorably with other nonextirpative leiomyoma treatments such as uterine artery embolization and laparoscopic radiofrequency ablation. Twelve-month surgical reintervention in the Sonography Guided Transcervical Ablation of Uterine Fibroids trial was 0.7% compared with 10% after uterine artery embolization in the REST trial and 0.7% after a single-arm prospective study of laparoscopic radiofrequency ablation with the Acessa System.[27,28] The percentage of patients who met the FDA-required bleeding endpoint at 12 months was higher for the Sonography Guided Transcervical Ablation of Uterine Fibroids trial (64.8%) than that seen in the pivotal trial of the Acessa System (40.2%).[28]

As demonstrated in the Sonography Guided Transcervical Ablation of Uterine Fibroids trial, transcervical leiomyoma ablation was associated with a significant reduction in leiomyoma symptoms with no device-related adverse events and a low surgical reintervention rate through 12 months. General anesthesia was not required except on clinical or patient and physician grounds. The findings from this study demonstrate the potential of the Sonata System to safely and effectively treat a variety of nonpedunculated leiomyoma types through a uterus-conserving, incisionless approach.

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Transcervical Radiofrequency Ablation of Symptomatic Uterine Fibroids: 2-Year Results of the SONATA Pivotal Trial

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Abstract

Objective: To report 2-year results of sonography-guided transcervical fibroid ablation (TFA) using the Sonata® system in women with symptomatic uterine fibroids.
Design: This is a prospective multicenter single-arm interventional trial.
Methods: Premenopausal women with up to 10 clinically relevant uterine fibroids, each ranging from 1 to 5 cm in diameter, were treated with sonography-guided TFA on an outpatient basis and returned for regular follow-up visits for 2 years. Assessed outcomes included changes in symptom severity, heath-related quality of life, general health status, work and activity limitations, treatment satisfaction, adverse events, surgical reintervention, and occurrence of pregnancy and associated outcomes.
Results: Among 147 enrolled women, 125 (85%) returned for follow-up at 2 years. Compared with baseline, symptom severity decreased from 55 ± 19 to 24 ± 18 ($p < 0.001$), health-related quality of life increased from 40 ± 21 to 83 ± 19 ($p < 0.001$), and EuroQol 5-Dimension scores increased from 0.72 ± 0.21 to 0.89 ± 0.14 ($p < 0.001$). Overall treatment satisfaction at 2 years was 94%. The mean percentage of missed work time, overall work impairment, and activity impairment significantly decreased at follow-up. Through 2 years, surgical reintervention for heavy menstrual bleeding was performed in 5.5% of patients. One singleton pregnancy occurred with a normal peripartum outcome.
Conclusions: TFA treatment with the Sonata system provides significant clinical improvement through 2 years postablation, with a low incidence of surgical reintervention. Other favorable outcomes included a rapid return to work and substantial improvements in quality of life, symptom severity, work productivity, and activity levels. (J GYNECOL SURG 00:000).

Keywords: transcervical fibroid ablation, radiofrequency ablation, leiomyoma, uterine fibroids, quality of life, ultrasonography

Introduction

Uterine fibroids are a highly prevalent gynecologic condition and can be identified in at least 70% of women by the age of 50 years.[1] Many women with fibroids are asymptomatic and require no intervention. However, at least one in three women with fibroids report symptoms such as heavy menstrual bleeding (HMB) and/or bulk symptoms that interfere with activities of daily living.[2] Women diagnosed with uterine fibroids also have a higher risk of anemia and infertility than women without this diagnosis.[3,4] Self-management of symptoms with nonprescription medication or lifestyle modification before seeking medical care is common, but often unsuccessful.[5]

Initial management of symptomatic fibroids may be guided by the patient's desire for future fertility. More than 200,000 hysterectomies are performed each year in the United States for the treatment of symptomatic fibroids.[6] However, there is growing concern that hysterectomy for fibroid treatment is overutilized[7] and patients are increasingly seeking less invasive uterus-preserving treatment options.[5] Myomectomy and uterine artery embolization (UAE)

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are uterus-preserving alternatives to hysterectomy that may be appropriate for well-selected patients. However, the acceptability of these treatments may be limited since 79% of women with symptomatic fibroids desire treatments that do not involve invasive surgery and 65% of women younger than 40 years prefer a treatment that preserves fertility.[5] In the case of UAE, future pregnancy is not recommended, and successful pregnancy outcomes are reduced after such treatment. Surgical reintervention rates for hysterectomy alternatives have been reported as high as 23.5% at 2 years.[8–11] Given the lack of treatment options that align with these preferences, women with symptomatic fibroids represent an underserved population who would benefit from the development of safer, less invasive, and equally or more effective treatment options.

Use of radiofrequency (RF) ablation as a therapeutic option for solid tumors has been increasing over the past two decades among various therapeutic areas. RF ablation heats targeted tissue, causing coagulative necrosis. To better address the needs of women with symptomatic fibroids, an incisionless uterus-preserving sonography-guided transcervical fibroid ablation (TFA) outpatient procedure has been developed. In the sonography-guided transcervical ablation of uterine fibroids (SONATA) pivotal trial, performed under an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA), clinically meaningful improvements in patient-reported symptoms, no device-related complications, and a surgical reintervention rate of <1% were reported through 1 year.[12] To characterize longer term safety and efficacy results with this procedure, we present 2-year results from this pivotal trial of sonography-guided transcervical RF ablation in women with symptomatic uterine fibroids.

Materials and Methods

Study design

SONATA was a prospective multicenter single-arm interventional trial of sonography-guided TFA in women with symptomatic uterine fibroids. The clinical trial was performed under an IDE approved by the FDA in the United States and the Federal Commission for Protection against Health Risks (COFEPRIS) in Mexico. Study enrollment began in April of 2015 and ended in October of 2016. Each patient provided informed consent to participate in the trial, and every clinical site obtained local institutional review board or ethics committee approval before commencing patient enrollment. The study was registered at ClinicalTrials.gov (NCT02228174).

Participants

Eligible subjects were premenopausal women aged 25 to 50 years with regular and predictable menstrual cycles, objective evidence of HMB, and with up to 10 fibroids of International Federation of Gynecology and Obstetrics (FIGO) types 1, 2, 3, 4, and/or 2–5 (transmural), each from 1 to 5 cm diameter. Types 5 and 6 subserous myomata were not counted in the total number of fibroids but could be ablated at the discretion of the investigator. At least one fibroid was required to have either indented or abutted the endometrial cavity (FIGO type 1, type 2, type 3, or types 2–5 fibroids). Women were excluded if they expressed a desire for future pregnancy, had any type 0 fibroids ≥1.0 cm or endometrial polyps ≥1.5 cm or multiple polyps of any size, bulk symptoms attributable to subserous fibroids, prior confounding procedures (endometrial ablation, UAE, uterine artery occlusion, or hyperthermic ablation of fibroids), uterine volume ≥1000 cm^3, presence of tubal implants for sterilization, and/or clinically significant adenomyosis.

Procedure

Clinical sites with community or academic gynecologists with generalist experience in hysteroscopic and/or laparoscopic surgery participated in the trial. Gynecologist training for the procedure entailed didactic instruction and practice on physical uterine models with various fibroid sizes, types, and locations. The sonography-guided TFA procedure used in the trial has been described in detail elsewhere.[12] The treatment device (Sonata® system; Gynesonics, Inc., Redwood City, CA) consists of an integrated intrauterine sonography probe and RF ablation handpiece that allows the gynecologist to identify, target, and ablate uterine fibroids. The integration of real-time ultrasound imaging enables the physician to visualize, target, and ablate a greater range of fibroids than could be approached through operative hysteroscopy.[12] A graphical interface is displayed on the live ultrasound image that identifies the target ablation area and the extent of subablative thermal heating. The gynecologist utilizes this information to confirm the ablation is within the fibroid while confining the thermal safety border to within the uterine serosa. A single ablation may suffice to treat a fibroid, but additional ablations may be necessary depending on fibroid size, location, and geometry. Anesthesia was individualized; general anesthesia was not a requirement.

Follow-up and outcomes

Patients returned for follow-up visits at 10 days, 30 days, 3 months, 6 months, 1 year, and 2 years. Follow-up remains ongoing in this trial through 3 years. Outcomes at 2 years included changes in symptom severity, health-related quality of life (HRQL), general health, and work/activity limitations; serious adverse events; surgical reintervention for HMB; and occurrence of pregnancy and associated outcomes. Symptom severity and quality of life were assessed with the symptom severity score (SSS) and HRQL subscales of the uterine fibroid symptom and quality-of-life questionnaire.[13] Scores are reported on a 0 to 100 scale where higher SSSs indicate more severe symptoms and lower HRQL scores indicate worse quality of life. Changes in general health status were assessed with the EuroQol 5-Dimension (EQ-5D) questionnaire. The EQ-5D consists of five questions that provide a description of the patient's health state with scores ranging from 0 (indicating death) to 1 (indicating perfect health). Patients self-reported their perceived treatment benefit at 2 years as *improved*, *no change*, or *worsened*. Treatment satisfaction was measured on a 6-item scale ranging from *very satisfied* to *very dissatisfied*. The work productivity and activity impairment questionnaire: specific health problem questionnaire[14] assessed change in work and activity patterns after treatment. Overall patient treatment outcome was assessed using the

overall treatment effect (OTE) scale. Adverse events were reported according to seriousness and relationship with the device or procedure.

Statistical analysis

Safety analyses included all treated patients and efficacy analyses excluded patients who reached menopause during follow-up. Data were reported using the mean and standard deviation for normally distributed continuous outcomes, median and interquartile range for non-normally distributed continuous data, and count and frequency for categorical data. The Wilcoxon signed-rank test assessed change over time for symptom severity, HRQL, general health, and work/activity limitation outcomes. Reintervention due to HMB was analyzed using Life-Table methods, with a sensitivity analysis using binomial methods (i.e., event count divided by evaluable sample size). Data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC). All statistical tests were two sided, and p-values of <0.05 indicated statistical significance.

Results

A total of 147 women (mean age 43 years, body mass index 29 kg/m^2) were enrolled at 22 sites (21 in the United States, 1 in Mexico). Demographic characteristics of the patients are provided in Table 1. All patients presented with HMB and their general health status measured on the EQ-5D was below the 25th percentile compared with sex- and age-matched population norms.[15] A mean of 3.0 (±2.1) fibroids per patient were treated with transcervical RF ablation. Patient characteristics and procedural details have been previously reported.[12] A total of 125 (85%) patients returned for follow-up at 2 years. Six patients missed the 2-year follow-up visit and 16 patients withdrew from the study before the 2-year follow-up visit (none due to an adverse event).

Over the 2-year follow-up period, mean values on the SSS decreased from 55 ± 19 to 24 ± 18 ($p < 0.001$), HRQL scores increased from 40 ± 21 to 83 ± 19 ($p < 0.001$) (Fig. 1), and EQ-5D scores increased from 0.72 ± 0.21 to 0.89 ± 0.14 ($p < 0.001$) (Fig. 2). Patient satisfaction with treatment at 2 years was 94% (75% of patients reported they were very satisfied, 13% were moderately satisfied, 6% were somewhat satisfied, 0% were somewhat dissatisfied, 4% were moderately dissatisfied, and 2% were very dissatisfied). At 2 years, 88% of patients reported improvement in fibroid symptoms on the OTE questionnaire compared with baseline. Indicators of work impairment due to fibroid symptoms significantly improved from baseline to 2 years. The percentage of missed work time significantly decreased from a mean of 2.9% to 1.3% ($p < 0.001$) and the overall percentage of work impairment also demonstrated significant improvement, being reduced from a mean of 51% to 14% ($p < 0.001$). Patients also reported significant reductions in the percentage of activity impairment due to fibroid symptoms over this period (mean of 58% to 14%, $p < 0.001$).

One-year safety outcomes with sonography-guided transcervical RF ablation in this trial were previously reported.[12] In brief, procedure-related serious adverse events

Table 1. Baseline Patient Characteristics

Variable	*Value (n = 147)*
Age, years	42.9 ± 4.3 [31, 50]
Ethnicity	
Hispanic or Latina	43 (29.3)
Not Hispanic or Latina	104 (70.7)
Race[a]	
American Indian or Alaska Native	3 (2.0)
Asian	2 (1.4)
Black or African American	49 (33.3)
Native Hawaiian or other Pacific	1 (0.7)
White	60 (40.8)
Other	33 (22.4)

Values are mean ± standard deviation [minimum, maximum], or count (percentage).

[a]Patients can be counted more than once if multiple races were indicated.

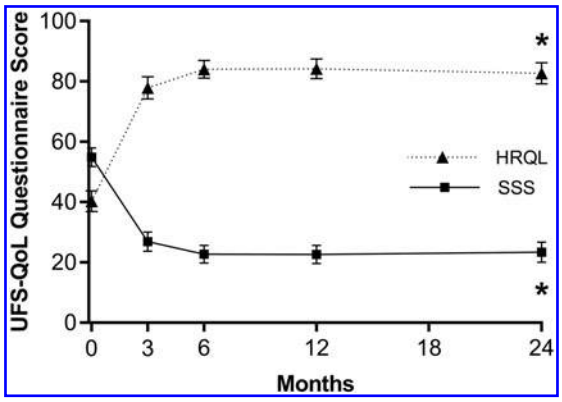

FIG. 1. Change in SSS and HRQL subscales of the UFS-QoL questionnaire for 2 years after sonography-guided transcervical fibroid ablation. Lower SSSs indicate less severe symptoms. Higher HRQL scores indicate better quality of life. Plotted values are mean and 95% confidence interval. *$p < 0.001$ for change from baseline. HRQL, health-related quality of life; SSS, symptom severity score; UFS-QoL, uterine fibroid symptom and quality of life.

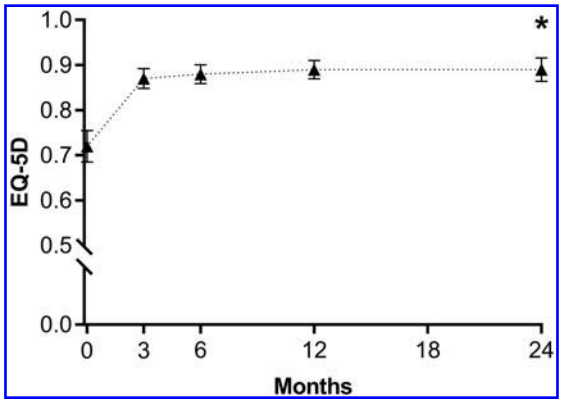

FIG. 2. Change in EQ-5D questionnaire score for 2 years after sonography-guided transcervical fibroid ablation. Plotted values are mean and 95% confidence interval. *$p < 0.001$ for change from baseline. EQ-5D, EuroQol 5-Dimension.

were reported in 2 (1.4%) patients during the first year of follow-up without any device-related adverse events during this period. Between the 1- and 2-year follow-up visits, there were no serious adverse events and no adverse events related to the device or procedure. The cumulative rate of surgical reintervention for HMB through 2 years was 5.2% (95% confidence interval [CI]: 2.5%–10.6%) using Life-Table methods and 5.5% (95% CI: 2.2%–11.0%) using binomial methods. One singleton pregnancy was reported in a 36-year-old multigravida who conceived 22 months after ablation. The patient delivered a liveborn male infant at 38 2/7 weeks gestation by elective repeat cesarean section with Apgar scores of $9^1/10^5$ and a birth weight of 4005 g. Visual inspection of the endometrial cavity appeared within normal limits and there was no evidence of uterine dehiscence or rupture.

Discussion

Women with symptomatic uterine fibroids are often treated with hysterectomy and other significantly invasive and potentially morbid procedures. Although hysterectomy is definitive treatment for fibroids, it removes the possibility of future pregnancy, and there are concerns about potential need for blood products; complications (including long-term effects such as pelvic prolapse), lost work time; possible earlier menopause; and increased osteoporosis risk.[5,16,17]

Most affected women prefer uterine-conserving treatments irrespective of their desire for childbearing.[5] Therefore, a safe, effective, and convenient less invasive treatment option for symptomatic fibroids would be welcomed by patients and health care providers alike. Sonography-guided TFA was developed to bridge this therapeutic gap. Although promising results with this technology have been reported in previous studies,[18,19] this study is the largest conducted to date. The 2-year results of the SONATA Pivotal IDE Trial demonstrate that sonography-guided TFA is a safe outpatient incisionless and uterus-preserving procedure, which provides significant durable symptom relief, and significantly improves general and condition-specific quality of life through 2 years.

Results with sonography-guided TFA in the current trial are comparable with those reported in previously published studies with this technology. A clinical trial (Fibroid Ablation Study-EU) in Europe and Mexico that followed 50 patients treated with the Sonata System (previously VizAblate®) for 1-year reported encouraging results.[19] During follow-up, fibroid volume decreased by 67%, fibroid symptoms significantly improved, and overall safety was excellent. Long-term results from the VITALITY Clinical Study demonstrated that symptom resolution persisted in 17 women treated with the Sonata System for 5.4 years mean follow-up, with no surgical reintervention for the first 3.5 years, a 11.8% rate of surgical reintervention at 5 years for HMB, and an overall surgical reintervention event rate of 2.2% per year.[20] One-year results from the current SONATA trial were previously reported in which fibroid volume decreased by 62%, fibroid symptoms significantly improved, and the surgical reintervention rate was 0.7%. The current report extends these previous results to 2 years, in which efficacy was durably maintained, one pregnancy with a normal peripartum outcome resulted, and no new safety concerns were identified. The 2-year surgical reintervention rate reported herein for TFA of uterine fibroids was 5.5%. This is noteworthy, considering the rates of reintervention for other procedures reported at 2 years were 23.5% for UAE, 18% for hysteroscopic myomectomy, 19% for endometrial ablation, and 8% for laparoscopic myomectomy.[9,21]

TFA was performed with acceptable safety in this study. Transcervical access involves no incisions and avoids the peritoneal cavity, which minimizes iatrogenic complication risks inherent with transperitoneal surgery such as wound infection or ureteral injury. Patients were discharged $\sim$2 hours after the procedure and treatment satisfaction was high. Although general anesthesia was used in 50% of patients largely due to patient or anesthesiologist preference, it is not a requirement and most patients treated with conscious sedation experienced minimal procedural discomfort. Because a varied mixture of community and academic generalist gynecologists were recruited and provided treatment after a brief standardized didactic and practical training program, this procedure appears to be generalizable to a broad range of gynecologists since specialized sonography expertise was neither required nor assumed. As with any new treatment, thoughtful patient selection and careful attention to the prescribed procedural technique are important for optimal results. Thorough differential diagnosis should be performed to determine whether patient symptoms are attributable to uterine fibroids or other causes such as anovulation, adenomyosis, or bleeding disorders. Shared decision-making between patient and provider should dictate the preferred procedure for symptomatic fibroid treatment. Published clinical results demonstrate that TFA is a safe and effective option that can be included in the gynecologist's armamentarium of treatment options among patients seeking treatment for symptomatic fibroids.

Conclusion

TFA treatment with the Sonata system provides significant clinical improvement through 2 years postablation, with a low incidence of surgical reintervention and a favorable safety profile. Other outcomes included a rapid return to work and substantial improvements in quality of life, symptom severity, work productivity, and activity levels.

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Author Disclosure Statement

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Three-Year Results of the SONATA Pivotal Trial of Transcervical Fibroid Ablation for Symptomatic Uterine Myomata

Andrea Lukes, MD,[1] and Minda A. Green, MD[2]

Abstract

Objective: This article reports on 3-year clinical outcomes of the Sonography Guided Transcervical Ablation of Uterine Fibroids (SONATA) pivotal trial of transcervical fibroid ablation (TFA) in women with symptomatic uterine myomata.

Materials and Methods: The SONATA, prospective, controlled, multicenter interventional trial enrolled 147 premenopausal women with symptomatic uterine fibroids who underwent uterus-preserving, sonography-guided TFA with the Sonata® System (Gynesonics, Inc., Redwood City, CA, USA). Clinical outcomes were assessed over 3 years and included surgical reinterventions, Symptom Severity Score (SSS), and Health-Related Quality of Life (HRQoL) subscales of the Uterine Fibroid Symptom and Quality-of-Life Questionnaire, EuroQol 5-Dimension (EQ-5D) questionnaire, Overall Treatment Effect, treatment satisfaction, physical activity, work impairment, pregnancy outcomes, and adverse events.

Results: The 3-year rates of surgical reintervention for heavy menstrual bleeding calculated by the binomial and Kaplan–Meier methods were 9.2% and 8.2%, respectively. Compared to baseline, mean SSS decreased from 55 ± 19 to 22 ± 21, HRQoL increased from 40 ± 21 to 83 ± 23, and EQ-5D increased from 0.72 ± 0.21 to 0.88 ± 0.16 (all $p < 0.001$). Treatment benefit on the SSS, HRQoL, and EQ-5Q exceeded the minimal clinically important difference at every follow-up visit over 3 years. At 3 years, 94% of the subjects reported treatment satisfaction, 88% reported reduced fibroid symptoms, work absenteeism due to fibroid symptoms decreased from 2.9% to 1.4%, and impairment due to fibroids decreased from 51% to 12% for work, and 58% to 14% for physical activity (all $p < 0.001$). No late complications occurred.

Conclusions: Women treated with sonography-guided TFA in the SONATA pivotal trial experienced significant and durable reduction of fibroid-related symptoms, with low surgical reintervention rates over 3 years of follow-up.

Keywords: leiomyoma, radiofrequency ablation, SONATA, TFA, transcervical fibroid ablation, uterine fibroid

Introduction

Uterine fibroids are the most common benign pelvic tumors in women, and are present in nearly 70% of white women and more than 80% of black women in the United States prior to menopause.[1] Among women with fibroids, more than one-half (54%) report myoma-associated symptoms, such as heavy menstrual bleeding (HMB) and about one-third of women with fibroids report symptoms severe enough to have a negative impact on activities of daily living (ADLs) such as sexual activity, work attendance and performance, and personal relationships.[2,3] The combined effect of the direct costs attributable to fibroid diagnosis and treatment, plus the indirect costs due to work absenteeism and loss of productivity, are responsible for a significant economic burden of $34 billion annually in the United States.[4]

A variety of treatment options are available to women with symptomatic uterine fibroids, each option with its own advantages and disadvantages. Because the etiology and location of fibroids as well as the presentation of symptoms

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is quite heterogeneous among affected women, the ideal therapy should be determined by shared decision-making between a woman and her gynecologist after full consideration of important factors, such as fibroid location/size, desire to preserve fertility and/or uterus, and willingness to undergo invasive surgery. In a survey of 968 women reporting symptoms caused by uterine fibroids, 79% expressed a desire for treatments that avoided invasive surgery and 51% favored treatments that preserved their uteri.[5]

To fill the existing uterine-fibroid treatment gap between the poor effectiveness of medical management and the invasiveness and radical approach of hysterectomy, less-invasive methods of fibroid treatment have been developed that conserve the uterus. Radiofrequency (RF) ablation—which can be delivered by laparoscopic, transvaginal, or transcervical approaches—has emerged as a safe and effective treatment option to fill this unmet need.[6–9] A meta-analysis of 32 studies with more than 1200 patients concluded that RF ablation provided statistically significant and clinically important reductions of fibroid-related symptoms and improvements in quality of life, with low surgical reintervention rates.[6] Transcervical fibroid ablation (TFA) has certain advantages that might appeal to patients, including a noninvasive delivery method, uterine preservation, ability to treat a wide range of fibroid types, avoidance of general anesthesia, and rapid recovery and return to ADLs following the procedure.

The Sonography Guided Transcervical Ablation of Uterine Fibroids (SONATA) trial was a U.S. Food and Drug Administration (FDA) Investigational Device Exemption (IDE) pivotal trial designed to assess the safety and efficacy of TFA in women with symptomatic uterine fibroids. Previously, the 1-year and 2-year results from this trial were reported.[10,11] Here, this article presents the 3-year results from the SONATA pivotal trial.

Materials and Methods

The SONATA trial was a prospective, controlled, multicenter interventional trial designed to assess the safety and efficacy of TFA for treatment of symptomatic uterine fibroids, compared to predefined objective performance criteria established by the FDA. Each participating site received institutional review board or ethics committee approval and all patients provided informed consent to participate in the trial. The clinical trial was registered at ClinicalTrials.gov (NCT02228174) and was approved by the FDA in the United States and by the Federal Commission for Protection against Health Risks (COFEPRIS) in Mexico.

The trial was specifically designed to enroll women experiencing symptoms caused by a wide range of uterine fibroid types, with each woman serving as her own control. The key inclusion criteria for the trial were premenopausal women ages 25–50 with regular and predictable menstrual cycles in order to minimize the effect of bias from rare naturally improving symptoms and to minimize inclusion of women with anovulatory abnormal uterine bleeding (AUB-O). In addition, patients had HMB with between 1 and 10 International Federation of Gynecology and Obstetrics (FIGO) type 1, 2, 3, 4, and/or 2–5 (transmural) uterine fibroids between 1 and 5 cm in diameter, at least 1fibroid of which must have indented or abutted the endometrial cavity (type 1, type 2, type 3 or type 2–5).

The key exclusion criteria were:

(1) Desire for future pregnancy
(2) Any type 0 fibroid ≥1.0 cm, endometrial polyps ≥1.5 cm, or multiple polyps of any size
(3) Bulk symptoms in association with subserous fibroids
(4) Previous endometrial ablation, uterine artery embolization (UAE), uterine artery occlusion, or hyperthermic ablation of fibroids
(5) Uterine volume ≥1000 cm^3
(6) Presence of tubal implants for sterilization, or
(7) Clinically significant adenomyosis

The TFA device and procedure used in the trial was described in detail previously.[9,12] TFA was performed using the Sonata® System (Gynesonics, Inc., Redwood City, CA, USA). Following the procedure, patients returned at 10 days, 30 days, 3 months, 6 months, and annually thereafter through the final follow-up visit at 3 years. The 24- and 36-month follow-up timepoints were included to gather longer-term data during the postmarket phase and were not included to support the application for FDA clearance.

The coprimary endpoint of surgical reintervention rate due to HMB was reported using Kaplan–Meier methods, with a sensitivity analysis using binomial methods wherein the event count was divided by the evaluable sample size. Secondary endpoint measurements included the symptom severity score (SSS) and health-related quality of life (HRQoL) subscales of the Uterine Fibroid Symptom and Quality-of-Life (UFS-QoL) Questionnaire.[13] Scores were reported on a 0–100 scale on which higher SSS scores indicated more-severe symptoms and lower HRQoL scores indicated worse quality of life. Change in general health status was assessed with the EuroQol 5-Dimension (EQ-5D) questionnaire. Patients self-reported their treatment benefit at 3 years as *improved*, *no change*, or *worsened* on the McMaster Overall Treatment Effect (OTE) scale. Treatment satisfaction was measured on a 6-item scale ranging from *very satisfied* to *very dissatisfied.* The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) questionnaire was used to assess change in work and activity patterns following treatment.[14] Adverse events (AEs) were reported according to seriousness and relationship to the device or procedure.

Safety analyses included all treated patients and efficacy analyses excluded patients who reached menopause, underwent surgical reintervention, or who withdrew from the trial during follow-up. The Wilcoxon signed-rank test was used to assess change over time for symptom severity, HRQoL, general health, and work/activity limitation outcomes.

To facilitate clinical interpretation of results, the treatment effects were also reported for SSS, HRQoL, and EQ-5D in standardized minimal clinically important difference (MCID) units, wherein the standardized MCID for each outcome was calculated as the mean change from baseline divided by the MCID.[15,16] The published MCID for each outcome is a 10-point decrease for SSS,[17] a 20-point increase for HRQoL,[13] and a 0.074-point increase for EQ-5D.[18] Treatment effects below 0.5 MCID units indicate that it is unlikely that an appreciable number of patients will show a clinically important benefit. Treatment effects between 0.5 and 1 MCID units indicate that a treatment might be beneficial to an appreciable number of patients. Treatment effects above 1

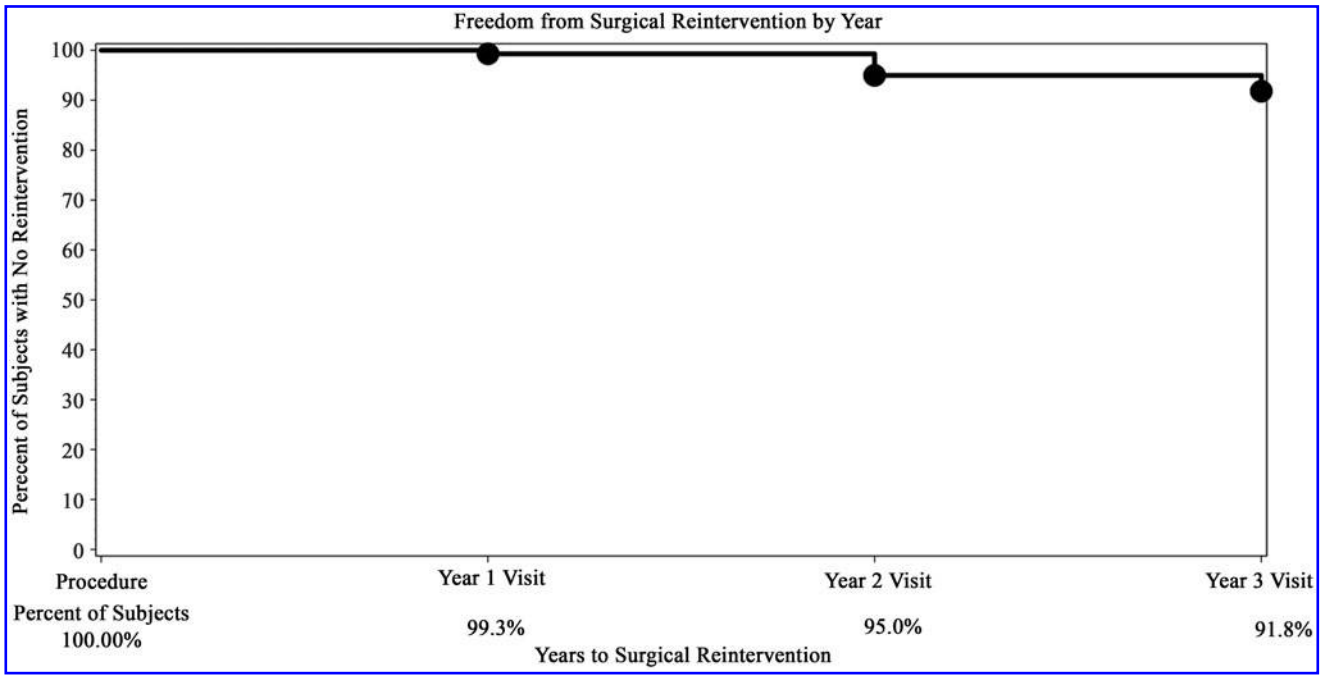

FIG. 1. Kaplan–Meier estimate of freedom from surgical reintervention due to heavy menstrual bleeding over 3 years following sonography-guided transcervical radiofrequency ablation.

MCID unit indicate that many patients might gain important benefits from treatment.[15,16] Data were analyzed using SAS, version 9.3 (SAS Institute, Cary, NC, USA). All statistical tests comparing 3-year results to baseline were 2-sided, and p-values <0.05 indicated statistically significant changes.

Results

Between April 2015 and October 2016, 147 women (mean age: 43) from 22 sites (21 in the United States, 1 in Mexico) were treated with TFA (mean: 3.0 ± 2.1 treated fibroids per patient; mean: 2.5 ± 1.2 cm per treated fibroid). Fifteen patients were lost to follow-up during the trial, with 132 (90%) patients accounted for at 3 years. Surgical reinterventions for HMB during follow-up included 10 hysterectomies and 1 endometrial ablation. The rates of surgical reintervention for HMB calculated with the binomial method were 0.7% at 1 year, 5.5% at 2 years, and 9.2% at 3 years during the postmarket phase. The corresponding rates using the Kaplan–Meier estimates were 0.7%, 5.0%, and 8.2%, respectively (Fig. 1).

The mean (± standard deviation) SSS decreased significantly from baseline to 3 months (55 ± 19 to 27 ± 19; $p < 0.001$), and this improvement was maintained durably where the final mean SSS was 22 ± 21 ($p < 0.001$) at the 3-year follow-up (Fig. 2).

Similarly, HRQoL scores increased from 40 ± 21 at baseline to 78 ± 22 at 3 months ($p < 0.001$), and to 83 ± 23 at 3 years ($p < 0.001$) (Fig. 3). EQ-5D increased from 0.72 ± 0.21 at baseline to 0.87 ± 0.13 at 3 months ($p < 0.001$), and to 0.88 ± 0.16 at 3 years ($p < 0.001$) (Fig. 4). When considering these treatment effects associated with TFA at each follow-up visit over 3 years in relation to established MCIDs, the improvements ranged from 2.8 to 3.2 MCID units for SSS, 1.9 to 2.2 MCID units for HRQoL, and 2.0 to 2.3 MCID units for EQ-5D (Fig. 5), indicating that, for each of these outcomes at each follow-up interval, ''many patients may gain important benefits from treatment.''[15,16]

At 3 years, 94% (99/105) of patients reported satisfaction with TFA treatment (71% very satisfied, 14% moderately satisfied, 9% somewhat satisfied) and 88% (92/105) of patients reported reduced fibroid symptoms, compared to baseline on the OTE questionnaire. All work productivity and activity level parameters improved significantly during the 3-year follow-up. Work absenteeism due to symptoms of uterine fibroids decreased by more than 50% (from 2.9% to 1.4% of total work time) during follow-up ($p < 0.001$). The magnitude of impairment due to uterine fibroids was dramatically reduced during the trial, with reductions from 51% to 12% for work impairment ($p < 0.001$) and from 58% to 14% for physical activity impairment ($p < 0.001$).

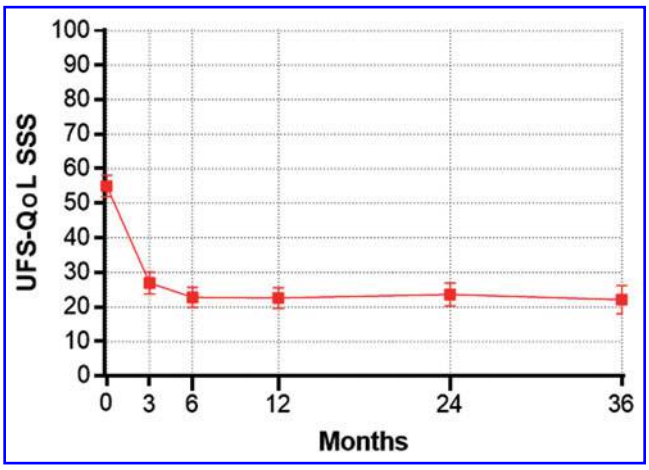

FIG. 2. Change in symptom severity score (SSS) subscale of the Uterine Fibroid Symptom and Quality-of-Life (UFS-QoL) questionnaire over 3 years following sonography-guided transcervical radiofrequency ablation. Plotted values are mean and 95% confidence interval.

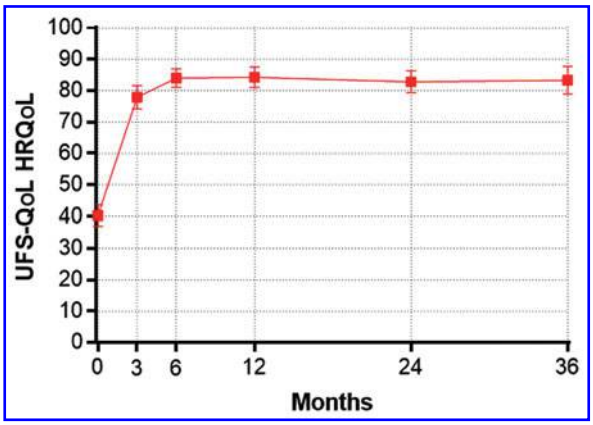

FIG. 3. Change in Health-Related Quality of Life (HRQoL) subscale of the Uterine Fibroid Symptom and Quality-of-Life (UFS-QoL) questionnaire over 3 years following sonography-guided transcervical radiofrequency ablation. Plotted values are mean and 95% confidence interval.

The 1-year safety outcomes with sonography-guided TFA in this trial were previously published,[10] wherein procedure-related serious AEs were reported in 2 (1.4%) patients (1 with a deep venous lower-extremity thrombus and 1 with a 1-day admission for sterile leukorrhea, pelvic pain, and an unconfirmed low-grade fever), nonserious procedure-related AEs were reported in 74 (50.3%) patients (most commonly leiomyoma sloughing), and no device-related AEs occurred during this time period. No serious complications or AEs related to the device or procedure occurred during the second or third year of patient follow-up. Two pregnancies were reported through 3 years. One pregnancy occurred in a 36-year-old patient who delivered at 38 2/7 weeks gestation by elective repeat Cesarean section, 31 months after TFA.[11] One miscarriage was reported in a 40-year-old subject 29 months after the Sonata treatment.

Discussion

Women who experience disruptive symptoms due to uterine fibroids comprise a challenging and underserved patient population. Only approximately one-third of women with symptomatic uterine fibroids seek treatment, and those who seek help often do so only after a considerable delay of nearly 4 years.[5] The availability of less-invasive, uterus-sparing procedures might help to facilitate earlier treatment for symptomatic uterine fibroids. This article presented the 3-year results from the SONATA trial in which 147 women with a wide variety of fibroid types were treated with TFA. Treatment with the Sonata System was shown to be safe with a low rate of procedure-related AEs, all occurring during the first year of follow-up. Furthermore, the magnitude of reduction of fibroid-related symptom severity and improvement in HRQoL was both clinically important and statistically significant at all follow-up intervals between 3 months and 3 years post-treatment. Finally, the rate of surgical reintervention for HMB was low and favorable, indicating that the treatment benefit was maintained durably over the 3-year follow-up time period.

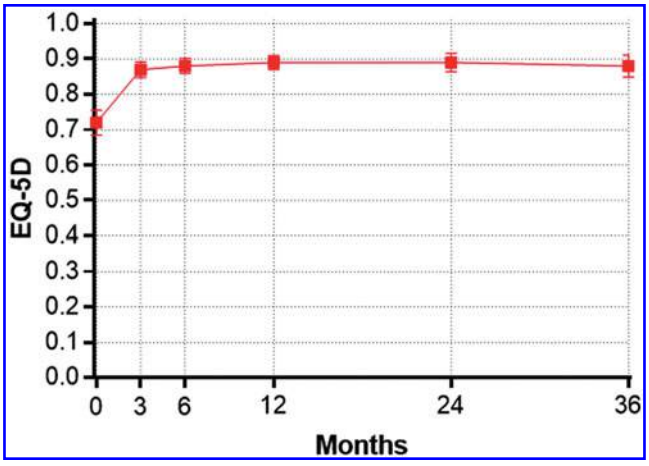

FIG. 4. Change in EuroQol 5-Dimension (EQ-5D) questionnaire score over 3 years following sonography-guided transcervical radiofrequency ablation. Plotted values are mean and 95% confidence interval.

There are several key attributes of TFA with the Sonata System that make it a preferable treatment option for appropriate women with symptomatic uterine fibroids. The procedure is incisionless, preserves the uterus, and has been shown to be safe and effective, producing durable symptom relief. Unlike operative hysteroscopy, TFA is designed for ablation of most nonpedunculated fibroid types. Among women treated with sonography-guided TFA in this trial, 8.2% underwent elective surgical reintervention for HMB over 3 years of follow-up.

These results appear to be favorable, compared to other common interventional and surgical procedures for uterine fibroids. For example, surgical reinterventions were performed in 11.0% of patients who were followed for 3 years after laparoscopic RF ablation of uterine fibroids.[19] In addition, in a meta-analysis involving more than 35,000 women, surgical reintervention rates over 3 years were 9% with abdominal myomectomy, 11% with laparoscopic myomectomy, 17% with UAE, 21% with hysteroscopic myomectomy, and 24% with endometrial ablation.[20]

The SONATA trial design specified 3 years of patient follow-up. There is published evidence showing that surgical reintervention rates have remained low beyond 3 years following TFA. In the VITALITY study that evaluated long-term clinical outcomes of TFA over 5.4 years of mean follow-up, the surgical reintervention rate was 11.8%.[21] Additional long-term data with the Sonata System will be available from the SAGE registry (ClinicalTrials.gov Identifier: NCT03118037), a worldwide observational postmarket study trial with the objective of characterizing long-term (5 years) outcomes after treatment of uterine fibroids with the Sonata System in real-world clinical practice settings.

The conclusions derived from this trial are robust and generalizable for several reasons. The trial enrollment included considerable ethnic and racial diversity of patients, with regional geographic representations from throughout the United States in participating centers (21 centers in the United States and 1 in Mexico). These results were achieved with 24 treating investigators, and included results from academic and community hospitals, ambulatory surgery centers, and office procedural rooms. Considering the demonstrated safety and efficacy of the Sonata treatment in a diverse patient population treated by a large number of treating physicians and different care settings, TFA is an

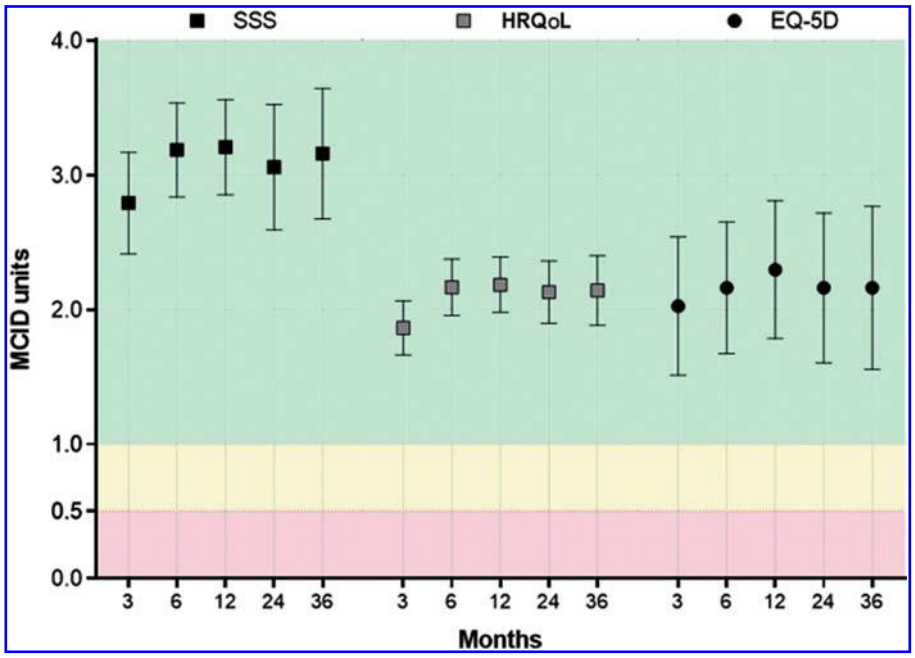

FIG. 5. Improvement in quality of life from baseline following sonography-guided transcervical radiofrequency ablation, reported in standardized minimal clinically important difference (MCID) units with 95% confidence intervals. The MCID is 10 points for Uterine Fibroid Symptom and Quality-of-Life (UFS-QoL) Symptom Severity Score (SSS), 20 points for UFS-QoL Health-Related Quality of Life (HRQoL), and 0.074 points for the EuroQol 5-Dimension (EQ-5D) questionnaire. Treatment effects below 0.5 MCID units (denoted by *red* background) indicate that it is unlikely that an appreciable number of patients will show a clinically important benefit. Treatment effects between 0.5 and 1 MCID units (denoted by *yellow* background) indicate that a treatment may be beneficial to an appreciable number of patients. Treatment effects above 1 MCID unit (denoted by *green* background) indicate that many patients might gain important benefits from treatment.[15,16]

appealing option with durable outcomes that can be included in a gynecologist's armamentarium of treatments for patients seeking treatment for symptomatic uterine fibroids.

Conclusions

Women treated with TFA for symptomatic uterine fibroids in the SONATA pivotal IDE trial experienced significant and durable reductions of fibroid-related symptoms with low surgical reintervention rates over 3 years of follow-up.

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ORIGINAL RESEARCH

The CHOICES Study: Facility Level Comparative Cost, Resource Utilization, and Outcomes Analysis of Myomectomy Compared to Transcervical Fibroid Ablation

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Purpose: The CHOICES study compared short-term resource utilization, facility costs, and perioperative patient outcomes between transcervical fibroid ablation (TFA) with the Sonata® system and myomectomy through a case-matched comparative trial design. This is the first facility-level comparative study conducted for TFA.

Patients and Methods: The study enrolled 88 patients from 4 centers equally divided among the two cohorts. The TFA arm consisted of 44 women who had enrolled in the SONATA Pivotal IDE trial, whereas the myomectomy arm included 44 patients who were identified through retrospective case-matching to the enrolled SONATA patients at the same 4 centers.

Results: TFA had a significantly lower mean operating room duration (90 minutes) and length of stay (5.2 hours) than myomectomy (143 minutes and 45.8 hours, respectively). The average total mean facility costs for TFA procedure ($7,563) were significantly lower than those associated with myomectomy ($11,425; p=0.002). TFA mean facility costs were also compared with other stratifications of myomectomy (inpatient or outpatient and surgical route). TFA facility costs were significantly lower than that associated with inpatient, abdominal, or laparoscopic myomectomy (all p<0.001).

Conclusion: TFA using the Sonata system has a significantly shorter operating room time and length of stay than myomectomy for the treatment of symptomatic uterine fibroids. All procedure, anesthesia, laboratory, pathology, and pharmacy costs were significantly higher for myomectomy as compared to TFA. TFA was also associated with significantly lower facility procedure-related costs compared to myomectomy, including inpatient, abdominal, or laparoscopic myomectomy.

Keywords: uterine fibroids, Sonata, transcervical ablation, uterine preserving, cost, radiofrequency ablation

Introduction

Uterine fibroids, also known as leiomyomata uteri, are common benign uterine tumors typically found in women of reproductive age. While the true prevalence is unknown and likely underestimated, it has been reported that the prevalence of fibroids in premenopausal women is 70–80% or greater, depending on ethnicity.[1,2] The symptoms of fibroids include heavy menstrual bleeding, subfertility, urinary frequency, pelvic pressure and pain, and dyspareunia.[1]

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Current treatment of uterine fibroids is economically burdensome, with costs estimated at $4.1 billion-$9.4 billion in annual US health care costs and an additional $1.55 billion-$17.2 billion lost in annual work hours, in part due to the invasive nature of existing interventions.[3,4] Myomectomy is the most common uterine-preserving surgical procedure to treat uterine fibroids.[5]

Uterine fibroids may also be treated with a less invasive approach such as transcervical fibroid ablation (TFA) with the Sonata system. The transcervical route eliminates the need for incisions and the complications related to open and laparoscopic surgery, preserves the uterus and uterine myometrium, and minimizes the disruption to a woman's life. The Sonata system combines a single-use radiofrequency ablation handpiece with a reusable intrauterine ultrasound probe to form a single integrated device, eliminating the need to coordinate multiple devices. The procedure has been associated with a significant reduction in symptoms, short recovery time, and length of stay (LOS).[6,7] The clinical safety and effectiveness of this procedure has been previously reported.[7–9]

The purpose of the CHOICES study was to compare short-term resource utilization, facility costs, and perioperative patient outcomes between TFA and myomectomy through a case-matched comparative study design. This is the first facility-level comparative study conducted for TFA with the Sonata system.

Patients and Methods

A comparative case-matched, 30-day outcomes and facility cost analysis was conducted. Costs and procedure-related complications data were collected prospectively for the TFA arm within a multi-center longitudinal clinical trial called SONATA and retrospectively for the myomectomy arm through case-matched patient data collection. As such, original SONATA trial centers were invited to participate if they fulfilled the following criteria: 1) their number of patients enrolled for the SONATA study was >5, 2) the center was interested in participating and had an adequate volume of myomectomy cases for inclusion in the comparator arm, and 3) is located within the continental United States.

Patient Selection

The TFA arm was derived from the SONATA clinical trial, a multicenter, prospective, longitudinal, single-arm clinical trial that verified the safety and effectiveness of the TFA procedure in the treatment of symptomatic uterine fibroids.[7] SONATA enrolled and treated patients with TFA between April 2015 and October 2016. Key patient eligibility criteria included women who were premenopausal and between 25 and 50 years of age, had experienced heavy menstrual bleeding associated with fibroids for at least the previous three months, had 1–10 fibroids of International Federation of Gynecology and Obstetrics (FIGO) types 1, 2, 3, 4, and/or type 2–5 with diameter between 1 and 5 cm, and had at least one fibroid that indented or abutted the endometrial cavity. Patients for the myomectomy arm were identified by case-matching to TFA arm participants at the same centers. Each site in the SONATA clinical trial gained local IRB approval or ethics committee approval, and the patients used in the SONATA trial provided appropriate consent for the data collected and reported in this study. The data in the myomectomy arm were collected retrospectively, and proper IRB approval or waiver was given by each site that provided data to the study. This study was in accordance with the Declaration of Helsinki. In addition, written informed consent was provided by the patients. See the Appendix for a list of institutions participating in this study. Data used in both the TFA arm and the myomectomy arm were collected from the same sites. There were no additional sites utilized for this study.

Comparator Arm Case-Matching Criteria

The criteria for identifying retrospectively matched myomectomy patients were based on 1) the dates during which SONATA patients were enrolled at that center, 2) the patient's Body Mass Index (BMI), and 3) the patient's age. Centers who agreed to participate were provided with data on the range of dates for TFA procedures at the center as well as the associated range of age and BMI from those cases to use in identifying matches. These ranges were based on the means and standard deviations (SDs) for patients recruited at those centers for TFA in the SONATA trial. The centers then reviewed their electronic medical records (EMR) to identify myomectomy patients meeting the criteria. If centers encountered difficulty in locating several matches equivalent to the number of TFA patients that participated at that center, the ranges for matching criteria were broadened until adequate matches were identified.

Data Collection

The primary outcomes of interest were operating room (OR) duration (defined as time patient entered treatment room to time patient exited treatment room), LOS (defined as time of

admission to time of discharge or time of eligibility for discharge as reported by the investigators), and the facility costs associated with the index procedure (TFA and myomectomy), including the index procedure hospitalization and any 30-day readmissions. Facility costs were derived from de-identified institution billing forms (UB-04) and health care provider billing forms (HCFA-1500) contributed by the centers for the procedures. A reimbursement specialist identified total charges from these forms and further divided them into the categories of procedure, anesthesia, supply (including the Sonata system), lab, pathology, and pharmacy charges based on each charge's description. For example, the procedure category included costs for operating room and recovery room time, among others, while supply costs included items such as sterile and non-sterile supplies. Fixed costs are defined by the NIH as those costs which do not vary with the quality of production. The categories defined above are the procedural fixed cost associated with each procedure. Once charges were identified for each center and study arm, cost-to-charge ratios (CCRs) were applied to each center to generate costs, with separate CCRs for procedures done in an inpatient or outpatient setting (Table 1). Specifically, all charges were converted into facility costs using each facility's own CCR obtained from the American Hospital Directory.[10]

The secondary outcome of interest was the occurrence of complications during the index procedure or hospital stay, and any 30-day readmissions following the procedure. TFA patients' perioperative complications and readmissions were reported in the SONATA trial and included in this analysis. Data on perioperative complications and readmissions for patients enrolled in the myomectomy arm were obtained from each facility's EMR.

Table 1 Cost-to-Charge Ratios by Center

Study Center	Setting	Cost-to-Charge Ratio
Center 01	Inpatient Outpatient	0.4670 0.6281
Center 02	Inpatient Outpatient	0.1237 0.0732
Center 03	Inpatient Outpatient	0.4787 0.2651
Center 04	Inpatient Outpatient	0.3392 0.6740

Analysis

All analyses were conducted in Stata (version 13; StataCorp LLC, College Station, Texas). Patient characteristics were reported for each study arm and compared with chi-square and Fisher's exact tests for categorical variables or paired t-tests for continuous variables. Means for OR duration, LOS, total costs, cost stratifications, and cost subcategories were reported (using 2016 dollars) and compared using paired t-tests for unequal variances. Stratifications included site of service (inpatient or outpatient) and procedure route (abdominal, laparoscopic, hysteroscopic). Cost subcategories included procedure, anesthesia, supply, laboratory (blood or serum collection and analysis), pathology (cell or tissue collection and analysis), and pharmacy costs. Median and interquartile range values for the same outcomes can be found in the Appendix. Finally, Fisher's exact test was used to compare the incidence of perioperative complications between the study arms. In all analyses, p-values <0.05 indicate statistical significance.

Results

Seven of the original 22 SONATA trial centers that fulfilled the inclusion criteria participated in this comparative case-matched study. Of the 7 centers that met the inclusion criteria, 1 center declined to participate and 2 centers were unable to provide cost data. As a result, 4 of the original SONATA trial centers provided 44 matched myomectomy patient records with usable cost, resource use, and perioperative outcomes data for this study. Thus, there were 44 patients in each of the 2 study arms (Table 2). TFA patients were compared with myomectomy patients on the demographic characteristics of age, BMI, race, and ethnicity. Because age was a matching characteristic, we expected the groups to be similar in this regard. However, some study centers had difficulty identifying myomectomy patients within the original age range requested, and in these instances the centers could extend the age range for matching patients to younger ages. Myomectomy patients were significantly younger than those in the TFA group, with a mean age of 37.5 ± 6.5 years as compared to 44.3 ± 3.6 ($p<0.001$). Mean BMI was significantly lower for myomectomy patients (27 ± 6 kg/m^2) than TFA patients (30 ± 7 kg/m^2; $p=0.010$). The study arms did not significantly differ in race ($p=0.250$) or in ethnicity ($p=0.494$).

OR Duration and LOS

Average OR duration and LOS were compared between the study arms (Table 3). Average OR duration (in minutes) was significantly lower for TFA (90 ± 38) than for

Table 2 Characteristics of Study Participants

Characteristic	Category	TFA (n=44)	Myomectomy (n= 44)	p-value
Age (Mean ± SD)		44 ± 4	38 ± 7	<0.001
BMI in kg/m^2 (Mean ± SD)		30 ± 7	27[a] ± 6	0.010
Race	**Black or African American** **White** **Other**	54.5% 36.4% 9.1%	41.9% 37.2% 20.9%	0.250
Ethnicity	**Hispanic** **Non-Hispanic**	0.0% 100.0%	4.5% 95.5%	0.494

Notes: *p*-value for age and BMI: *t*-test assuming unequal variances. *p*-value for race and ethnicity: chi-square for race, Fisher's exact test for ethnicity. [a]N=37 as height and weight data were unavailable from one site. Other category includes American Indian or Alaskan Native, Asian, Native Hawaiian or other Pacific Islander, and other races.
Abbreviations: BMI, body mass index; SD, standard deviation; TFA, transcervical fibroid ablation.

Table 3 Average OR Duration and Length of Stay

Index Procedure	Mean OR Duration (Minutes) Mean ± SD	p-value[a]	Mean LOS (Hours) Mean ± SD	p-value[a]
TFA (n=44)	90 ± 38	ref	5.2 ± 1.4	ref
Myomectomy (n=44)	143 ± 79	<0.001	45.8 ± 53.7[b]	<0.001

Notes: [a]Duration comparisons to TFA are both statistically significant. *p*-value: *t*-test assuming unequal variances; [b]n=43 due to missing data.
Abbreviations: LOS, length of stay; OR, operating room; SD, standard deviation; TFA, transcervical fibroid ablation.

myomectomy (143 ± 79; $p<0.001$). Similarly, LOS was significantly lower for TFA (5.2 ± 1.4 hours) than for myomectomy (45.8 ± 53.7 hours; $p<0.001$).

Procedure Costs

Figure 1 shows the total mean facility costs of the index procedure inclusive of hospital stay for each arm. The total mean facility costs were significantly lower for TFA ($7,563 ± $2,369) than for myomectomy ($11,425 ± $7,608; $p=0.002$). Each arm was further stratified by site of service and costs were compared (Table 4). Since TFA is an outpatient procedure, there is no cost data for inpatient. As shown, the total mean costs of TFA ($7,563 ± $2,369) were significantly lower than inpatient myomectomy procedures ($19,811 ± $6,330; $p<0.001$). The cost of TFA did not significantly differ from outpatient myomectomy procedures, inclusive of hysteroscopic procedures ($7,087 ± $3,420; $p=0.517$).

An additional analysis was carried out to compare costs by procedure route (Table 5). As shown, the total mean facility costs of TFA ($7,563 ± $2,369) were significantly lower than both abdominal myomectomy ($18,373 ± $5,548; $p<0.001$) and laparoscopic myomectomy ($10,352 ± $7,161; $p<0.001$). As there were only 7 cases of hysteroscopic myomectomy in the myomectomy arm, a statistical comparison could not be made; however, the mean cost of this procedure, which were all outpatient, trended lower in comparison to TFA.

Finally, total costs for the TFA and myomectomy arms were broken down by specific subcategories of facility costs, including procedure, anesthesia, supply, laboratory, pathology, and pharmacy costs. As shown in Table 6, all non-supply-related costs associated with TFA were significantly lower than those associated with myomectomy. As expected, supply costs of TFA (which included the Sonata treatment device)

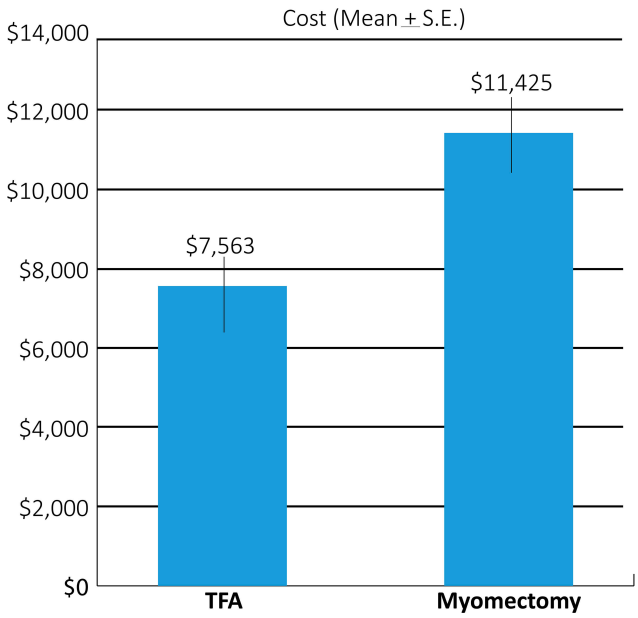

Figure 1 Mean facility costs.
Note: $p = 0.002$.
Abbreviations: SE, standard error; TFA, transcervical fibroid ablation.

Table 4 Procedure Cost by Site of Service

Index Procedure	Cost ($) Mean ± SD	p-value
TFA	7,563 ± 2,369	Ref
Inpatient (n=0)	N/A	-
Outpatient (n=44)	7,563 ± 2,369	Ref
Myomectomy	11,425 ± 7,608	0.002
Inpatient (n=15)	19,811 ± 6,330	<0.001
Outpatient (n=29)	7,087 ± 3,420	0.517

Note: *p*-value: *t*-test assuming unequal variances.
Abbreviations: SD, standard deviation; TFA, transcervical fibroid ablation.

Table 5 Procedure Cost by Route

Index Procedure	Cost ($) Mean ± SD	p-value
TFA (All Transcervical; n=44)	7,563 ± 2,369	Ref
Myomectomy	11,425 ± 7,608	0.002
Abdominal (n=11)	18,373 ± 5,548	<0.001
Laparoscopic (n=26)	10,352 ± 7,161	<0.001
Hysteroscopic (n=7)	4,493 ± 583	

Notes: *p*-value: *t*-test assuming unequal variances, value not reported when n<10.
Abbreviations: SD, standard deviation; TFA, transcervical fibroid ablation.

were significantly higher than the supply costs of myomectomy, which are mainly surgical tools. However, despite this difference in supply costs, the total mean facility costs of TFA remained significantly lower than myomectomy. This may be explained by the reduced procedure time and LOS associated with TFA due to the efficient transcervical route of delivery.

Complications

The 30-day complications requiring readmission and associated costs were sought for all patients, but no such readmissions were reported for either study arm. As such, total costs reflect the index procedure and hospitalization only. Patient outcome comparisons, in the form of complications, also reflect the index procedure hospitalization only. Any complications serious enough to require readmission within 30 days would have been captured in the study data. The occurrence of complications between TFA and myomectomy was compared. There were 3 complications reported in this study, all being blood loss requiring transfusion in the myomectomy arm patients (p=0.078; Table 7).

Table 7 Complications During Index Procedure or Index Procedure Hospitalization Compared to Sonata

Complications (Freq, %)	Sonata	Myomectomy	p-value
	n=44	n=44	
Acute myocardial infarction	0 (0.00)	0 (0.00)	-
Adhesions	0 (0.00)	0 (0.00)	-
Blood loss requiring transfusion	0 (0.00)	3 (6.82)	0.078
Bowel obstruction	0 (0.00)	0 (0.00)	-
Bowel or bladder perforation/injury	0 (0.00)	0 (0.00)	-
Death	0 (0.00)	0 (0.00)	-
Deep vein thrombosis (DVT)	0 (0.00)	0 (0.00)	-
Hematoma	0 (0.00)	0 (0.00)	-
Hemorrhage	0 (0.00)	0 (0.00)	-
Pelvic prolapse	0 (0.00)	0 (0.00)	-
Pneumonia	0 (0.00)	0 (0.00)	-
Pulmonary embolism (PE)	0 (0.00)	0 (0.00)	-
Sepsis	0 (0.00)	0 (0.00)	-
Surgical site infection (SSI)	0 (0.00)	0 (0.00)	-
Ureteral injury	0 (0.00)	0 (0.00)	-
Vaginal cuff dehiscence	0 (0.00)	0 (0.00)	-

Note: *p*-value: Fisher's exact test.

Table 6 Procedure and Hospitalization Cost

Index Procedure	TFA (n=44) Mean ± SD ($)	Myomectomy (n=44) Mean ± SD ($)	p-value
Total costs	**7,563 ± 2,369**	**11,425 ± 7,608**	**0.002**
Procedure costs	2,998 ± 2,062	6,427 ± 4,913[a]	<0.001
Anesthesia costs	451 ± 317	1,082 ± 1,165[a]	<0.001
Supply costs	4,084 ± 331	1,461 ± 936	<0.001
Lab costs	9 ± 18	193 ± 431	0.007
Pathology costs	17 ± 43	165 ± 137	<0.001
Pharmacy costs	3 ± 10	473 ± 749[a]	<0.001

Notes: *p*-value: *t*-test assuming unequal variances; [a]n=43 due to missing data.
Abbreviations: IQR, interquartile range; SD, standard deviation; TFA, transcervical fibroid ablation.

Discussion

CHOICES is the first comparative study evaluating myomectomy and TFA with the Sonata system. Results for procedure costs, resource utilization, and perioperative patient outcomes favored TFA over myomectomy. Specifically, TFA had a significantly lower OR duration and LOS. Furthermore, TFA had a significantly lower total mean facility cost than myomectomy (all combined), inpatient myomectomy, abdominal myomectomy, and laparoscopic myomectomy. The subcategories of all hospital costs other than the procedure supplies were significantly lower for TFA than myomectomy. Many of these cost differences may be associated with the significantly longer OR duration and LOS for myomectomy as compared to TFA. Neither arm reported any 30-day readmissions, and the only perioperative complications noted occurred in the myomectomy arm.

To identify possible cost drivers, various stratification analyses were conducted. Stratifications included site of service (inpatient or outpatient) and procedure route (abdominal, laparoscopic, hysteroscopic). Cost subcategories included procedure, anesthesia, supply, laboratory, pathology, and pharmacy costs. Stratification analyses by site of service and procedure route yielded predictable results. When comparing outpatient myomectomy procedures with TFA, costs did not significantly differ, as one would expect, because TFA is an outpatient treatment. In addition, cost of hysteroscopic myomectomy trended lower than TFA. Hysteroscopic myomectomy is a transcervical procedure with a limited range of treatable fibroid types (ie, only submucosal fibroids) and a different cost profile from either laparoscopic or abdominal myomectomies.[11] TFA can treat all non-pedunculated fibroids (including submucosal, transmural, intramural, and selected subserosal fibroids) that are not amenable to hysteroscopic myomectomy (which is limited to intracavitary and small indenting fibroids). Therefore, the treatment of fibroids with laparoscopic or abdominal myomectomies vs TFA is the more relevant comparison given the range of treatable fibroid types. Despite this lower cost trend for hysteroscopic myomectomy, the total mean facility cost of TFA was significantly lower than all combined myomectomy procedures.

Analysis of hospital cost subcategories also yielded expected results. All non-supply-related costs were significantly lower for TFA than myomectomy. Predictably, the mean cost of TFA supplies, which is mainly driven by the Sonata device cost, was higher than cost of supplies (ie, surgical tools) for myomectomy.

Facility costs reported elsewhere in the literature vary substantially for surgical myomectomy, depending on the source of the cost data, which costs were considered, and if procedure route data were collected. Mauskopf et al examined uterine fibroid treatment costs in the United States and found a range of $8,058 to $18,199 for myomectomies (converted from 2004 dollars to 2016 dollars).[12] The highest mean cost by route reported in our study ($18,373 for abdominal myomectomy) was closely aligned with the highest estimates found in Mauskopf's review. However, our lower mean cost by procedure route ($10,352 for laparoscopic myomectomy) was slightly higher than the lower estimate provided in the literature. In Mauskopf et al, 2005, some of the studies included hysteroscopic myomectomy data, which as we report is considerably lower than the other routes (mean $4,493).[12] This could explain why average laparoscopic myomectomy cost in our study was slightly higher than the low estimate, but still within the reported ranges.

Blood loss-related complications reported for the myomectomy patients in this study were also frequently reported in the literature. An article by Sheyn et al reported perioperative blood transfusion as the most common complication for laparoscopic myomectomy within 30 days of the index procedure.[13] Several other complications reported by the same article, namely, intraoperative cystotomy, superficial surgical site infection, and wound dehiscence as well as perioperative transfusion, which are possibly due to the more invasive nature of myomectomies, would be eliminated with TFA given the incisionless transcervical approach.

The same study centers were used for the myomectomy comparison arm as those who participated in the original SONATA trial. Myomectomy procedures that occurred at the same time frame as the SONATA trial procedures were selected for data collection. Furthermore, patients were matched based on age and BMI (although in practice, myomectomy patients were younger as a group). This supports our conclusions by controlling for potential biases such as prior procedural experience, internal procedures and protocols, and billing practices of the study centers. The pool of myomectomies included in the study represented a mix of inpatient and outpatient, and abdominal, laparoscopic, and hysteroscopic procedures. Therefore, the cost comparisons reported here are relevant to health care facilities as they utilize a wide mix of treatment routes and patient setting in performing the procedure.

The two groups had statistically significant differences in both age and BMI. The age difference between the TFA and myomectomy patients may reflect the original SONATA trial inclusion criteria.[7] The BMI difference is complicated by missing data from one center, but represents a real, but clinically insignificant difference.

As this was a comparative case-matched study, the sample size was restricted by the number of patients enrolled in the original, prospective SONATA clinical trial centers. This limited our ability to match the patients between the two study arms using multiple variables while also maintaining a meaningful sample size. Because of this, we were unable to use patient fibroid characteristics as a matching criteria. The small sample sizes in each arm also may have limited detection of adverse events and hospital readmissions. Therefore, the low number of adverse events and lack of complications seen in the study was not clinically meaningful, and may not be generalizable to a larger population.

While information on fibroid characteristics would have strengthened the comparison between the two patient arms, the lack of appropriate data made a comparison unfeasible. Available details on the myomectomy procedures were limited to the definitions of the CPT codes used to retrospectively identify these patients (Appendix, Table 5). For example, code 58146 is defined as

> Myomectomy, excision of fibroid tumor(s) of uterus, 5 or more intramural myomas and/or intramural myomas with total weight greater than 250 grams, abdominal approach.[14]

Under this definition the number of fibroids, their location, and the total mass of the fibroids are uncertain. As participants in a clinical trial design, the TFA patients had data on some specifics, such as the number of fibroids treated. However, it was not possible to categorize the TFA patient fibroids in such a way that a direct comparison between the two arms would be appropriate. Despite this limitation, the TFA and myomectomy patients were similar enough in fibroid characteristics that the study sites determined both groups could be treated using procedures that preserved the uterus. Considering this study does not evaluate effectiveness or clinical outcomes, strict case matching based on clinical details, while ideal, was not absolutely necessary for this health economic study.

Although each site provided an equal number of patients in both arms, we were unable to control for the confounding that occurs as a result of collecting from four different sites. Each site may have had different protocols for collecting LOS, OR time, or adverse events for the retrospectively identified myomectomy procedures, so the site contributing the most number of patients may have disproportionally influenced the data. However, given the magnitude of the measured differences in LOS, specifically, it is unlikely that differences in protocols changed the results in a meaningful way.

A notable difference among the study arms pertains to the procedure settings. TFA is an entirely outpatient procedure, and therefore, the comparison to inpatient myomectomy may not be most appropriate. Despite remaining a fully outpatient procedure, TFA has been shown to successfully treat the same types of fibroids traditionally treated by abdominal or laparoscopic myomectomy.[7] This makes a comparison between the two procedures appropriate, regardless of patient care setting.

These results provide the first comparative analysis of costs and outcomes for TFA as compared to myomectomy. The data demonstrate that TFA offers facilities the potential for reduced health care resource utilization and related costs in comparison to myomectomy procedures.

Conclusion

TFA using the Sonata system has a significantly shorter operating room time and length of stay than myomectomy for the treatment of symptomatic uterine fibroids. All procedure, anesthesia, laboratory, pathology, and pharmacy costs were significantly higher for myomectomy as compared to TFA. TFA was also associated with significantly lower facility procedure-related total costs compared to most stratifications of myomectomy, including inpatient, abdominal, or laparoscopic myomectomy.

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Disclosure

EAB, RLB, MWY, CAL, and AZ-W are employees of TTi Health Research & Economics. DRD is now affiliated with Virtua Ob/Gyn, Voorhees, NJ, USA. The authors report no other conflicts of interest in this work.

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ORIGINAL ARTICLE

The FAST-EU trial: 12-month clinical outcomes of women after intrauterine sonography-guided transcervical radiofrequency ablation of uterine fibroids

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Abstract The FAST-EU Trial was designed to establish the effectiveness and confirm the safety of transcervical intrauterine sonography-guided radiofrequency ablation with the VizAblate™ System in the treatment of symptomatic uterine fibroids. This was a multicenter, prospective, single-arm trial involving academic and community hospitals in the United Kingdom, the Netherlands, and Mexico. Women with qualifying uterine fibroids and heavy menstrual bleeding underwent intrauterine sonography-guided transcervical radiofrequency ablation (RFA) with the VizAblate System; anesthesia was individualized. Patients were required to have up to five fibroids from 1 to 5 cm in diameter. The primary trial endpoint was the percentage change in perfused fibroid volume, as assessed by contrast-enhanced MRI at 3 months by an independent core laboratory. Secondary endpoints, evaluated at 6 and 12 months, included safety, percentage reductions in the Menstrual Pictogram (MP) score, and the Symptom Severity Score (SSS) subscale of the Uterine Fibroid Symptom-Quality of Life (UFS-QOL) questionnaire, along with the rate of surgical reintervention for abnormal uterine bleeding and the mean number of days to return to normal activity. Additional assessments included the Health-Related Quality of Life (HRQOL) subscale of the UFS-QOL, nonsurgical reintervention for abnormal uterine bleeding, anesthesia regimen, patient satisfaction, and pain during the recovery period. An additional MRI study was performed at 12 months on a subgroup of patients. Fifty patients (89 fibroids) underwent transcervical radiofrequency ablation with the VizAblate System. At 3 and 12 months, perfused fibroid volumes were reduced from baseline by an average of 68.1±28.6 and 67.4±31.9 %, respectively, while total fibroid volumes were reduced from baseline by an average of 54.7±37.4 and 66.6±32.1 %, respectively (all $P<.001$ compared with baseline; Wilcoxon signed-rank test). At 12 months, mean MP score and SSS decreased by 53.8±50.5 and 55.1±41.0 %, respectively; the mean HRQOL score increased by 277±483 %. There were four surgical reinterventions (8 %) within 12 months. This is the first report of the 12-month follow-up for patients in the FAST-EU Trial. In concert with previously reported 3- and 6-month endpoint data, the 12-month results of the FAST-EU Trial suggest that in addition to substantially reducing the perfused and total volume of targeted uterine fibroids, the VizAblate System is safe and effective through 12 months in providing relief of abnormal uterine bleeding associated with submucous, intramural, and transmural fibroids.

Keywords Fibroids · Radiofrequency ablation · VizAblate · Intrauterine sonography · Ultrasound

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Introduction

Uterine fibroids are highly prevalent and the primary indication for over 200,000 hysterectomies performed annually in

the USA [1, 2]. While various fibroid treatments exist, they have limitations, such as being invasive, requiring general anesthesia, or being not optimally suited for treatment of both intramural and submucous myomata.

Radiofrequency ablation (RFA) involves the placement of one or more needle electrodes into a solid tumor in order to deliver thermal energy, resulting in thermal fixation and coagulative necrosis within the treated tissue [3, 4]. Recent studies have been performed using RFA in conjunction with simultaneous, real-time sonography to guide volumetric ablations, resulting in volume reduction and symptom improvement [3, 5, 6].

The VizAblate System (Gynesonics; Redwood City, CA) combines radiofrequency ablation with intrauterine sonography and is CE-marked and commercially available in the European Union. VizAblate permits real-time imaging and transcervical treatment of uterine fibroids, including those that are not amenable to hysteroscopic resection such as type 3, type 4, and types 2–5 (transmural) fibroids as well as large type 1 and type 2 myomata [7]. The Fibroid Ablation Study-EU (FAST-EU) was designed to examine the safety and effectiveness of transcervical radiofrequency ablation of uterine fibroids under intrauterine sonography guidance with the VizAblate System. The trial endpoints, reached at 3 and at 6 months, have previously been reported [8]. This paper presents the 12-month efficacy and safety results of women treated under the FAST-EU Trial.

Patients and methods

This was a prospective, single-arm, multicenter trial. The primary endpoint was the percentage change in target fibroid perfused volume as assessed by contrast-enhanced MRI by an independent core laboratory at baseline and at 3 months. Additional endpoints, reached at 6 months, included safety, percentage reductions in the Menstrual Pictogram (MP) score and the Symptom Severity Score (SSS) subscale of the Uterine Fibroid Symptom-Quality of Life (UFS-QOL) questionnaire, the rate of surgical reintervention for abnormal uterine bleeding, and the mean number of days to return to normal activity. The Health-Related Quality of Life (HRQOL) subscale of the UFS-QOL questionnaires, along with anesthesia regimen, patient satisfaction, and recovery pain, was also assessed.

Patients were enrolled across seven sites in three nations: Mexico (one site), the United Kingdom (two sites), and the Netherlands (four sites). The trial included women with one to five uterine fibroids of FIGO types 1, 2, 3, 4, and 2–5 (transmural) measuring between 1 and 5 cm in maximum diameter. Fibroids that did not contain an edge within the inner half of the myometrium were not counted in this total and were not targeted for ablation, as they were believed to be less likely to materially contribute to abnormal uterine bleeding (AUB). At least one fibroid was required to indent the endometrial cavity.

Patients were 28 years of age or older and not pregnant, with regular, predictable menstrual cycles and heavy menstrual bleeding for at least 3 months. A Menstrual Pictogram score ≥120 was also required for inclusion along with a baseline UFS-QOL SSS ≥20. The Menstrual Pictogram was first described by Wyatt and colleagues and is a variant of the Pictorial Blood Loss Assessment Chart (PBAC) that patients complete to provide a visual assessment of menstrual blood loss during a single cycle [9, 10]. Unlike the original PBAC described by Higham and colleagues, the Menstrual Pictogram includes a greater range of icons representing different saturations of sanitary products, clots, and losses in a toilet and also distinguishes different absorbency levels of sanitary napkins and tampons [11].

Exclusions included a desire for future fertility, the presence of one or more type 0 fibroids, cervical dysplasia, endometrial hyperplasia, active pelvic infection, clinically significant adenomyosis (>10 % of the junctional zone measuring more than 10 mm in thickness as measured by MRI), and the presence of one or more treatable fibroids that were significantly calcified (defined as <75 % fibroid enhancement by volume on contrast-enhanced MRI). Screening included transvaginal sonography, as well as hysteroscopy or hysterosonography, contrast-enhanced MRI, endometrial biopsy, and a pregnancy test.

All records were de-identified and only the range of each patient's age was documented, as per clinical trial requirements in the Netherlands. Women were followed at 7–14 days, 30 days, 3 months, 6 months, and 12 months post-treatment. All MRI studies were forwarded to an independent core laboratory (MedQIA, Los Angeles, CA, USA) for quality control and interpretation to reduce variability in the measurements; the core laboratory also developed standardized imaging protocols for use at the individual trial sites, credentialed the sites, and trained MRI technologists at each trial site. Fibroid measurements consisted of the total voxel volume and perfused voxel volume via contrast-enhanced MRI at the specified time points.

Procedure

The VizAblate System, as well as its use, has previously been described in detail and includes a reusable intrauterine ultrasound (IUUS) probe and a single-use, articulating radiofrequency ablation handpiece that are combined into an integrated treatment device that is inserted transcervically (Fig. 1) [8]. A custom graphical interface provides the gynecologist with a real-time, image-guided treatment system that indicates the borders of the thermal ablation (Ablation Zone) as well as the border beyond which tissues are safe from ablation (Thermal Safety Border). Because the deployment path is

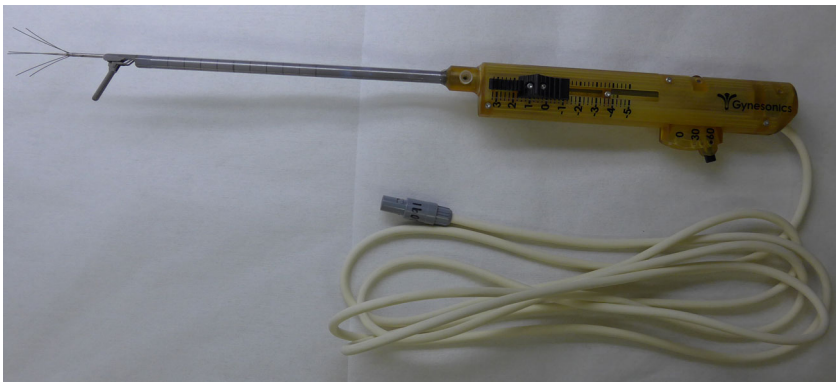


Fig. 1 The VizAblate treatment device

predictable relative to the ultrasound image, one can plan the ablation location and size before introducing any electrode elements into a fibroid. Additionally, the guidance software provides graphics that allow the gynecologist to maintain a safe margin from the ablation to the serosal margin and extrauterine viscera. Mechanical stops provide definitive tactile limits, ensuring that the needle electrodes are deployed to the proper distance to achieve the ablation size as selected by the gynecologist. The radiofrequency generator modulates power (up to 150 W) to maintain a constant temperature of 105 °C at the needle electrode tips, and the ablation time is preset based on the ablation size. Depending on the width of the ablation, the distance from the Ablation Zone to the Thermal Safety Border will vary from 6.0 to 9.5 mm.

In this trial, the method of anesthesia was chosen by each investigator based on individual patient characteristics in consultation with an anesthesiologist. Treated fibroids received one or more ellipsoidal ablations under real-time intrauterine sonographic guidance, ranging from 1 to 4 cm in width and 2 to 5 cm in length. The number of ablations, along with their sizes, was at the discretion of the investigator and was chosen in order to maximize the ablation volume of the fibroid while maintaining the Thermal Safety Border within the uterine serosal margin.

Statistical analysis

The primary endpoint was the percentage change in target fibroid perfused volume at 3 months. The null hypothesis for the primary trial endpoint at 3 months was H_0: probability of success <50 % versus the alternative H_a: probability of success ≥50 %. A sample of 40 patients was sufficient to detect this difference of 22 % in probability of success with a power of 82 % using a one-group chi-square test with a 0.05 two-sided significance level. Allowing for an expected drop-out rate of 20 % at the 12-month follow-up visit, the minimum recommended sample size for the initial trial protocol was 48. The primary trial endpoint success criterion was achievement of >30 % reduction in mean target fibroid perfused volume in at least 50 % of patients at 3 months.

The data in this report consist of the Full Analysis dataset. This includes all patients enrolled who provided a baseline fibroid volume assessment and received treatment with the VizAblate System. Patients who received a surgical reintervention were considered treatment failures, and their subsequent data was imputed using the last observation carried forward (LOCF) method. Missing data was not imputed for patients who conceived or who neglected to complete a questionnaire.

All statistical analyses were performed with SAS 9.3 (SAS, Cary, NC). Values were considered significant at the level of α=0.05. The Wilcoxon signed-rank test was used to test if a change was significantly different from 0.

Ethics

The protocol was approved by the Ethics Committees of the respective institutions as well as by the Federal Commission for Protection against Health Risks (COFEPRIS) in Mexico. All enrolled patients provided written informed consent for treatment with the VizAblate System prior to enrollment. The trial overview was published on ClinicalTrials.gov (identifier: NCT01226290) and conducted in accordance with Standard ISO 14155 (Clinical investigation of medical devices for human subjects – Good clinical practice) of the International Organization for Standardization (ISO), the Helsinki Declaration of 1975, as revised in 2008, and the ethical standards of applicable national regulations and institutional research policies and procedures governing human experimentation.

Results

Patients

Fifty patients were treated in the FAST-EU trial at seven sites. Baseline characteristics for all treated patients are provided in Table 1. Anesthesia was provided as noted in Table 2.

Table 1 Baseline subject characteristics

Subjects treated	50
Most frequent age range	41–45 years of age[a]
Mean Menstrual Pictogram (MP) score	423±253 (range 119–1582)
Mean UFS-QOL SSS	61.7±16.9 (range 28.1–100.0)
Mean UFS-QOL HRQOL score	34.3±19.0 (range 0.0–73.3)
Total number of target fibroids identified on MRI	118
Mean number of target fibroids per patient	2.4±1.7 (range 1–7)[b]
Mean diameter of target fibroids	2.9±1.4 cm (range 1.0–6.9 cm)
Mean perfused fibroid volume	18.3±20.6 cm^3 (range 0.3–77.0 cm^3)
Mean total (perfused+nonperfused) fibroid volume	18.8±21.4 cm^3 (range 0.3–77.0 cm^3)

UFS-QOL Uterine Fibroid Symptom-Quality of Life Questionnaire, *SSS* Symptom Severity Score subscale, *HRQOL* Health-Related Quality of Life subscale

[a] Subject ages were specified as a range by each site to protect subject privacy

[b] Two small additional fibroids, beyond the upper limit of 5 target fibroids/patient, were identified on review of one MRI series after treatment

One patient (three fibroids) was excluded from analysis of the primary endpoint. This patient was deemed by the core MRI laboratory to have had unusable imaging for making precise baseline fibroid measurements, although eligibility based on fibroid diameter ≤5 cm and location was not in question. This patient was treated as she met the eligibility requirements and her treatment could contribute to patient-reported and safety data for the trial. Consequently, while 92 fibroids were ablated, accurate baseline volume measurements could only be performed for 89. One patient reported a pregnancy at the time of her 6-month follow-up visit and was thus excluded from the 6- and 12-month analyses. While all patients provided baseline MP data, one patient each at 3, 6, and 12 months declined to submit a Menstrual Pictogram. One patient did not turn in her baseline HRQOL portion of the UFS-QOL; her HRQOL data was not included in the analysis. A flow diagram depicting sample sizes for MRI and patient-reported outcomes at baseline and 3-, 6-, and 12 months is provided in Fig. 2.

The protocol required a baseline and 3-month MR study for the primary endpoint analysis (reduction in perfused fibroid volume). Approximately 14 months after the first patient was treated, the protocol was amended to add an MR evaluation at 12 months in order to provide longer-term information about the effects of transcervical RFA. Twenty-eight patients (58.3 %) provided their informed consent to undergo another MR examination with contrast enhancement at 12 months post-ablation and underwent such imaging.

Table 2 Anesthesia provided to FAST-EU subjects

Anesthesia option	No. of subjects
General anesthesia alone	15 (30.0 %)
Conscious sedation alone	15 (30.0 %)
Spinal anesthesia alone	8 (16.0 %)
Conscious sedation+epidural anesthesia	8 (16.0 %)
Epidural anesthesia alone	2 (4.0 %)
Paracervical blockade alone	1 (2.0 %)
General anesthesia+epidural anesthesia	1 (2.0 %)

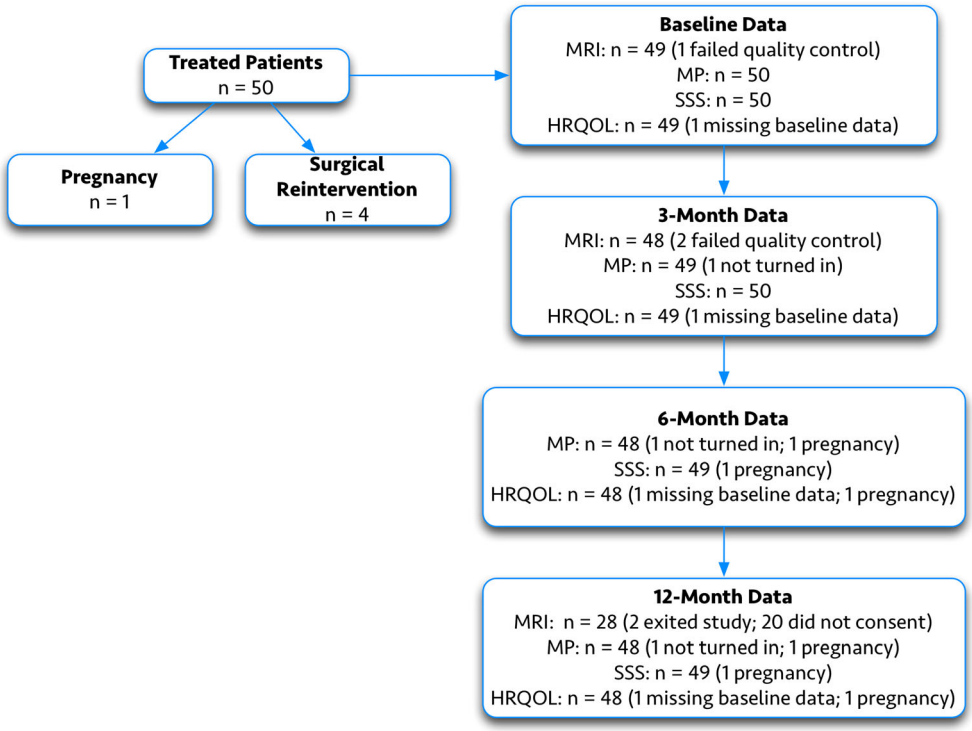
Effects on fibroid volume

Characteristics of fibroids that were ablated are shown in Table 3, and results of fibroid ablation on total and perfused volume at 3 and 12 months are provided in Table 4. Fibroids are classified in Table 3 as per the FIGO classification system [12]. Radiofrequency ablation with the VizAblate System was associated with statistically significant reductions (68.1 and 54.7 %, respectively) in both total and perfused fibroid volumes at 3 and 12 months. Seventy-nine of 89 treated fibroids (88.8 %) in all 49 patients with measurable MRI data met the primary trial endpoint success criterion at 3 months (achievement of >30 % reduction in mean target fibroid perfused volume at 3 months in at least 50 % of patients). By 12 months post-ablation (n=28 patients; 43 fibroids), treated fibroids experienced a mean reduction in total fibroid volume of 66.6± 32.1 % (P<.001). Thirty-seven fibroids (86.0 %) in 100 % of the 28 patients imaged at 12 months demonstrated >30 % reduction in perfused fibroid volume at 12 months.

Patient-reported outcomes

Patient-reported secondary endpoint data through 12 months are provided in Table 5. The mean MP score declined through 12 months, with mean and median reductions of 53.8 and 72.3 % at 12 months, respectively (all P<.001). By 3 months post-ablation, 44 of 49 patients (89.8 %) experienced a reduction in menstrual blood loss as reflected by their Menstrual

Fig. 2 Patient flow diagram



Pictogram scores. Of these 49 patients at 3 months, 28 (57.1 %) had >50 % reduction in MP scores; this proportion increased to 35 of 48 patients (72.9 %) at 6 months and was realized by 31 of 48 patients (64.6 %) at 12 months. The proportion of patients achieving >50 % bleeding reduction at 6 months was not significantly different from the proportion at 12 months (P=.095).

Lukes and colleagues reported that a 22 % or greater reduction in menstrual blood loss was meaningful to the majority of women [13]. In the FAST-EU Trial, 37 of 49 (75.5 %) patients had achieved such clinically meaningful reductions in menstrual bleeding by 3 months. This increased to 41 of 48 patients (85.4 %) at 6 months and 38 of 48 patients (79.2 %) at month 12, which was not significantly different from 6 months (P=.175).

As shown in Table 5, the reductions in the transformed SSS subscale of the UFS-QOL questionnaire at 3, 6, and 12 months were statistically significant, as were the increases in the transformed HRQOL subscale. Patients experienced a 55.1 % reduction in SSS at 12 months, corresponding to a mean reduction in transformed SSS of 35.3 points from baseline. At all post-ablation time points studied, the majority of patients experienced at least a clinically significant 10-point reduction in SSS (82 % of patients at 3 months, 86 % at 6 months, 78 % at 12 months).

Adverse events

There were 34 adverse events deemed possibly, probably, or definitely related to the VizAblate System or overall

Table 3 Characteristics of ablated fibroids

Total number of ablated target fibroids[a]	92
Mean number of ablated target fibroids per subject	1.8±1.1 (range 1–5)
Total number of type 0 ablated fibroids	0
Total number of type 1 ablated fibroids	14
Total number of type 2 ablated fibroids	42
Total number of type 3 ablated fibroids	3
Total number of type 4 ablated fibroids	25
Total number of type 2–5 (transmural) ablated fibroids	8
Mean diameter of ablated fibroids	3.2±1.4 cm (range 1.1–6.9 cm)

[a] Includes three fibroids that were ablated in a subject whose MRI data was not evaluable with regard to precise fibroid measurements

Table 4 Reduction in mean perfused and total fibroid volumes through 12 months

	Baseline	3 months	% Reduction from baseline	*P* value[a]	12 months[b]	% Reduction from baseline	*P* value[a]
No. of ablated fibroids	89	89			43		
No. of subjects	49	49			28		
Perfused fibroid volume (cm^3)	18.3±20.6 9.5 (0.3–77.0)	5.8±9.6 1.6 (0.0–45.7)	68.1±28.6 % 76.9 % (−33.3 to 100 %)	<.001	6.6±11.3 1.0 (0.0–56.1)	67.4±31.9 % 73.3 % (−32.7 to 100 %)	<.001
Total fibroid volume (cm^3)	18.8±21.4 9.5 (0.3–77.0)	8.0±12.0 1.9 (0.0–56.3)	54.7±37.4 % 62.5 % (−85.7 to 100 %)	<.001	6.8±11.4 1.2 (0.0–56.1)	66.6±32.1 % 73.3 % (-32.7–100 %)	<.001

Data are mean±standard deviation; median (range)

[a] Wilcoxon signed-rank test, null hypothesis of no change

[b] A 12-month MRI study was added through a protocol amendment after several patients had been treated, and 28 patients provided informed consent to undergo this additional imaging study

procedure over a 12-month period. These included seven women with dysmenorrhea, six with abnormal uterine bleeding above baseline, four with pelvic pain and/or cramping, two urinary tract infections (both within 30 days of treatment), and one fibroid expulsion that had no significant consequences. There were two readmissions within 30 days of the procedure. One patient was admitted overnight on post-procedure day #9 to receive parenteral antibiotics for lower abdominal pain believed secondary to cystitis (one of the two instances of urinary tract infection previously noted) and was discharged on the following day. Another patient developed bradycardia down to 38 bpm shortly after the procedure and was kept overnight in the hospital for successful treatment with atropine and observation.

Surgical reintervention

Four patients (8 %) underwent surgical reintervention, all after 6 months post-ablation. One patient underwent hysteroscopy and nonresectoscopic endometrial ablation (ThermaChoice®; Ethicon, Somerville, NJ) at 10 months. At the time of her endometrial ablation, hysteroscopy confirmed the presence of a normal endometrial cavity; no residual fibroid tissue was noted. Two patients, both treated by the same investigator, underwent hysteroscopic myomectomy at 6.5 and 7 months post-ablation, respectively, due to AUB felt secondary to fibroid sloughing. In both cases, the ablated fibroids had a 70–85 % reduction in perfused volume at 3 months. A fourth patient underwent total abdominal hysterectomy at 11 months secondary to abnormal uterine bleeding above baseline. The patient was noted post-operatively to have had an abnormal bleeding duration at baseline that had not been reported in her menstrual history, constituting a protocol violation. The patient may have had a component of anovulation contributing to her abnormal uterine bleeding.

Pregnancy

There was a single pregnancy reported within the first 6 months after ablation with the VizAblate System. The patient presented with 12 weeks of amenorrhea at her 6-month trial visit, had a positive pregnancy test at that time, and delivered a live-born male infant at term via elective repeat Cesarean section [14].

Return to normal activity, patient satisfaction, and pain during recovery

Forty-eight patients provided results of a 10-point visual analogue scale (VAS) regarding their pain during the recovery period (up to 14 days post-treatment). On average, they reported a mean VAS score of 3.0±1.7 (median 3.0, range 0–9). Forty-seven patients completed a recovery diary relating to how long it took them to return to their normal activities of daily life. On average, return to normal activity took 4.4±3.1 days (median 4.0 days, range 1–14 days). There was an overall satisfaction rate of 87.8 % (43/49 patients) at 12 months; 69.4 % were "very satisfied," 10.2 % were "satisfied," and 8.2 % were "somewhat satisfied," with their treatment. At 12 months, 49 patients provided a mean scoring of 8.8±2.4 out of 10 in terms of how likely they would be to recommend the treatment to a friend or relative.

Discussion

It is of particular importance to determine how well patients fared beyond the previously reported 3- and 6-month endpoints from the FAST-EU Trial. The results outlined in this report confirm and extend the results of the 3- and 6-month endpoints and demonstrate that intrauterine sonography-

Table 5 Improvement in patient-reported outcomes through 12months

	Baseline	3months	Change from baseline	% Change from baseline	*P* value[a]	6months	Change from baseline	% Change from baseline	*P* value[a]	12 months	Change from baseline	% Change from baseline	*P* value*
MP	50	49	49	49	<.001	48	48	48	<.001	48	48	48	<.001
	423±253	202±202	221±290	45.2±57.9%		181±209	244±302	51.9±59.8%		173±200	243±296	53.8±50.5%	
	361 (119–1582)	170 (0–1011)	191 (−700, 1265)	56.9% (−225–100%)		107 (0–1011)	191 (−700, 1307)	68.6% (−225–100%)		85 (0–786)	217 (−343, 1543)	72.3% (−103–100%)	
SSS	50	50	50	50	<.001	49	49	49	<.001	49	49	49	<.001
	61.7±16.9	31.7±20.1	30.0±22.2	46.7%±32.8%		25.1±19.3	36.7±22.6	57.6±31.4%		26.6±24.0	35.3±26.9	55.1±41.0%	
	60.9% (28.1–100%)	31.3% (0.0–93.8%)	31.3 (−18.8, 84.4)	52.5% (−33.3–100%)		18.8 (0.0–78.1)	37.5 (−6.3, 75.0)	66.7% (−22.2–100%)		21.9 (0.0–78.1)	37.5 (−18.8, 93.8)	62.5% (−66.7–100%)	
HRQOL	49	49	49	49	<.001	48	48	48	<.001	48	48	48	<.001
	34.3±19.0	76.4±22.2	42.1±25.6	336±846%		79.5±22.7	44.5±26.7	266±475%		80.7±24.7	45.7±30.5	277±483%	
	30.2 (0.0–73.3)	83.6 (5.2–100)	40.5 (−7.8, 95.7)	123% (−11.1–5550%)		85.3 (0.9–100)	45.3 (−5.2, 96.6)	118% (−28.6–2800%)		91.4 (0.9–100)	45.7 (−33.6, 96.6)	127% (−54.2–2800%)	

Data are number of subjects; mean±standard deviation; median (range)

MP Menstrual Pictogram, *SSS* Symptom Severity Score, *HRQOL* Health-Related Quality of Life

[a] Wilcoxon Signed-Rank Test, null hypothesis of no change

guided transcervical radiofrequency ablation of fibroids provides significant reductions in fibroid volume and bleeding symptoms through 12 months.

Transcervical radiofrequency ablation avoids many of the potential complications associated with a laparoscopic or open procedure for the treatment of fibroids. There are no incisions, eliminating the potential for wound infection, seroma, and hematoma. The peritoneal cavity is not entered nor is the serosa penetrated or coagulated, so that intraperitoneal adhesiogenesis is unlikely. There is no overt risk of ureteral injury, unlike hysterectomy. In contrast to operative hysteroscopy, only a small quantity of hypotonic fluid is used for acoustic coupling, no large venous sinuses are exposed, and intrauterine pressure is not raised to levels above mean arterial pressure, avoiding the risk of significant fluid intravasation. The integral intrauterine sonography probe permits real-time visualization of the myometrium and serosa, providing a perspective of the myometrium and intramyometrial pathology that are not achievable with a hysteroscope and enabling treatment of intramural and transmural fibroids as well as larger submucous myomata.

The trial success criterion was >30 % reduction in mean target fibroid perfused volume at 3 months in at least 50 % of patients. This success criterion stems from the MR-guided focused ultrasound data of Stewart and colleagues, which found that sustained relief of fibroid symptoms up to 24 months is associated with nonperfused volume ratios >20 % after hyperthermic ablation [15]. Initially, it was not known if total fibroid volume would be significantly reduced at that early time point, which was the rationale for using reduction in perfused fibroid volume (measured via contrast-enhanced MRI) as the primary endpoint as opposed to reduction in total fibroid volume. In the FAST-EU Trial, contrast-enhanced MRI demonstrated significant mean reductions at 3 months in both the volume of perfused fibroid tissue as well as in total fibroid volume at 3 months (68.1 and 54.7 %, respectively). At 12 months, patients demonstrated significant reductions (67.4 and 66.6 %, respectively) in mean perfused and total fibroid volumes. It has been previously demonstrated that hyperthermic ablation of >20 % of a fibroid may provide sustained relief from fibroid symptoms [15].

There were statistically significant reductions in menstrual blood loss, as evidenced by 45.2, 51.9, and 53.8 % reductions in the menstrual pictogram at 3, 6, and 12 months, respectfully, as well as significant improvements in both subscales of the UFS-QOL questionnaire. The majority of patients (57.1–72.9 %, depending on time point) realized more than a 50 % reduction in their menstrual pictogram scores, with 75.5 % of patients achieving a clinically meaningful reduction in menstrual bleeding as early as 3 months after treatment. Similarly, 78–86 % patients realized at least a 10-point reduction in SSS (depending on time point), with a mean reduction from baseline of 35.3 points at 12 months; a 10-point reduction in SSS

represents a moderate effect size and was required by the US Food and Drug Administration for the approval of MRgFUS [16].

Patients typically experienced mild or no pain through the first post-ablation visit. Return to normal activity was just over 4 days and patient satisfaction was high (87.8 %). Two patients (4 %) were hospitalized overnight, one for abdominal pain secondary to apparent cystitis and the other for observation after bradycardia that responded to atropine. Neither event was deemed to have been related to the VizAblate System upon review by an independent medical advisory board.

This trial has several noteworthy attributes. Care was taken to exclude women with abnormal uterine bleeding secondary to anovulation through strict adherence to the inclusion criterion regarding the menstrual history. Additionally, at least one fibroid was required to have indented the endometrial cavity, making it more likely that a patient's bleeding symptoms are largely or exclusively secondary to fibroids rather than another etiology. A core MRI facility was used to reduce variability and bias in MRI imaging quality, interpretation, and measurements relative to the primary trial endpoint. In addition, the use of multiple clinical sites included academic medical centers as well as community hospitals to provide a more realistic assessment of the use of the VizAblate System in different treatment locations.

As a nonrandomized single-arm trial that does not directly compare against another fibroid treatment, this trial cannot be used to compare treatment with VizAblate to standard fibroid therapy. Only a subset of patients (28/48 eligible; 58.3 %) underwent MRI at 12 months. Finally, follow-up was limited to 12 months; longer surveillance and greater numbers of patients will be required to establish definitive efficacy and safety data. Toward that end, a larger clinical trial is underway.

Conclusions

These results from the FAST-EU Trial demonstrate that the initial endpoint results reported at 3 and 6 months were sustained in the treated population through 12 months. Patients realized significant reductions in perfused and total fibroid volume, menstrual bleeding, overall symptoms, and improvements in quality of life. The data demonstrate the potential of intrauterine sonography-guided, transcervical radiofrequency ablation with the VizAblate System as a promising uterus-preserving technology for the treatment of submucous, intramural, and transmural fibroids without incisions or the need for general anesthesia.

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Conflict of interest This is a Gynesonics-initiated trial, which is fully sponsored by Gynesonics. Drs. Brölmann, Bongers, Veersema, Quartero, and Gupta have no personal conflicts of interest to disclose; their respective institutions received reimbursement from Gynesonics for expenses incurred in the performance of this trial. Dr. Garza is a consultant for Gynesonics. Dr. Toub is Medical Director of Gynesonics.

Adherence to ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Informed consent Informed consent was obtained from all patients included in the trial.

Contributions of the Authors Doctors Bongers, Brölmann, Gupta, Veersema, Quartero, and Garza-Leal were responsible for the conception and design of the study, data collection, patient recruitment, and preparation of the manuscript and were the responsible surgeons. Dr. Toub was responsible for the conception and design of the study, data collection, data analysis and interpretation, statistical analysis, and preparation of the manuscript.

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Long-Term Clinical Outcomes of Transcervical Radiofrequency Ablation of Uterine Fibroids: The VITALITY Study

Jose Gerardo Garza-Leal, MD

Abstract

Objective: The aim of this research was to learn the long-term (> 5 years) clinical outcomes of transcervical radiofrequency ablation of uterine fibroids.

Materials and Methods: For this retrospective, single-arm, long-term data-collection study, 23 women with heavy menstrual bleeding secondary to fibroids were treated with transcervical radiofrequency ablation guided by integrated intrauterine sonography (using the Sonata® System, Gynesonics, Redwood City, CA). This study was within the 12-month Fibroid Ablation Study-EU clinical trial in Mexico. Symptoms were assessed using the Uterine Fibroid Symptom and Quality-of-Life's Symptom Severity Score (SSS) and Health-Related Quality of Life (HRQoL) subscales. Patients were queried regarding pregnancy and surgical reinterventions.

Results: Seventeen women (73.9%) provided long-term follow-up information, with a mean of 64.4 months ±4.5 months (range: 57–73 months). From baseline, mean SSS decreased significantly from 64.9 ± 16.9 to 27.6 ± 36.1, and mean HRQoL improved significantly from 27.2 ± 22.4 to 76.0 ± 32.6 ($p = 0.002$, and $p = 0.0001$, respectively). There were no surgical reinterventions through the first 3.5 years post-treatment. There was an 11.8% incidence of surgical reinterventions over 5.4 years of average follow-up, with 2 hysterectomies occurring after 3.5 and 4 years postablation, respectively (event rate: 2.2% per year; 95% confidence interval; 0.3%, 7.9%). Freedom from surgical reintervention at 1, 2, and 3 years was 100%, and, at 4 and 5 years, was $88.2\% \pm 7.8\%$. There was a single pregnancy occurring within the first year of treatment leading to a normal-term delivery by elective repeat cesarean section.

Conclusions: Transcervical radiofrequency ablation with the Sonata System produced substantial durable clinical benefits beyond 5 years with a low reintervention rate. (J GYNECOL SURG 35:19)

Keywords: radiofrequency ablation, intrauterine ultrasound, uterine fibroids

Introduction

Uterine fibroids are a common gynecologic disorder associated with heavy menstrual bleeding, pelvic pressure, urinary frequency, subfertility, and other symptoms, imposing a significant burden on women and their healthcare systems through the age of menopause.[1,2] The most prevalent treatment for symptomatic fibroids remains hysterectomy, and fibroids are also the most frequent indication for benign hysterectomy.[3] While hysterectomy is generally available, data from a national survey show that women are particularly resistant to invasive surgical options, often delaying treatment, on average, by 5 years, and that uterine-conserving procedures are of particular interest to women regardless of future desire for pregnancy.[3] Access to less-radical treatment options, however, may not be sufficient in many regions, in part because of a lack of specialized surgical capabilities that limit treatment options, adequate payor coverage, and other factors.[4]

Transcervical radiofrequency ablation (RFA) with the Sonata® System (Gynesonics, Redwood City, CA; formerly

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known as the VizAblate™ System) is a minimally invasive, incisionless, uterine-conserving outpatient treatment for the majority of uterine fibroid types.[5–8] Because of being guided by an integrated intrauterine sonography probe, this procedure allows the physician to visualize, target, and ablate all nonpedunculated fibroids. This includes deeper intramural, subserous, and hybrid fibroids (International Federation of Gynecology and Obstetrics [FIGO] type 3, type 4, type 5, type 6, and type 2–5 [transmural]) that are not accessible via operative hysteroscopy, in addition to (nonpedunculated) submucous fibroids (FIGO type 1 and type 2 myomata). FIGO fibroid classification has been published previously.[9] The Sonata System, which has a CE Mark, has been described in detail and provides a real-time graphical interface (SMART Guide™) that displays the location of each ablation on a live ultrasound image along with the extent of subablative thermal heating.[5,8]

The Fibroid Ablation Study-EU (FAST-EU) was a 12-month multicenter, prospective trial involving 7 clinical sites in the United Kingdom, The Netherlands, and Mexico. The trial was designed to establish effectiveness and confirm the safety of transcervical RFA of symptomatic uterine fibroids with the Sonata System.[5,6] Fifty premenopausal women were enrolled and treated in the FAST-EU clinical trial and were followed through 12 months post-treatment. Patients were eligible if they had from 1–5 uterine fibroids of FIGO types 1, 2, 3, 4, and 2–5, between 1 cm and 5 cm in maximum diameter. All enrolled patients had to have at least 1 myoma that indented the endometrial cavity (e.g., type 1, type 2 or type 2–5), as these are most relevant to abnormal uterine bleeding (AUB).

The FAST-EU trial demonstrated significant reduction in menstrual bleeding along with diminished perfused and total fibroid volumes. There were also significant improvements in the Uterine Fibroid Symptom and Quality-of-Life (UFS-QoL) subscales—the Symptom Severity Score (SSS) and Health-Related Quality of Life (HRQoL)—scores and a significant improvement in overall health status, as measured by the EuroQoL-5D (EQ-5D) questionnaire. These improvements were reported as early as 3 months post-ablation and were durable through 12 months.[6] Treatment with the Sonata System was accompanied by low rates of serious adverse events and surgical reinterventions, with 92% of patients free from surgical reintervention at 12 months. To characterize the long-term clinical outcomes in patients treated with the Sonata System further, the VITALITY study was designed to collect retrospective follow-up information beyond 12 months of patients treated in the FAST-EU trial at an academic medical center in Monterrey, Mexico.

Materials and Methods

VITALITY was a retrospective, single-arm long-term (> 5 years) data collection study conducted at a FAST-EU trial study site in Monterrey, Mexico.

The VITALITY study was designed to collect long-term clinical outcomes of patients with symptomatic fibroids who had been treated with transcervical RFA using the Sonata System. Patients who had been previously enrolled and treated with the Sonata System in the FAST-EU clinical trial were eligible for inclusion in the VITALITY study. The study protocol was approved by the ethics committee at the Hospital Universitario de Universidad Autonoma de Nuevo León, Monterrey, Mexico, and patients were contacted for participation. Informed consent was obtained from interested patients before enrollment in the study.

Patients who enrolled in the VITALITY study provided responses to the UFS-QoL questionnaire, which is used to assess both SSS and HRQoL, via these 2 subscales over the previous 3 months. Both subscales are normalized on a scale from 1 to 100. Higher SSS scores are generally suggestive of a higher degree of symptom severity.[10] The HRQoL subscale consists of 29 questions examining 6 dimensions (concern, activities, energy/mood, control, self-consciousness, and sexual function). Higher HRQoL scores are desirable as they reflect patients reporting a better HRQoL. The EQ-5D instrument was an additional questionnaire completed by patients in the FAST-EU clinical trial to obtain a descriptive profile of patient health status at baseline and post-procedure. The EQ-5D includes a visual analogue scale (VAS) from 0 to 100, in which higher scores represent better health states, as well as 5 questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are scored on a 1–5 scale (ranging from ''no problem'' to ''extreme problems'') and then converted to create a summary index that is representative of overall health status.[11]

Patients were also queried regarding surgical reinterventions for AUB as well as any pregnancy occurrences and outcome. While the original FAST-EU utilized Menstrual Pictogram (MP) bleeding diaries for patients to score their menstrual bleeding prospectively for the month, collection of the MP was not used for the VITALITY clinical trial to minimize the follow-up requirements for patients and increase the probability of successful long-term data collection. The UFS-QOL SSS subscale is used assess for the presence and significance of AUB.[10]

Statistical analyses were accomplished with SAS 9.3 (SAS, Cary, NC). Changes in variables were assessed using a paired *t*-test. Values were considered significant at the level of $\alpha = 0.05$.

Results

Of the 23 patients treated in the FAST-EU trial at the site in Monterrey, Mexico, 17 (73.9%) were able to be contacted and provided informed consent to be enrolled in the VITALITY study. The mean follow-up was 64.4 months ±4.5 months (range: 57–73 months). The initial characteristics of the patients and their fibroids are shown in Table 1.

At baseline, the mean SSS ($N = 17$) was 64.9 ± 16.9, and this significantly decreased to 27.6 ± 36.1 at the time of long-term follow-up ($p = 0.002$). The HRQoL, which had been 27.2 ± 22.4 on average at baseline ($N = 17$) significantly increased to 76.0 ± 32.6 at long-term follow-up ($p = 0.0001$). The HRQoL responses indicated significant improvements in all 6 dimensions (as noted above, these are concern, activities, energy/mood, control, self-consciousness, and sexual function) through the mean 64.4 months of follow-up.

Regarding the EQ-5D, there was significant mean improvement in the VAS scores from baseline to the long-term follow-up visit ($N = 17$). The baseline mean VAS score was 70.3 ± 22.2 and this significantly increased to 79.8 ± 25.5 ($p = 0.042$). The mean EQ-5D summary index increased

Table 1. Initial Subjects' Characteristics

Characteristics	*Statistics*
# of subjects	17
Most frequent age range (in years)[a]	41–45[a]
Mean gravidity, parity	3.4, 2.9
Mean UFS-QoL SSS	64.9 ± 16.9
Mean UFS-QoL HRQoL	27.2 ± 22.4
Mean EQ-5D VAS	70.3 ± 22.2
Mean EQ-5D summary index	0.79 ± 0.23
Total # of ablated fibroids	35
Mean # of ablated fibroids per subject	2.1
Total # of type 1 ablated fibroids	7
Total # of type 2 ablated fibroids	10
Total # of type 3 ablated fibroids	2
Total # of type 4 ablated fibroids	14
Total # of type 2–5 (transmural) ablated fibroids	2
Mean diameter of ablated fibroids (in cm)	2.5 ± 1.2

[a]Subjects' ages were specified as a range by the site to protect subjects' privacy.

UFS-QoL, Uterine Fibroid Symptom and Quality-of-Life; HRQoL, Health-Related Quality of Life; EQ-5D, EuroQol-5D; VAS, visual analogue scale.

from 0.79 ± .23 at baseline to 0.83 ± 0.26 at long-term follow-up ($p = 0.599$).

No surgical reinterventions occurred through the first 3.5 years. At no time was any patient treated medically with selective progesterone-receptor modulators, gonadotropin-releasing hormone agonists, or any other drugs used to treat AUB. There were 2 hysterectomies reported, 1 after 3.5 years postablation and the other after ~4 years after treatment; both of these hysterectomies were performed to address AUB. The overall incidence for this 17-patient cohort was 11.8% over 5.4 years of average follow-up. This corresponds to an event rate of 2 reinterventions per 91 total patient–years of follow-up, or an event rate of 2.2% per year (95% confidence interval: 0.3%, 7.9%). Freedom from surgical reintervention at 1, 2, and 3 years was 100% and, at 4 and 5 years, was 88.2% ± 7.8% (Fig. 1).

Among the 17 patients, there was a single pregnancy, occurring within the first year of treatment, that was previously reported.[12] This resulted in delivery by elective repeat cesarean section at term, with an unremarkable antenatal and perinatal course other than maternal gestational diabetes mellitus.

Discussion

Alternatives to hysterectomy, as they are not definitive treatments (unlike hysterectomy), are associated with the potential for fibroid recurrence due to further growth and/or *de novo* growth of fibroids. When recurrent fibroids become symptomatic, surgical reintervention may be indicated. One study by Reed and colleagues found a 4.6% annual incidence of surgical reinterventions after myomectomy (including abdominal, laparoscopic, and hysteroscopic routes) during 2766.5 patient–years of follow-up.[13] Among 628 eligible patients, there was a 23.5% cumulative incidence of surgical reintervention at 5 years, and this rose to 30% at 7 years. For laparoscopic myomectomy, specifically, Doridot and colleagues found a 4.6% surgical reintervention rate (8 of 173 patients) with a mean follow-up of 47.4 months.[14] The cumulative recurrence risk was 12.7% at 2 years and 16.7% at 5 years. Differences in reintervention rates can be due to a variety of factors, including differences in length of follow-up, challenges in long-term surveillance, and treatment by general obstetrician/gynecologists versus specialists.[13] Two randomized controlled trials of uterine artery embolization reported 5-year reintervention rates of 28.4%–32.0%.[15,16]

The results of this single-center, retrospective data-collection study of transcervical RFA suggest its long-term (> 5 years) durability of reductions of symptoms and rate of surgical reintervention for fibroids could be at least comparable to other available alternatives to hysterectomy and might be greater. The FAST-EU clinical trial previously demonstrated significant reductions through 12 months with regard to heavy menstrual bleeding and other fibroid-associated symptoms along with marked improvement in HRQoL after

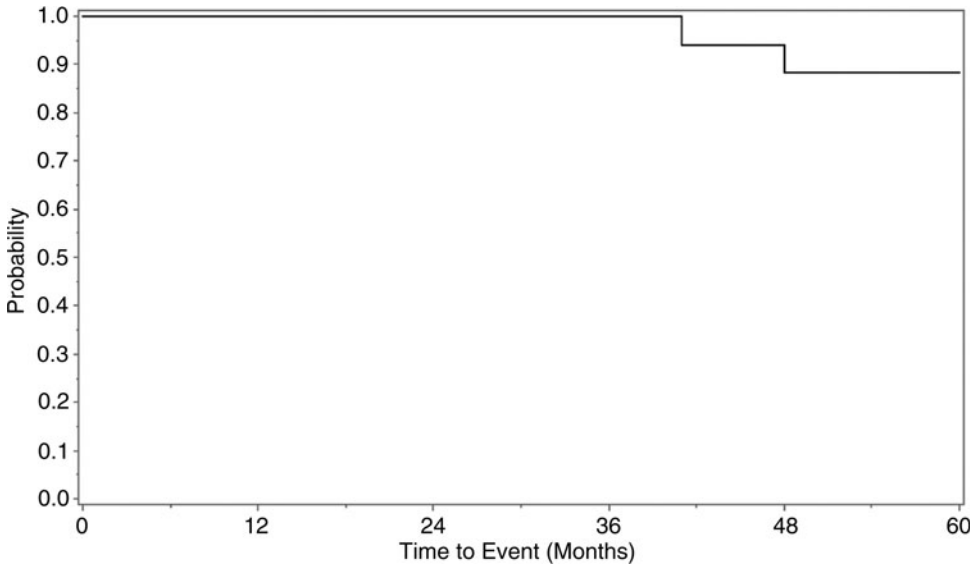

FIG. 1. Kaplan–Meier survival curve for surgical reintervention after treatment with the Sonata® System (Gynesonics, Redwood City, CA).

treatment with the Sonata System.[6] The VITALITY study demonstrated that these significant improvements in SSS and HRQoL persisted through an average of 64.4 months after treatment with the Sonata System. Of note, no surgical reinterventions occurred within the first 3.5 years post-treatment, with an overall 2.2% event rate. This is consistent with other reports of low surgical reintervention rates among patients treated with a variety of single- and multiple-needle electrode RFA systems.[17–20]

As noted, long-term self-reported VAS scores for the EQ-5D questionnaire showed a significant improvement in health status, compared with baseline. The EQ-5D summary index, while not statistically significant, did indicate stable health status over 5 years of average follow-up, with a possible trend toward improvement. The results of the VAS and summary index were thus not discordant and were also consistent with the positive UFS-QoL results and reintervention rate.

The single pregnancy, which resulted in a positive perinatal outcome, was also encouraging. It should be noted that a desire for future fertility was an exclusion criterion in the FAST-EU clinical trial.[5] While a definitive risk profile regarding pregnancy after RFA in general remains to be established and compared against myomectomy, there is a growing body of evidence that supports the use of hyperthermic ablation for fibroids in women who desire fertility.[12,21–24] The ability of the Sonata System to target and ablate uterine fibroids accurately in an incisionless fashion without resecting adjacent endometrium and myometrium holds promise as a fertility-conserving transcervical method of fibroid treatment.

Strengths of this study include a single operator, which provided consistency regarding perioperative management and long-term follow-up, as well as a high ($\sim$ 75%) patient long-term follow-up rate and inclusion of symptom and QoL data to complement the surgical reintervention histories. The study is limited by a relatively small patient cohort.

Conclusions

The VITALITY study demonstrated that transcervical RFA of uterine fibroids with the Sonata System can provide significant long-term (> 5-year) reduction of symptoms and improvement in QoL through more than 5 years, as well as a low rate of surgical reintervention (0% reintervention rate through 3.5 years). These durable benefits are conferred through an incisionless, uterus-conserving outpatient procedure that can reduce the acute morbidity associated with more-invasive fibroid-treatment options.

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Author Disclosure Statement

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Nonresective treatments for uterine fibroids: a systematic review of uterine and fibroid volume reductions

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Nonresective treatments for uterine fibroids: a systematic review of uterine and fibroid volume reductions

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ABSTRACT

Patients are increasingly seeking uterus-preserving, minimally invasive treatments for symptomatic uterine fibroids. This has led to a greater use of nonresective treatments such as uterine artery embolization (UAE), focused ultrasound (FUS) and more recently, radiofrequency ablation (RFA) of fibroids. This systematic review, following PRISMA guidelines, examines the change in uterine and fibroid volumes associated with UAE, FUS, and RFA. Pubmed and MedlinePlus databases were searched from 1956 to 2016. The keywords used were 'radiofrequency ablation,' 'magnetic resonance guided focused ultrasound,' 'ultrasound guided focused ultrasound', 'uterine artery embolization,' 'uterine fibroid embolization,' and 'leiomyoma' or 'fibroid'. Publications with at least 20 patients were included. Data were collected and analyzed using Microsoft Excel® (Microsoft Corporation, Redmond, WA) software. Eighty-one relevant papers were identified: 52 related to UAE, 11 to RFA, 17 to FUS, 1 compared UAE and FUS. We report the published uterine volume and fibroid volume changes seen in these studies at 1 to 36 months. The pooled fibroid volume reductions at six months seen with RFA were 70%, UAE 54% and FUS 32%. All three types of nonresective treatment result in fibroid volume reduction. However, fibroid volume reduction is most marked with RFA, with UAE resulting in the next most volume reduction. Additional larger cohort studies, including those that are randomized and/or comparative, would enable definitive conclusions. This is the first systematic review comparing uterine and fibroid volume reduction after RFA, UAE and MRgFUS.

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Radiofrequency ablation; magnetic resonance-guided focused ultrasound; ultrasound-guided focused ultrasound; uterine artery embolization; uterine fibroid embolization; leiomyoma; fibroid; volume

Introduction

Uterine fibroids may be present in over 70% of the premenopausal population [1,2], with a prevalence that increases with age [3]. It is estimated that as many as 50% of leiomyomas are symptomatic [4] and represent the most common indication for hysterectomy in many countries. Fibroids account for approximately 240 000 cases, or 40% of all hysterectomies performed annually in the United States [5] and nearly 20 000 inpatient admissions in the United Kingdom [6]. Uterus-sparing treatment options have been increasing in usage because of many women's desire to preserve fertility and/or their uteri, as well as to avoid major surgery; income, education and insurance type also may play a role in the choice of fibroid treatment [7]. In a prospective study on management options chosen by 933 women with symptomatic leiomyomas, only 16% had hysterectomy, 27% had at least one uterus-sparing procedure, and 57% chose nonprocedural interventions [8].

Uterus-sparing procedures include myomectomy (transabdominal, laparoscopic or hysteroscopic routes), radiofrequency ablation (RFA), uterine artery embolization (UAE), and focused ultrasound (FUS), which can be performed under magnetic resonance guidance (MRgFUS) or ultrasound guidance (USgHIFU). Of note, alternatives to hysterectomy that leave treated fibroids *in-situ* (e.g., RFA, UAE and FUS) are effective with regard to durable symptom relief if and only if there is some degree of reduction in total fibroid volume [9]. While data from studies involving MRgFUS have suggested that nonperfused volumes >20% are associated with sustained symptom relief at 24 months, it is also expected that higher percentages of fibroid ablation are more likely to result in improved clinical outcomes [10–12]. Similarly, the percentage of fibroid tissue that is infarcted during UAE is also predictive of clinical outcome [13]. With this understanding that greater ablation is associated with higher treatment success, the aim of this systematic review is to compare and contrast the existing literature on fibroid and uterine volume changes among current nonresective uterus-sparing treatment modalities: RFA, UAE and FUS. This is the first systematic review of its kind. There has not previously been a study that collates data from primary studies on fibroid or uterine volume changes with these three uterine sparing, nonresective treatments nor have these modalities been compared to

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Supplemental data for this article can be accessed here.

one in another in this way. The aim is to identify all reported fibroid and uterine volume changes with RFA, UAE and FUS with the hope to inform the clinician and patient as part of the decision making process regarding the best treatment option.

Materials and methods

PRISMA guidelines were used to perform this systematic review. The PICO model was used to formulate the search criteria. The population were patients having treatments for their fibroids. The interventions were RFA, UAE and FUS. The outcome was change in fibroid or uterine volume. PubMed and MedlinePlus databases were searched from October 1956 to September 2016. Two authors, S.K. and M. T, independently searched the databases to identify all relevant papers. The keywords used were 'radiofrequency ablation,' 'magnetic resonance-guided focused ultrasound,' 'ultrasound-guided focused ultrasound', 'uterine artery embolization,' 'uterine fibroid embolization,' and 'leiomyoma' or 'fibroid.' Initially, all identified paper titles and abstracts were reviewed and any abstract that may have had relevant data had a full paper review by the authors. All papers were reviewed by 2 of the 3 authors MT, KS and CP using an established standardized scoring system. The NIH quality assessment tool for observational cohort and cross-sectional studies were used. Relevant papers which scored a value of good or fair were included. It was agreed that any papers where there was disagreement about inclusion would be discussed; however, there were no papers where there was disagreement. Publications in the English language that were retrospective, prospective, and case series that had at least 20 patients were included. If the study reported on more than one treatment, each treatment arm had to include 20 or more patients. Any papers that provided data on change in uterine or fibroid volumes at any time, following treatment in patients who had been treated with UAE, RFA or FUS, were included. Papers that included patients who also had adenomyosis were excluded. Studies from the same research group were compared to ensure that there was no repetition of data.

Measurements by ultrasound scan, MRI or CT scan were included and analyzed together. Radiofrequency ablation via the laparoscopic or transcervical routes were included, as was data with and without concurrent imaging guidance. For MRgFUS studies, data on nonperfused fibroid volumes and fibroid intensity on T2-weighted MRI images were also collected, when available (nonperfused fibroid volume refers to the volume of a fibroid that has been devascularized secondary to the treatment, and thus does not demonstrate contrast enhancement on MR imaging). Nonperfused volume (NPV) is usually provided as the percentage of fibroid volume that lacks contrast enhancement. The signal intensity of the fibroid is determined by its appearances on T2-weighted MRI scan; hyperintense lesions are brighter than skeletal muscle, isointense appear equivalent and hypointense are darker. Signal intensity relates to blood flow within the fibroid with hyperintense fibroids being the most vascular. Articles that focused on pregnant patients and patients without leiomyomas were excluded. Data were collected and analyzed using Microsoft Excel® (Microsoft Corporation, Redmond, WA) software.

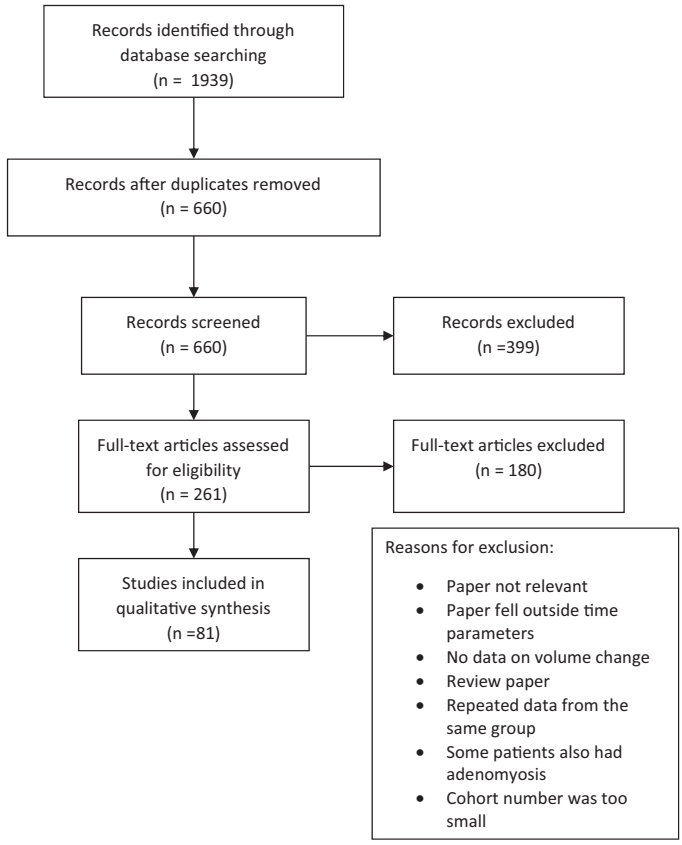

Figure 1. Flowchart of process to select eligible papers.

Results

The literature search yielded 660 abstracts; 579 of these were excluded using the criteria as detailed in the methodology. Figure 1 summarizes the results of the literature search and the selection process for eligibility. Of the 81 remaining papers, 11 related to RFA, 52 to UAE and 17 to FUS (three of these ultrasound-guided and the remaining magnetic resonance guided) and 1 paper directly compared MRgFUS and UAE. Table 1 shows a summary of the basic demographic data for each treatment modality. The mean age stated in the studies ranged from 32.4 to 52 years.

There was heterogeneity in the reporting of data between the papers. A percentage volume reduction of the uterus or fibroids was stated or could be calculated from all the included papers. However, not all publications provided a standard deviation or range for this data. Based on the published data available, in view of this heterogeneity, a meta-analysis could not be performed. In some studies, fibroid volume reduction was measured only in the dominant fibroid and in others, all treated fibroids were included. The results here show these categories combined as reduction in size of fibroids.

Radiofrequency ablation

Eleven papers reported on changes in uterine or fibroid volume reduction after RFA, mostly with noncommercial, 'off the shelf' devices often repurposed from other RFA systems designed for hepatic tumors. Two papers compared two groups. Galen et al. [14] presented multi-center, multi-study data of patients from pilot studies of a commercial laparoscopic RFA system. Yin et al. [15] split their patient group into premenopausal and menopausal cohorts. However, the definition of this was not provided and menopausal women appeared to be menstruating from the study description. Data are also available for two commercial devices. The commercial laparoscopic system (Acessa®, (Halt Medical, Brentwood, CA) was associated with a 45.1% reduction in total fibroid volume at 12 months [16]. A transcervical device (the Sonata® System, Gynesonics, Redwood City, CA), which is in commercial use in Europe and the United States, demonstrated a 66.6% reduction in total fibroid volume at 12 months [17,18]. Table 2 reports pooled data of fibroid volume reductions from the RFA studies. The means of the studies at each time point were pooled. The minimum and maximum reported fibroid volume reductions are reported as well as the number of studies reporting data at each time point.

Four papers reported on uterine volume reductions following RFA. The maximum uterine volume reductions at any time point ranged from 20% to 40%, with the minimum reported reduction of 15%.

Uterine artery embolization

Fifty-two papers reported on changes in fibroid or uterine volume size after treatment with UAE. Four of these compared two groups, both undergoing UAE but with different cohorts, treatment protocols or successful outcome definitions. Toor et al. [19] reported on patients thought to have had a successful embolization against those thought to have had an unsuccessful procedure. Treatment was considered to have failed if a patient's symptoms worsened or failed to improve, and/or if patients actively sought or had secondary treatment for their fibroids. Bilhim et al. [20] compared UAE with small polyvinyl alcohol particles (350–500 μm) and large (500–700 μm) particles. Kim et al. [21] compared patients who had utero-ovarian anastomoses with those who did not have anastomoses, as demonstrated at angiography. Song et al. [22] compared two embolization particles with one group having nonspherical polyvinyl alcohol particles and the other having gelatin sponge particles. Ikink et al. [23] compared MRgFUS to UAE. Table 3 reports pooled data of fibroid volume reductions from the RFA studies. The means of the studies at each time point were pooled. The minimum and maximum reported fibroid volume reductions are reported as well as the number of studies reporting data at each time point. No papers reported on fibroid volume reductions at 36 months.

Forty-two papers reported on uterine volume reductions following UAE. The maximum uterine volume reductions at any time point ranged from 25% to 75%, with the minimum reported reduction of 13%.

Table 1. Summary of basic demographic data for RFA, UAE and FUS.

Modality	RFA	UAE	FUS
Years of study	2007–2016	2000–2015	2004–2015
Uterine Volume Studies			
Total number of studies	4	42	2
Total *N* for all studies	274	3863	91
Pooled starting volume ± SD	253.75 ± 49.06	575.80 ± 272.27	885.35 ± 132.02
Fibroid Volume Studies			
Total number of studies	8	46	18
Total N for all studies	1757	4101	682
Pooled starting volume ± SD	84.35 ± 85.06	208.32 ± 112.41	209.98 ± 77.83

Focused ultrasound

Eighteen papers reported on changes in fibroid or uterine volume size after treatment with FUS, with either MR guidance or real-time sonographic imaging. This includes the paper by Ikink et al. [23] comparing it to UAE. Table 4 reports pooled data of fibroid volume reductions from the RFA studies, and Figure 2 illustrates the relationship between NPV achieved and fibroid volume reduction in these studies.

Two papers reported on uterine volume reductions following FUS. The maximum uterine volume reductions at any time point ranged from 16% to 28%, with the minimum reported reduction of 11%.

A full table of NPV, fibroid intensity and fibroid volume reduction is available in Table S4.

Table 2. Pooled data of fibroid volume reductions from the RFA studies.

Follow up period	3 months	6 months	9 months	12 months	24 months	36 months
Pooled mean fibroid volume reduction ± SD	55% ± 9%	70% ± 5%	78%	75% ± 15%	83% ± 8%	84%
Minimum	40%	63%	78%	45%	73%	84%
Maximum	70%	78%	78%	90%	90%	84%
No. of papers	7	6	1	7	4	1

Table 3. Pooled data of fibroid volume reductions from the UAE studies.

Follow up period	3 months	6 months	9 months	12 months	24 months
Pooled mean fibroid volume reduction ± SD	44% ± 9%	54% ± 10%	61% ± 10%	66% ± 10%	70% ± 11%
Minimum	20%	35%	35%	51%	60%
Maximum	60%	78%	75%	91%	86%
No. of papers	31	28	5	16	4

Table 4. Pooled data of fibroid volume reductions from the FUS studies.

Follow up period	3 months	6 months	12 months	24 months	36 months
Pooled mean fibroid volume reduction ± SD	21% ± 6%	32% ± 11%	28% ± 16%	34% ± 8%	32%
Minimum	12%	13%	9%	28%	32%
Maximum	29%	50%	50%	40%	32%
No. of papers	4	11	4	2	1
Follow-up period	3 months	6 months	12 months	24 months	36 months
Pooled mean fibroid volume reduction ± SD	21% ± 6%	32% ± 11%	28% ± 16%	34% ± 8%	32%
Minimum	12%	13%	9%	28%	32%
Maximum	29%	50%	50%	40%	32%
No. of papers	4	11	4	2	1

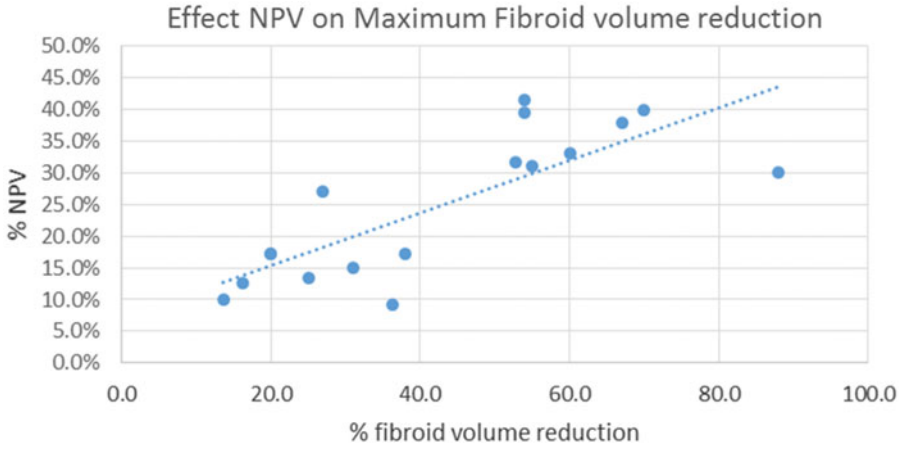

Figure 2. The relationship between nonperfused volume (NPV) and fibroid volume reductions in FUS studies.

Comparing modalities

Figure 3 demonstrates percentage fibroid volume reductions at three and six months for each treatment modality.

The full set of all collected data is summarized in the appendices. Table S1 shows all data on basic demographic data including starting uterine and fibroid volumes. Table S2 shows data on the fibroid volume reductions and Table S3 on uterine volume reductions. Table S4 reports the available data on NPV and fibroid intensity in the FUS studies.

Discussion

The aim of this systematic review is to compare the published data on fibroid and uterine volume reductions following nonresective, uterus-conserving treatments for fibroids. While the heterogeneity of the data meant that meta-analysis was not possible, meaningful trends can be observed in the collected data.

Fibroid and uterine volume reductions have been demonstrated with UAE, RFA and FUS (MRgFUS and USgHIFU). The fibroid volume reductions appear more marked with RFA and UAE than with FUS, which is clearly demonstrated by both the pooled volume reductions in Tables 2–4 and as illustrated in Figure 2. At six months post-treatment, pooled fibroid volume reductions are 70% for RFA, 54% for UAE and 32% for FUS. Only one paper directly compared two of the studied modalities [23]. Ikink and colleagues compared UAE with MRgFUS and found at three-month follow-up that uterine and fibroid percentage volume reductions were significantly greater in the UAE group compared with the MRgFUS cohort. While MRgFUS provides modest fibroid volume reductions relative to those associated with UAE and RFA, MRgFUS may still be associated with symptom relief through 24 months postablation. However, when there is a desire for significant reductions in bulk fibroid volume or for longer-lived symptom relief, MRgFUS may be less effective than other modalities. It should be noted that initial studies using MRgFUS in the United States were limited by Food and Drug Administration (FDA) imposed restrictions regarding the size of the ablation within the fibroids. These restrictions have been since changed, and further data regarding the success of this modality may reflect this.

It is known that with treatment with MRgFUS, higher nonperfused volumes are associated with greater improvements in quality of life scores and symptoms [24]. It has also been seen that larger nonperfused volumes are seen with less vascular fibroids with hypo-intense appearances on T2-weighted MRI [25,26]. In this systematic review, there does seem to be a positive trend between NPV and volume reduction, as illustrated in Figure 2. Three papers comment on the MRI intensity of the studied fibroids, as shown in Table S4. Funaki et al. [27] note that more signal-intense fibroids are associated with both lower NPVs and lesser degrees of fibroid volume reduction, with some fibroids increasing in size, rather than decreasing, within this cohort.

While reductions in fibroid volumes have been correlated with durable symptom relief after MRgFUS [10], only three of the studied papers looked directly at the link between

uterine volume change and symptoms, all involved treatment with UAE. Scheurig et al. [28] showed a moderate positive correlation between the change in symptom severity score and percentage uterine volume reduction. Pron et al. [29], in contrast, found that improvement in abnormal uterine bleeding and life impact scores were not related to uterine volume reductions. They did suggest that this improvement in uterine bleeding may be a result of vascular disruption produced by vessel occlusion. Smith et al. [27] reported contradictory results. They found no association between the changes in symptom severity scores or health related quality of life scores and uterine volume reductions. However, they did find a significant association ($p = .01906$) between global satisfaction and the percentage change in uterine volumes. It would be logical to expect that greater fibroid and uterine fibroid volumes would be associated with greater symptom improvement; however, the data from this review are insufficient to draw firm conclusions and further studies are needed.

Comparing UAE and RFA, the data suggest that individual fibroid volume reductions are more impressive with RFA but that overall uterine volume reductions are greater with UAE. Analyzing the full data set in appendices, a greater number of larger fibroids are treated in patients undergoing UAE compared to RFA. This is consistent with known practice trends, and the fact that UAE is a global fibroid therapy while RFA (like FUS) is a focal treatment modality. Across all studies, reporting of the median or mean number of fibroids treated was inconsistent and often lacking. However, papers more commonly reported on the percentage of patients with a single-treated fibroid. Of the included UAE studies, 21 papers reported on 23 cohorts of patients. In only four of the 23 cohorts (i.e. 17%) did >60% of the patients have a single fibroid, which implies that patients undergoing UAE tend to have multiple fibroids. In the reported RFA studies, four papers commented on single fibroids, and in three of these, >60% of the patients had a single diagnosed fibroid, implying that the majority of patients undergoing RFA were having treatment to a single fibroid. Uterine and dominant fibroid volumes also seem to be larger in the UAE studies than in the RFA studies. Mean uterine volumes <300 cc were seen in 75% of the studies on RFA but only 9% of the UAE studies. Similarly, mean dominant fibroid volumes of <80 cc were seen in 80% of the RFA studies, but only 4% of the UAE studies.

While volume reductions of both fibroids and uteri after treatment with UAE and RFA tend to materially increase with increasing time from treatment, the fibroid volume reductions following MRgFUS peaked at 6 months. This is consistent with reports that MRgFUS is most effective for women over the age of 45 who are approaching menopause. It is also consistent with a less durable effect of MRgFUS, in line with published data on reintervention rates of at least 50% at five years, [30] even with NPVs greater than 50% [30].

The effect of UAE on fibroid volumes over time is shown in Table 1 and Figure 3. UAE was the treatment modality with the greatest number of published studies and is arguably, the modality with which clinicians have the greatest

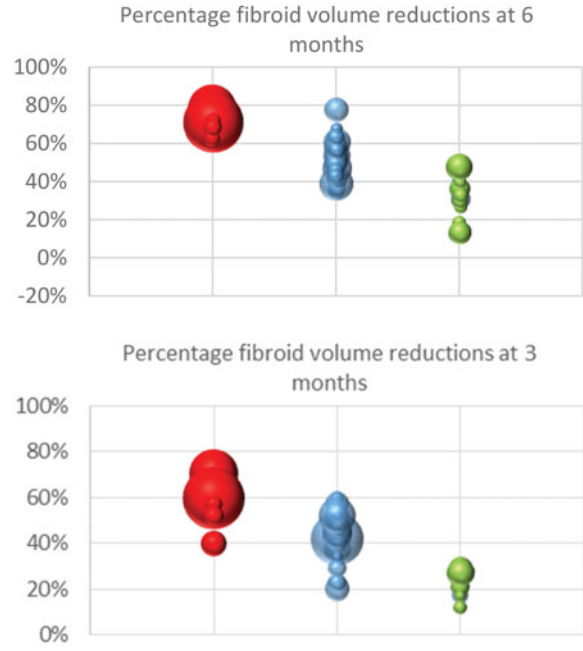

Figure 3. Bubble charts of fibroid volume reductions at three and six months post-treatment.

experience. The collected data show consistent reductions in both uterine and fibroid volumes with a maximal reduction of pooled fibroid volume of 70% at 24 months.

RFA also results in consistent reductions in uterine and fibroid volumes. Maximal pooled fibroid volume reductions of 84% were seen at 36 months.

The link between reintervention and uterine or fibroid volume reductions were explored by six studies. Funaki et al. [27] were the only group to address this in patients undergoing MRgFUS. They showed a trend of greater reintervention (21.6%) in patients with lower fibroid volume reductions (9.1%) at six months in women with hyperintense fibroids, but no comment was made on whether this met statistical significance. The remaining studies to investigate reintervention involved patients undergoing UAE. Lohle et al. [31] and Hald et al. [32] both found that reintervention was significantly more likely in patients with lower percentage fibroid or uterine volume reductions. Toor et al. [19] also found that patients who had failed treatment had significantly lower total fibroid volume reductions. Volkers et al. [33], however, used multiple regression analysis and found no association between volume reduction and failure. Dueholm et al. [34] also found that uterine or fibroid volume reductions of less than 45% were not associated with an increased risk of major reintervention (hysterectomy, myomectomy or repeat embolization). Reintervention rates of 20–30% at five years have been reported in the literature [35,36]. None of the included studies correlated volume reductions with reintervention rates after RFA. However, reintervention rates of 11% at 36 months [37] and 8% at 12 months [17] have been reported for Acessa™ and Sonata™, respectively.

This review has focused on volume reductions in fibroids and uteri after nonresective procedures. Medical therapy with a GnRH analog such as leuprolide acetate or with the selective progesterone receptor modulator ulipristal acetate

will also result in fibroid volume reduction [38]. It is known that these medications have to be continued in order to see a maintained reduction in fibroid size and as such, have mostly been used in the short-term neoadjuvant setting, given the risks to bone density associated with longer use of GnRH analogues and known association of ulipristal with progesterone receptor modulator-associated endometrial changes. While some medical therapies has been approved for long-term use, many patients will choose the convenience and security of a single treatment such as RFA, UAE or FUS.

This study did not directly compare the differences in symptom improvement, reintervention rates or pregnancy outcomes among the three treatment modalities, although these will be important considerations for patients and their clinicians. In particular, effects on fertility and pregnancy following RFA have not yet been systematically studied, although case series do suggest that RFA may be compatible with future fertility [39–42]. Reports of the effects of UAE on fertility and fecundity have been contradictory, and there is a risk of altered ovarian blood supply and premature ovarian failure in these patients [43–46]. On the other hand, MRgFUS has been approved in women who desire fertility in the United States. As an ablative treatment for fibroids, the compatibility of MRgFUS with future pregnancy suggests that RFA might similarly be found to be suitable as its evidence base increases [18].

Although publication bias cannot be absolutely excluded, the inclusion of all identified studies that reported on volume reductions should ensure that these data is as comprehensive as possible.

Conclusions

Women with symptomatic fibroids are increasingly seeking minimally invasive, uterus-sparing treatment options. This systematic review aimed to summarize the reductions in fibroid and uterine volumes with three such treatments, UAE, RFA and FUS. All three modalities result in fibroid and uterine volume reduction, but these were most significant with RFA, followed by UAE. This pattern was seen consistently at all time points. At six months, pooled fibroid volume reductions were 70% with RFA, 54% with UAE and 32% with FUS. The effects of RF and UAE seem to be prolonged with reductions in fibroid volumes at least up to 24 months post-treatment. A meta-analysis with original data from the authors would help to statistically analyze the trends observed in this review. Furthermore, a randomized controlled trial with head-to-head comparators of various fibroid interventions is needed to establish which the more effective treatment is and whether different patient groups see better results with either treatment, so that clinicians may best advise their patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Clinical Performance of Radiofrequency Ablation for Treatment of Uterine Fibroids: Systematic Review and Meta-Analysis of Prospective Studies

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Abstract

Background: Radiofrequency ablation (RFA) has emerged as a safe and effective treatment option for women with symptomatic uterine fibroids and can be delivered by laparoscopic, transvaginal, or transcervical approaches. The evidence regarding typical patient outcomes with RFA has not previously been examined in a comprehensive fashion.

Materials and Methods: We performed a systematic review of prospective studies for treatment of uterine fibroids with RFA. Main outcomes were procedure time, patient recovery metrics, change in fibroid volume, symptom severity score (SSS), health-related quality of life (HRQL), and reinterventions. Data were analyzed with random effects meta-analysis and metaregression.

Results: We identified 32 articles of 1283 unique patients (median age: 42 years) treated with laparoscopic RFA (19 articles), transvaginal RFA (8 articles), or transcervical fibroid ablation (5 articles). Mean procedure time was 49 minutes, time to discharge was 8.2 hours, time to normal activities was 5.2 days, and time to return to work was 5.1 days. At 12 months follow-up, fibroid volume decreased by 66%, HRQL increased by 39 points, and SSS decreased by 42 points (all $P < .001$ versus baseline). The annual cumulative rate of reinterventions due to fibroid-related symptoms was 4.2%, 8.2%, and 11.5% through 3 years.

Conclusions: RFA of uterine fibroids significantly reduces fibroid volume, provides significant durable improvements in fibroid-related quality of life, and is associated with favorable reintervention rates.

Keywords: laparoscopic, leiomyoma, myoma, radiofrequency, transcervical, transvaginal

Introduction

Uterine fibroids are the most common benign solid pelvic tumor in women, developing in ~70% to 80% of women by 50 years of age.[1] More than 1 in 3 women with uterine fibroids report symptoms that interfere with activities of daily living such as heavy menstrual bleeding and/or bulk symptoms.[2] Self-management with nonprescription medication or lifestyle modification is common, but often unsuccessful.[3] Several surgical and interventional treatments are available to women with persistent symptoms attributable to uterine fibroids, including hysterectomy, myomectomy, and uterine artery embolization. However, patient acceptance of these treatments may be limited due to the increasing demand for less invasive therapies that preserve the uterus.[3]

Radiofrequency ablation (RFA) has emerged as a safe and effective treatment alternative as the procedure can be delivered in a minimally invasive fashion. RFA may be delivered by a laparoscopic, transvaginal, or transcervical approach into the uterine fibroid to induce coagulative necrosis[4] with subsequent reduction in fibroid-related symptoms. Previous reviews, often limited to a single device or treatment route, have reported patient outcomes following

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laparoscopic RFA.[5,6] To the authors' knowledge, no systematic review has evaluated the clinical utility of each RFA delivery approach for the treatment of uterine fibroids. We hypothesized that RFA would provide significant decreases in fibroid volume and improvements in quality of life for women with symptomatic uterine fibroids. The primary aim of this study was to report the effectiveness of RFA for symptomatic uterine fibroids by means of a systematic review and meta-analysis.

Materials and Methods

Eligibility criteria and search strategy

The conduct, analysis, and reporting of this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[7] Prospective studies of RFA for symptomatic uterine fibroid treatment were eligible for inclusion in this systematic review. We considered randomized trials, comparative cohort studies, and non-comparative cohort studies for this review, and extracted data only from the RFA arms of the study. We excluded case reports and studies with less than 10 patients, studies in which patients received concomitant surgeries due to a potential for confounding of patient outcomes, and studies that reported no main outcomes. No date or language restrictions were applied to the searches. We performed systematic searches of Medline, Embase, and the Cochrane Central Register of Controlled Trials for potentially eligible studies. Additional searches were conducted in the Directory of Open Access Journals and Google Scholar. Manual searches of the reference lists of included articles and relevant meta-analyses were performed. The search strategy included combinations of anatomic-, diagnosis-, and treatment-specific keywords. The Medline search strategy is provided in Supplementary Table S1; the search strategy for other databases was adapted as necessary.

Two researchers with expertise in systematic reviews independently screened titles and abstracts for eligibility. Full-text articles were obtained for all potentially relevant studies. To account for multiple articles derived from the same primary study or subsamples of the primary study, we preferentially extracted data from the article reporting the longest follow-up duration on the entire cohort and supplemented any missing data using other articles derived from that study. Thus, all reported data were derived from unique patients. Disagreements related to study eligibility were resolved by discussion and consensus. The final searches were performed on May 31, 2019.

Data extraction

Researchers independently extracted data from eligible studies using standardized data collection forms. For each study, we recorded metadata, patient characteristics, study characteristics, treatment regimens, and main outcomes. Main outcomes included procedure time, length of stay, time to normal activities, time to return to work, change in uterine fibroid volume, change in symptom severity score (SSS) and health-related quality of life (HRQL) on the Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire (UFS-QoL),[8] and surgical reinterventions.

We extracted fibroid volume, SSS, and HRQL data at baseline, 3 months, 6 months, 12 months, and beyond 12 months, where the last interval consisted of the latest follow-up interval beyond 12 months reported in each study. The rate of surgical reinterventions for fibroid-related symptoms was calculated at 6 months and annually thereafter through 3 years. Reinterventions were conservatively assumed to be performed for fibroid-related symptoms unless explicitly stated otherwise in the article. We used the National Institute of Health assessment tool for before/after studies to evaluate the methodological quality of eligible studies.[9] Data extraction discrepancies between the two researchers were resolved by discussion and consensus.

Statistical analyses

Procedure time, length of stay, time to normal activities, and time to return to work were reported using the weighted mean statistic. Change in uterine fibroid volume was reported as a weighted percent change from baseline. Change in SSS and HRQL was reported using the weighted mean difference relative to baseline. The surgical reintervention rate was reported as a weighted event rate. Outcome estimates were calculated for each study and the overall pooled result was reported along with the 95% confidence interval (CI). We prospectively specified an inverse variance random effects model for all analyses given the variation among study designs and methods of RFA delivery. We evaluated temporal trends in fibroid volume, UFS-QoL scores, and reinterventions by pooling data at distinct follow-up intervals.

We estimated heterogeneity among studies with the I^2 statistic, where a value of 0% represented no heterogeneity and larger values represented increasing heterogeneity.[10] In accordance with Cochrane Collaboration recommendations, we performed metaregression analysis for any outcome reported in at least 10 studies. We tested the robustness of the meta-analysis conclusions with three sensitivity analysis, including a reanalysis using a fixed-effects meta-analysis model, a one-study removed analysis where the meta-analysis was recalculated following iterative one-at-a-time removal of each study, and reanalysis of only the studies with the highest methodological quality. *P*-values were two sided with a significance level <.05. Analyses were performed using Stata v14.2 (StataCorp).

Results

Study selection

We identified 505 articles in our searches and ultimately included 32 articles of 1283 unique patients treated with RFA for uterine fibroids in this systematic review. A PRISMA flow diagram depicting the study identification and selection process is provided in Figure 1. Among the full-text articles that were reviewed, 51 were excluded, with review articles (25), case reports (7), and non-RFA treatments (6) the most common reasons (Supplementary Table S2).

Patient and study characteristics

Baseline patient characteristics in each study are reported in Table 1. Among included studies, mean patient age ranged from 39 to 45 years (median 42 years), the number of treated fibroids ranged from 1 to 5 (median 1.7) per patient, and fibroid volume ranged from 10 to 305 cm^3 (median 74 cm^3). Baseline UFS-QoL scores ranged from 22 to 77 for HRQL (median 49) and 32 to 76 for SSS (median 55). Study

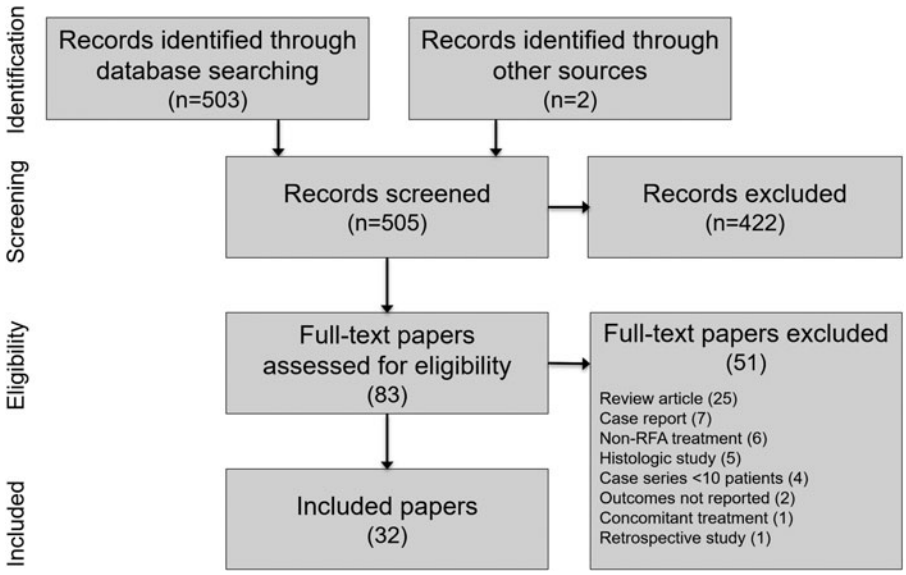

FIG. 1. PRISMA study flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RFA, radiofrequency ablation.

design characteristics are reported in Table 2. Among the 32 articles, 19 reported laparoscopic RFA, 8 reported transvaginal RFA, and 5 reported transcervical fibroid ablation (TFA). RFA was delivered using ultrasound guidance in 90% of the studies. Patient follow-up in each study ranged from in-hospital to 5.3 years (median 12 months).

Among the 20 prospective primary studies in this review (reported in 32 articles), study quality was rated as good or fair for 19 of 20 studies. The study design elements that were most frequently missing from published reports were interrupted time-series design (20 of 20 studies), blinded outcome assessors (20 of 20 studies), analyses that failed to adjust for attrition (19 of 20 studies), and no justification for sample size (15 of 20 studies) (Supplementary Table S3).

Procedure and recovery results

The weighted mean procedure time was 49 minutes (95% CI: 41–56 minutes). Procedure time was significantly different among RFA delivery approaches (laparoscopic, 73 minutes; TFA, 44 minutes; transvaginal, 24 minutes), where all pairwise comparisons were $P \leq .002$. Time to discharge, time to normal activities, and time to return to work were reported inconsistently and, therefore, comparisons of RFA delivery approaches were reported descriptively only. The weighted mean time to discharge was 8.2 hours (95% CI: 6.3–10.0 hours), including 10.7 hours for laparoscopic RFA, 2.5 hours for TFA, and 2.5 hours for transvaginal RFA. The weighted mean time to normal activities was 5.2 days (95% CI: 3.3–7.1 days), including 9.0 days for laparoscopic RFA, 3.3 days for TFA, and no studies for transvaginal RFA. The weighted mean return to work was 5.1 days (95% CI: 3.7–6.5 days), including 6.5 days for laparoscopic RFA, 3.6 days for TFA, and no studies for transvaginal RFA (Table 3). Substantial heterogeneity among studies was observed for each of these outcomes, with I^2 ranging from 85% to >99% (all $P < .001$).

Temporal trends in fibroid volume, fibroid-related quality of life, and reinterventions

Following RFA, mean fibroid volume decreased by 47% at 3 months, 55% at 6 months, 66% at 12 months, and 71% at >12 months follow-up (Fig. 2). Low-to-moderate heterogeneity among studies was observed at each follow-up interval (I^2 values of 54% [$P = .02$], 0% [$P = .44$], 43% [$P = .07$], and 0% [$P = .42$] at 3, 6, 12, and >12 months, respectively). The percent change in fibroid volume 12 months after RFA was consistent across the range of treated fibroid volumes (Fig. 3). In metaregression that adjusted for differences in baseline fibroid volume, using laparoscopic RFA as the reference comparator, fibroid volume reduction was 4% greater with TFA ($P = .81$) and 10% greater with transvaginal RFA ($P = .47$) at 12 months.

Quality of life, where higher HRQL scores indicate better quality of life, improved relative to baseline by 30 points at 3 months, 37 points at 6 months, 39 points at 12 months, and 31 points at >12 months follow-up (all $P < .001$ versus baseline). Fibroid symptoms, where lower SSS scores indicate lower symptom severity, decreased by 29, 36, 42, and 40 points relative to baseline over this same period (all $P < .001$ versus baseline) (Fig. 4). Considerable heterogeneity was evident at each follow-up interval for HRQL (I^2 ranged from 86% to 99%, all $P < .001$) and SSS (I^2 ranged from 46% to 99%, all $P \leq .06$). The heterogeneity in HRQL (Fig. 5) and SSS (Fig. 6) changes was largely explained by the strong inverse association with the baseline value for that variable.

The cumulative rate of surgical reinterventions for fibroid-related symptoms was 4.2%, 8.2%, and 11.5% at annual follow-up intervals through 3 years (Fig. 7). The reintervention rate at 12 months was comparable among TFA (2.7%), laparoscopic RFA (3.8%), and transvaginal RFA (5.3%), where $P \geq .52$ for all pairwise comparisons. The conclusions of this meta-analyses were unchanged among several sensitivity analyses (Supplementary Table S4).

Table 1. Patient Characteristics in Studies Included in the Meta-Analysis

Study	Age (years)	Patients desiring future fertility	Fibroid types (%)					No. of treated fibroids per patient	Total fibroid volume (cm^3)	HRQL[a]	SSS[a]
			Submucous	Intramural	Subserous	Transmural	Unspecified				
Bongers et al.[15] Brölmann et al.[16]	43[b]	Excluded	61	30	0	9	0	1.8±1.1	10 (<1, 77)[c]	34±19	62±17
Garza-Leal[17]	43[b]	Excluded	49	46	0	6	0	2.1	—[d]	27±22	65±17
Braun et al.[18]	40±7	Included	4	35	49	5	7	4.2±3.3	—[d]	—	—
Brucker et al.[19] Hahn et al.[20] Krämer et al.[21]	40±8	Included	0	49	51	0	0	2.9±2.6	—[d]	77	40
Carrafiello et al.[22]	40 (27, 51)[e]	Excluded	9	45	0	0	45	1 (1, 1)[c]	102 (45, 278)[e]	62 (37, 86)[e]	50 (32, 67)[e]
Cho et al.[23]	43±4	Excluded	0	0	0	0	100	—	65±13	59±16	49±11
Cho et al.[24]	40±7	Included	100	0	0	0	0	—	112±53	46±13	76±9
Chudnoff et al.[25] Galen et al.[26] Guido et al.[27] Berman et al.[28]	43±5	Excluded	21	46	25	5	2	5.0±4.4	80±84	39±19	60±19
Chudnoff et al.[29] Miller and Osman[30]	43 (31, 50)[c]	Excluded	21	49	10	21	0	3.0±2.1	71±85	40±21	55±19
Galen et al.[31] Garza-Leal et al.[32] Robles et al.[33]	42±6	Excluded	6	50	38	3	3	3 (1, 20)[c]	—	49±24	54±23
Ghezzi et al.[34] Bergamini et al.[35]	42 (40, 50)[c]	Excluded	0	100	0	0	0	1 (1, 3)[c]	77 (15, 333)[c]	63 (23, 94)[c]	44 (13, 91)[c]
Iversen and Dueholm[36] Iversen et al.[37]	45±7	Excluded	20	80	0	0	0	1 (1, 3)[c]	123 (24, 675)[c]	22±21	61±17
Jiang et al.[38]	41±6	Included	9	78	13	0	0	1 (1, 3)[c]	60 (7, 321)[c]	72±13	32±15
Kim et al.[39]	40±7	Included	6	0	0	0	94	2 (1, 3)[c]	305 (48, 1022)[e]	—	57±21
Lee et al.[40]	45 (42, 51)[e]	Excluded	100	0	0	0	0	1 (1, 1)[c]	58[b]	49±15	71±8
Marcos et al.[41]	44±5	Included	0	71	29	0	0	1 (1, —)[c]	112±65	—	—
Meng et al.[42]	39±6	Excluded	13	66	21	0	0	1 (1, 3)[c]	70±59	—	—
Rattray et al.[43]	39±7	Included	0	0	0	0	100	3.4±2.4	—[d]	40±26	62±20
Rey et al.[44]	39±9	Included	100		0	0	0	—	122±183	—	—
Turtulici et al.[45]	45±8	Excluded	0	0	0	0	100	1.7 (1, 3)[e]	14 (5, 42)[e]	68±36	—
Wu et al.[46]	41 (32, 52)[c]	Excluded	21	79	0	0	0	1.2 (1, 3)[e]	32 (1, 78)[c]	65±41	45±34

[a]Derived from the UFS-QoL questionnaire.
[b]Estimated.
[c]Median (min, max).
[d]Diameter reported only.
[e]Mean (min, max).
HRQL, health-related quality of life; SSS, symptom severity score; UFS-QoL, Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire.

Table 2. Design Characteristics of Studies Included in the Meta-Analysis

Study	*Study ID*	*Treatment period*	*Number and location of sites*	*No. of patients*	*RFA trade name (manufacturer)*	*RFA delivery*	*Follow-up (months)*
Bongers et al.[15] Brölmann et al.[16]	FAST-EU; NCT01226290	—, 2013[a]	7 Intercontinental	50	Sonata (Gynesonics)	TFA; US guidance	12 (6, 12)[b]
Garza-Leal[17]	VITALITY	—	1 Mexico	17	Sonata (Gynesonics)	TFA; US guidance	64 (57, 73)[b]
Braun et al.[18]	TRUST postmarket	2014, 2016	4 United States, Canada	40	Acessa (Acessa Health)	PL; US guidance	2 (0, 2)[b]
Brucker et al.[19] Hahn et al.[20] Krämer et al.[21]	NCT01750008	2012, 2013	1 Germany	25	Acessa (Acessa Health)	PL; US guidance	21 (—, 24)[b]
Carrafiello et al.[22]	—	2006, 2008	1 Italy	11	RF3000 (Boston Scientific)	PL; US guidance	9 (3, 12)[c]
Cho et al.[23]	—	2004, 2006	1 Korea	153	M-1004 (RF Medical System)	TV; US guidance	— (—, 18)[b]
Cho et al.[24]	—	2009, 2012	1 Korea	24	M-1004 (RF Medical System)	TV	— (—, 24)[b]
Chudnoff et al.[25] Galen et al.[26] Guido et al.[27] Berman et al.[28]	Halt Phase III; NCT00874029	2009, 2011	9 United States, Latin America	135	Acessa (Acessa Health)	PL; US guidance	31 (—, 36)[b]
Chudnoff et al.[29] Miller and Osman[30]	SONATA; NCT02228174	2015, 2016	22 United States, Mexico	147	Sonata (Gynesonics)	TFA; US guidance	22 (—, 24)[b]
Galen et al.[31] Garza-Leal et al.[32] Robles et al.[33]	Halt Phase II	—, 2008[a]	2 Latin America	69	Acessa (Acessa Health)	PL; US guidance	11 (3, 12)[b]
Ghezzi et al.[34] Bergamini et al.[35]	—	2003, 2005	3 Italy	25	Model 1500X (AngioDynamics)	PL	24 (12, 36)[c]
Iversen and Dueholm[36] Iversen et al.[37]	—	2007, 2010	2 Norway, Denmark	66	Model 1500X (AngioDynamics)	PL; US guidance	59 (37, 74)[b]
Jiang et al.[38]	—	2009, 2012	— China	46	BBT-RF-B (Ban Bian Tian)	TV; US guidance	— (—, 18)[b]
Kim et al.[39]	—	2004, 2008	— Korea	69	M-2004 (RF Medical System)	TV; US guidance	— (—, 12)[b]
Lee et al.[40]	—	2005, 2007	1 Korea	58	M-1004 (RF Medical System)	TV; US guidance	— (—, 18)[b]
Marcos et al.[41]	—	2011, 2012	1 Spain	17	RF3000 (Boston Scientific)	PL; US guidance	6 (—, 6)[b]
Meng et al.[42]	—	2009, 2009	1 China	50	Cool-Tip (Medtronic)	PL; US guidance	<1[d]
Rattray et al.[43]	TRUST; NCT015663783	2012, 2017	≥2 Canada	23	Acessa (Acessa Health)	PL; US guidance	— (—, 3)[b]
Rey et al.[44]	—	2015, 2017	1 Spain	205	VIVA (STARmed)	TV; US guidance	— (—, 12)[b]
Turtulici et al.[45]	—	2017, 2018	1 Italy	19	VIVA (STARmed)	TV; US guidance	6 (6, 6)[b]
Wu et al.[46]	—	2010, 2012	1 China	51	DS98F-D (Huanghe)	TV; US guidance	11 (6, 12)[b]

[a]Estimated.
[b]Mean (min, max).
[c]Median (min, max).
[d]In-hospital follow-up only.
PL, percutaneous laparoscopic; RFA, radiofrequency ablation; TFA, transcervical fibroid ablation; TV, transvaginal; US, ultrasound.

Table 3. Procedure and Recovery Results of Studies Included in the Meta-Analysis

Study	*Procedure time (minutes)*	*Time to discharge (hours)*	*Time to return to normal activities (days)*	*Time to return to work (days)*
Bongers et al.[15]	39 ± 23	—	4.4 ± 3.1	—
Brölmann et al.[16]				
Garza-Leal[17]	—	—	—	—
Braun et al.[18]	114 ± 60	6.8 ± 3.2	—	—
Brucker et al.[19]	66 ± 24	10.0 ± 5.5	20.5 (5, 103)[a]	10.0 (2, 86)[a]
Hahn et al.[20]				
Krämer et al.[21]				
Carrafiello et al.[22]	20 (15, 25)[b]	—	—	—
Cho et al.[23]	— (10, 40)	—	—	—
Cho et al.[24]	—	—	—	—
Chudnoff et al.[25]	126 ± 60	—	9.0 (2, 60)[a]	5.0 (0, 29)[a]
Galen et al.[26]				
Guido et al.[27]				
Berman et al.[28]				
Chudnoff et al.[29]	47 ± 30	2.5 ± 1.2	2.2 ± 2.2	3.6 ± 2.6
Miller and Osman[30]				
Galen et al.[31]	140 (42, 290)[a]	—	4.5 (1, 11)[b]	4.0 (2, 10)[a]
Garza-Leal et al.[32]				
Robles et al.[33]				
Ghezzi et al.[34]	25 (20, 45)[a]	18[c]	—	—
Bergamini et al.[35]				
Iversen and Dueholm[36]	—	—	—	—
Iversen et al.[37]				
Jiang et al.[38]	25 (20, 30)[b]	—	—	—
Kim et al.[39]	18 ± 5	—	—	—
Lee et al.[40]	—	—	—	—
Marcos et al.[41]	36 ± 11	12.0 (8, 24)[b]	—	—
Meng et al.[42]	—	—	—	—
Rattray et al.[43]	73 ± 26	6.7 ± 3.0	—	11.1 ± 7.6
Rey et al.[44]	17 (11, 44)[b]	—	—	—
Turtulici et al.[45]	28 (16, 43)[b]	—	—	—
Wu et al.[46]	— (20, 40)	2.5[c]	—	—
POOLED RESULT[d]	49 (41–56)	8.2 (6.3–10.0)	5.2 (3.3–7.1)	5.1 (3.7–6.5)
Laparoscopic RFA	73 (56–91)	10.7 (5.9–15.5)	9.0 (3.8–14.1)	6.5 (3.8–9.2)
Transvaginal RFA	24 (20–28)	2.5 (2.4–2.6)	—	—
TFA	44 (36–51)	2.5 (2.3–2.7)	3.3 (1.1–5.4)	3.6 (3.1–4.1)

[a]Median (min, max).
[b]Mean (min, max).
[c]Estimated value.
[d]Pooled results derived from random effects meta-analysis and reported as weighted mean (95% confidence interval).
RFA, radiofrequency ablation; TFA, transcervical fibroid ablation.

Discussion

RFA has been used with increasing frequency over the last decade to treat women with uterine fibroids who wish to preserve their uteri and possibly avoid more invasive surgery. Yet there is a paucity of comprehensive reviews regarding RFA of uterine fibroids that synthesize published evidence to help inform women and their gynecologists about typical acute and longer term results. In this systematic review and meta-analysis, the mean RFA procedure time was 49 minutes and performed on an outpatient basis in most cases. Patients returned to normal activities and to work in 5 days, on average, after RFA. We observed significant variability among studies for several outcomes, which was largely attributable to differences in baseline fibroid volume, quality of life, and RFA delivery approaches. Despite this variability, there was strong evidence of sustained fibroid volume reduction, significant improvements in HRQL and SSS, and favorable surgical reintervention rates following RFA.

Several systematic reviews have reported results of RFA for uterine fibroids. Lim et al.[5] reported that laparoscopic

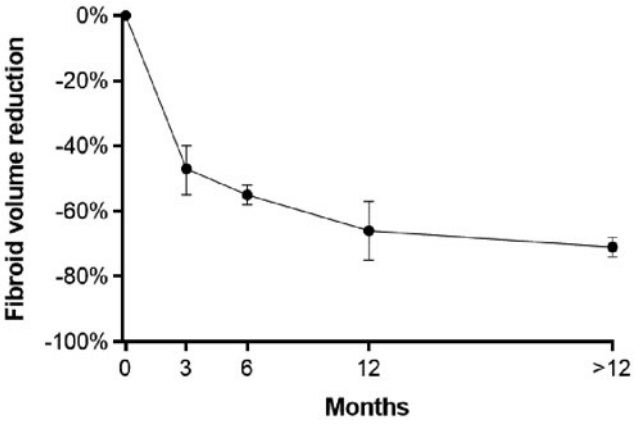

FIG. 2. Temporal trends in uterine fibroid volume following radiofrequency ablation of uterine fibroids. Plotted data are mean percent change from baseline and 95% confidence interval. Fibroid volumes at each follow-up interval were significantly smaller than baseline (all $P < .001$). Heterogeneity estimates were $I^2 = 54\%$ ($P = .02$) at 3 months, $I^2 = 0\%$ ($P = .44$) at 6 months, $I^2 = 43\%$ ($P = .07$) at 12 months, and $I^2 = 0\%$ ($P = .42$) after 12 months.

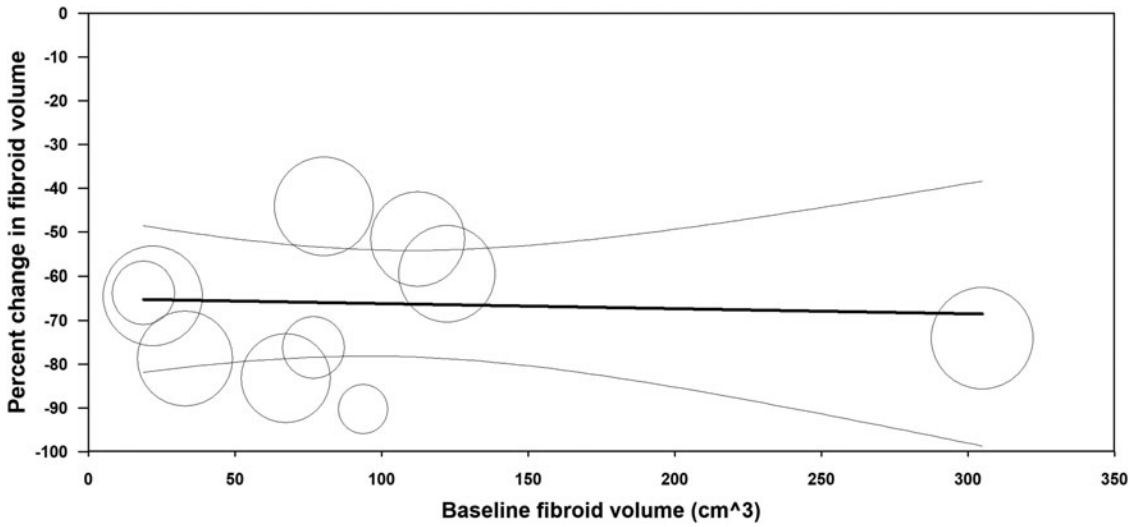

FIG. 3. Relationship between uterine fibroid volume at baseline with percent change in uterine volume following radiofrequency ablation. Plotted data are the metaregression line (dark line) and 95% confidence interval (light lines), with results of individual studies denoted by circles, where circle size is proportional to the weighting of the study in the meta-analysis. Percentage of between-study variance explained by baseline fibroid volume (R^2 analog) = 0% ($P = .83$).

RFA reduced uterine fibroid volume by 81 cm^3 ($P < .001$), reduced SSS by 43 points ($P < .001$), and improved HRQL by 38 points ($P < .001$), with a reintervention rate of 2.7% over follow-up ranging from 9 to 36 months. More recently, Lin et al.[6] performed a similar review that included the same RFA studies and ultimately reached the same conclusions.

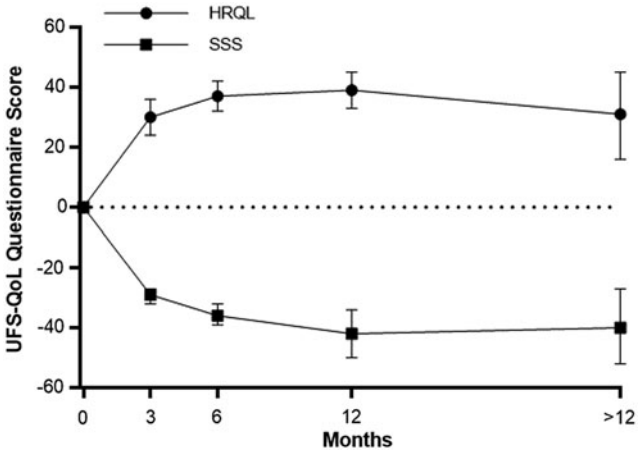

FIG. 4. Temporal trends in UFS-QoL subscores following radiofrequency ablation of uterine fibroids. Plotted data are mean absolute change from baseline and 95% confidence interval. HRQL values at each follow-up interval were significantly higher than baseline (all $P < .001$). SSS values at each follow-up interval were significantly lower than baseline (all $P < .001$). Heterogeneity estimates for HRQL were $I^2 = 89\%$ ($P < .001$) at 3 months, $I^2 = 86\%$ ($P < .001$) at 6 months, $I^2 = 91\%$ ($P < .001$) at 12 months, and $I^2 = 99\%$ ($P < .001$) after 12 months. Heterogeneity estimates for SSS were $I^2 = 46\%$ ($P = .06$) at 3 months, $I^2 = 77\%$ ($P < .001$) at 6 months, $I^2 = 96\%$ ($P < .001$) at 12 months, and $I^2 = 99\%$ ($P < .001$) after 12 months. HRQL, health-related quality of life; SSS, symptom severity score; UFS-QoL, Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire.

Sandberg et al.[11] reported a reintervention rate of 0.3% at 1 year and 10.4% at 3 years, reductions in SSS of 37 points at 1 year, and increases in HRQL of 35 points at 1 year after laparoscopic RFA. Taheri et al.[12] published a review comparing uterine artery embolization, various routes of RFA, and focused ultrasound and found that RFA provided a significantly greater percentage of fibroid volume reduction compared with the other treatments. No previous report has analyzed aggregate outcomes of transvaginal RFA or TFA studies. In this study, we report temporal trends in RFA outcomes, provide comparisons of outcomes by RFA delivery approach, and performed several sensitivity analyses to determine whether the meta-analysis conclusions were robust to various assumptions. Thus, the current review provides novel clinical evidence that arguably represents the most thorough meta-analysis results of RFA for treatment of uterine fibroids.

RFA was used to treat a wide variety of fibroid types and sizes in the included studies. Analysis of fibroid volume decreases in relation to baseline fibroid volumes suggests that RFA provides ~65% reductions in fibroid volume across a broad range of fibroid sizes. Similarly, despite variation in baseline quality of life scores among studies, RFA provided significant improvements in SSS and HRQL at all follow-up intervals and across the entire range of preprocedural quality-of-life scores.

We also analyzed patient outcomes by RFA delivery approach, which revealed several important observations. First, TFA was associated with a brief mean procedure time, short mean length of stay, and, on average, a faster return to normal activities and work compared with laparoscopic RFA. Transvaginal RFA was also associated with short procedure time and length of stay, but no data related to time to return to normal activities or work were reported. It would be expected that the transvaginal and transcervical routes of RFA would provide similar outcomes, although in theory, TFA may be expected to be the safer of the two options given the need with transvaginal RFA to violate the uterine serosa with a charged

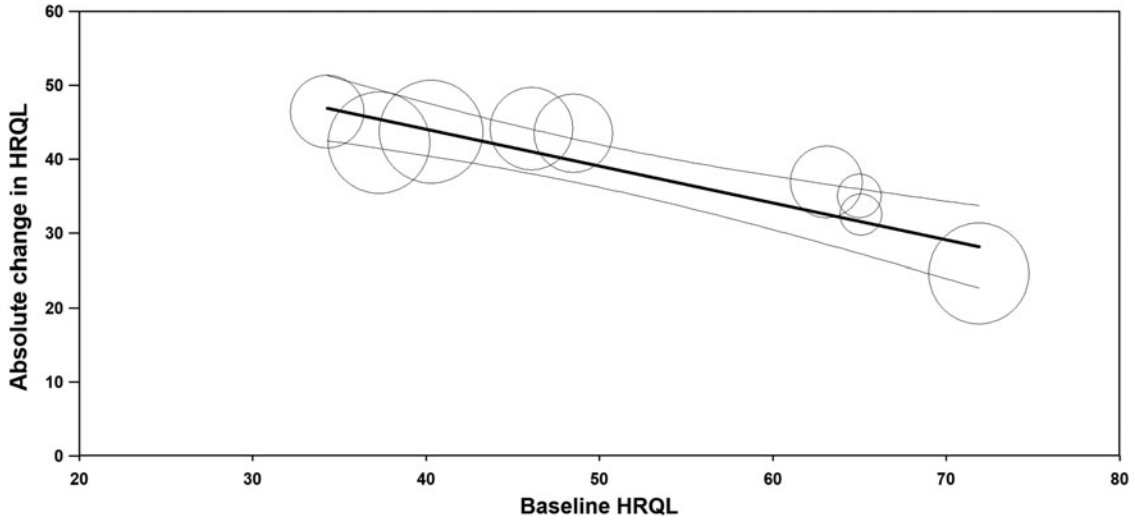

FIG. 5. Relationship between HRQL at baseline with HRQL change at 12 months following radiofrequency ablation. Plotted data are the metaregression line (dark line) and 95% confidence interval (light lines), with results of individual studies denoted by circles, where circle size is proportional to the weighting of the study in the meta-analysis. Percentage of between-study variance explained by baseline HRQL (R^2 analog) = 93% ($P < .001$). HRQL, health-related quality of life.

electrode or electrode array. Second, RFA delivery approaches were similarly effective in reducing fibroid volume and improving quality of life. Third, surgical reintervention rates for fibroid-related symptoms were favorable after RFA and did not significantly differ among RFA delivery approaches. Furthermore, the rate of reintervention at 3 years was 11.5% in the current review, which favorably compares with reported rates of 17% for uterine artery embolization, 21% for hysteroscopic myomectomy, 24% for endometrial ablation, and 11% for laparoscopic myomectomy over the same period.[13]

Main strengths of this review included adherence to PRISMA guidelines, excellent generalizability of results given the inclusion of almost 1300 patients, and robust conclusions that were unchanged in various sensitivity analyses. There are also several limitations pertaining to the quality of the included studies that may influence conclusions. First, there is less precision in the RFA results after 12 months of follow-up since fewer studies reported longer term data. Second, the number of included studies was insufficient to perform statistical comparisons among RFA delivery approaches for several outcomes. In these cases where we

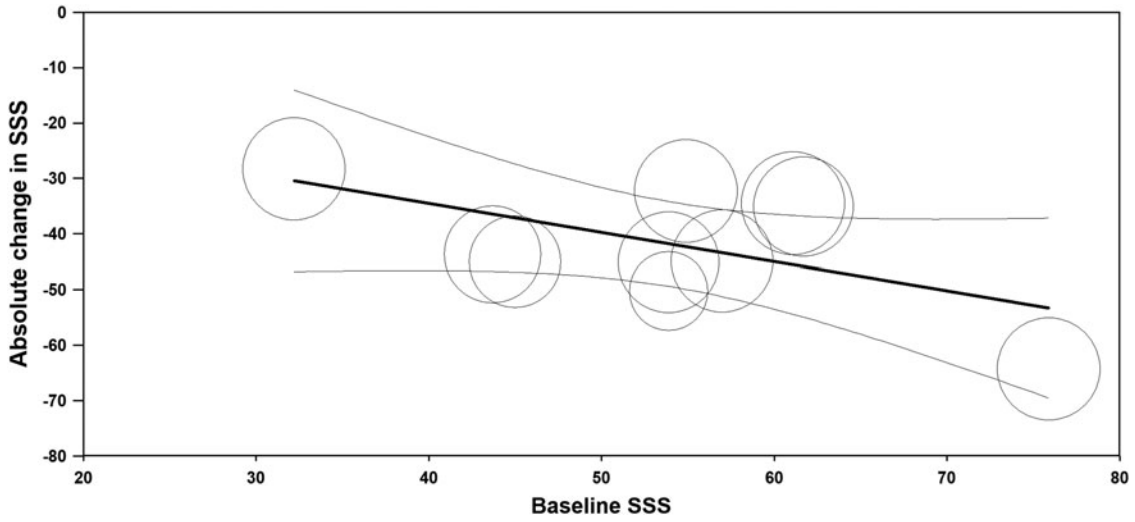

FIG. 6. Relationship between SSS at baseline with SSS change at 12 months following radiofrequency ablation. Plotted data are the metaregression line (dark line) and 95% confidence interval (light lines), with results of individual studies denoted by circles, where circle size is proportional to the weighting of the study in the meta-analysis. Percentage of between-study variance explained by baseline SSS (R^2 analog) = 44% ($P = .05$). SSS, symptom severity score.

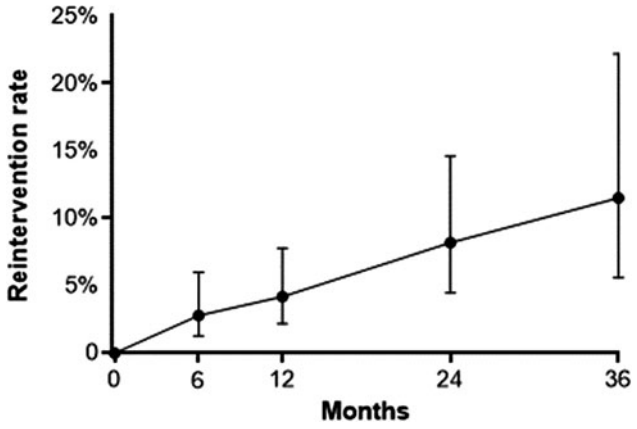

FIG. 7. Cumulative reintervention rate following radiofrequency ablation. Error bars are 95% confidence intervals.

reported the results descriptively, it is plausible that clinically important differences in patient outcomes existed among RFA delivery approaches that were not detectable in our meta-analysis due to insufficient statistical power. Importantly, since the comparative RFA outcomes reported in this study were derived from different studies and analyzed through metaregression, the *post hoc* results should be considered hypothesis generating only. Third, it is not possible to determine from this analysis whether RFA efficacy was influenced by fibroid type or volume due to concerns of aggregation bias whereby real associations observed at the patient level (e.g., fibroid volume in each patient) often do not agree with those observed at the study level (e.g., mean fibroid volume in each study).[14] Finally, we planned to report the frequency of complications in this meta-analysis. Unfortunately, complication reporting was highly inconsistent and inadequate such that any attempts at reporting these data would have led to inaccurate and misleading results. For example, most articles provided no criteria or definitions regarding complication reporting. Furthermore, several articles simply reported that no complications occurred without any further commentary. Regardless, no serious procedural complications such as death or iatrogenic injury to the bowel, bladder, or ureter were reported in any study. Authors of future RFA studies are encouraged to provide detailed definitions of complications and a complete listing of reported complications during follow-up, with further specification of event seriousness and relationship to the RFA procedure. Lastly, RFA was utilized across a broad range of fibroid types and volumes, suggesting that this therapy is appropriate for most women with symptomatic uterine fibroids.

Conclusion

RFA of uterine fibroids significantly reduces fibroid volume, provides significant improvements in fibroid-related quality of life, and is associated with favorable reintervention rates.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4

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Full length article

Evaluation of uterine patency following transcervical uterine fibroid ablation with the Sonata system (the OPEN clinical trial)

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ABSTRACT

Objective: Standard transcervical fibroid treatment via hysteroscopic myomectomy can result in a significant rate of intrauterine adhesiogenesis. The primary objective of this study was to document the incidence of de novo uterine adhesions after transcervical fibroid ablation (TFA) of symptomatic uterine fibroids with the Sonata® system.

Study design: In this European postmarket prospective, multicenter, single-arm interventional trial, patients were eligible for inclusion if they chose TFA with the Sonata System for symptomatic fibroids and had at least 1 type 1, type 2 or type 2–5 myoma. The presence or absence of intrauterine adhesions was assessed by diagnostic hysteroscopy at baseline and at 6 weeks post-ablation. The hysteroscopy videos were scored by a committee of 3 independent readers.

Results: A total of 6 sites enrolled 37 patients. Fifty fibroids with a mean diameter of 3.4 ± 1.8 cm (range 1–8 cm) were ablated. Of the 37 enrolled subjects, 35 completed the study follow-up and 2 electively withdrew from the study prior to the completion of study follow-up. Thirty-four out of 35 pairs of baseline and 6-week hysteroscopies were evaluated by the independent readers with none having de novo adhesions at 6 weeks after treatment with Sonata, including 6 patients with apposing myomata. One patient was excluded from the analysis due to an unevaluable hysteroscopy video.

Conclusion: Intrauterine adhesiogenesis was not seen post-TFA with the Sonata system. These results suggest the potential for adhesiogenesis after TFA, including in women with apposing submucous and/or transmural myomata, may be minimal.

Introduction

Uterine fibroids are the most common benign tumors in women, occurring in approximately 20–50% of premenopausal women, and the prevalence increases with age [1]. In White women, the lifetime risk of developing fibroids is as high as 70% and in black women as high as 80% [2]. Based on a 2010 population estimate, approximately 588,164 women seek treatment for symptomatic uterine fibroids annually in the United States [3]. Although often asymptomatic, uterine fibroids may cause a number of symptoms such as heavy menstrual bleeding, dyspareunia, dysmenorrhea, pelvic/abdominal pressure and subfertility. Uterine fibroids can negatively impact quality of life and are commonly associated with invasive and expensive treatments [4].

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Although hysterectomy is definitive treatment for fibroids, less invasive and uterine-conservative techniques can be used to manage symptomatic uterine fibroids. For submucous fibroids, hysteroscopic myomectomy is an established treatment that can preserve fertility and fecundity. However, there is an overall 1.5% risk of adhesiogenesis 1–3 months after hysteroscopic resection of solitary myomata, and this risk has been reported to be as high as 78% after excision of 2 or more apposing myomata [5]. Hysteroscopic myomectomy involves resection of extensive areas of the endometrium, including the basalis layer, disruption of which is thought to be a requirement for adhesion formation [6]. While some studies have evaluated patients up to 3 months after hysteroscopic myomectomy, adhesions were noted as early as 1–2 weeks postoperatively, and many studies recommend early second-look hysteroscopy (within 1–4 weeks) for early detection and lysis of intrauterine adhesions [7–10].

Radiofrequency (RF) and other forms of hyperthermic energy have been used to ablate a variety of solid tumors, including uterine fibroids [11–22]. The Sonata® system (Gynesonics, Redwood City, CA, USA) is an FDA-cleared and CE marked transcervical device that was developed to provide a uterus-conserving, transcervical (incisionless) treatment for a wide range of fibroid types and sizes, including all nonpedunculated uterine myomata (International Federation of Gynecology and Obstetrics [FIGO] types 1,2, 3, 4, 5, 6 and 2–5 myomata; Supplementary Fig. 1). Sonata utilizes a single-use Radiofrequency Ablation Handpiece connected to a reusable Intrauterine Ultrasound Probe, forming a single integrated device to ablate uterine fibroids. This integration of real-time ultrasound imaging enables the physician to visualize, target and ablate a greater range of fibroids than can be approached via operative hysteroscopy [11].

Because several transcervical procedures (e.g., hysteroscopic myomectomy, dilatation and curettage, endometrial ablation) can be associated with a propensity to incite intrauterine adhesions that could affect fertility and, in severe cases, result in Asherman syndrome, it was of interest to determine if transcervical fibroid ablation (TFA) can result in intrauterine adhesions. Thus, the OPEN clinical trial was undertaken to document the presence or absence of intrauterine adhesions after treatment with the Sonata system when used in women with submucous and/or transmural fibroids in accordance with product labeling.

Materials and methods

The clinical trial was reviewed by the Bundestinstitut für Arzneimittel und Medizinprodukte (BfArM) and received exemption from the permit requirement according to article 7 of the regulation over Clinical Testing of Medical Products (MPKPV) per §20.1 of the German Act of Medical Devices. The protocol was also reviewed and approved by the central and local ethics committees, and all participants provided written informed consent in accordance with local hospital Ethics Committee requirements. The OPEN clinical trial is registered with ClinicalTrials.gov (NCT02844920).

Study design

The OPEN clinical trial was a post-market, prospective, multicenter, single-arm, observational study of patients undergoing TFA for symptomatic fibroids conducted at 6 academic and community hospitals in the United Kingdom, the Netherlands, Switzerland, and Germany. The trial was not intended to be statistically powered. The primary endpoint was the incidence of newly formed adhesions after treatment with the Sonata system as ascertained by second-look hysteroscopy at 6 weeks. Additional analyses included adverse events, treatment recovery duration and any surgical reintervention. Videos of baseline and post-ablation hysteroscopy were scored by a committee of 3 independent readers, using the European Society of Hysteroscopy (ESH) intrauterine adhesion classification system [23].

Participants

Patients were eligible for inclusion in the study if they were 18 years of age and older at the time of enrollment and selected TFA with the Sonata system for treatment of symptomatic fibroids. In addition, potential subjects had to have at least 1 submucous myoma (type 1, type 2) or transmural fibroid (type 2–5). Exclusion criteria included the presence of preexisting adhesions within the endometrial cavity as indicated by an ESH score $\geq$1 or the existence of type 0 fibroids and/or endometrial polyps of any size. Prior intrauterine procedures were not an exclusion, as any associated adhesions would have been present at the baseline hysteroscopy and thus such patients would be excluded.

Procedure

Potential subjects with symptomatic fibroids (assessed by transvaginal sonography) who elected treatment with the Sonata system underwent a baseline diagnostic hysteroscopy evaluation after providing their informed consent. Subjects with no adhesions identified by the treating physician and who did not have other exclusions were enrolled in the OPEN clinical trial and underwent treatment with the Sonata system. The Sonata procedure has been detailed previously [24–28]. No adjunctive measures that would prevent adhesiogenesis or concomitant procedures that would promote adhesions (such as dilation and curettage) were permitted. Otherwise, the patients were treated as per the Instructions for Use of the Sonata system, and there were no set limits on fibroid size or number.

At the time of treatment with the Sonata system, the number, maximum and minimum diameters and location (including FIGO type) of all identified and ablated fibroids were recorded along with the number of ablations performed per treated fibroid. Patients were then assessed at 6 weeks after ablation by second-look hysteroscopy for the presence of adhesions. Video of the baseline and second-look hysteroscopies were submitted to the independent readers for their review. The outcome was determined based on agreement in hysteroscopy evaluation by 2 of 3 independent readers. Patients submitted a completed treatment recovery questionnaire at their 6-week visits and were also queried about any reintervention or adverse events during the previous 6 weeks.

Results

Thirty-seven patients (mean age 42.4 $\pm$ 7.2 years) were enrolled at 6 sites. Fifty fibroids were ablated (mean of 1.4 $\pm$ 0.6 fibroids per patient). As noted in Table 1, nearly a third of treated fibroids had a maximal diameter >4 cm, with the mean ablated fibroid diameter 3.4 $\pm$ 1.8 cm (range 1–8 cm). The mean length of stay (time from Sonata device insertion to time of discharge) for patients who underwent the procedure was 22.1 h $\pm$ 17.99 h (median 23.2 h; range 2.2–69.9 hours). All fibroid ablations were performed in a single procedure with a mean of 2.0 $\pm$ 1.09 ablations per subject.

Two (2) patients withdrew from the study after treatment with the Sonata system as they did not return to undergo second-look hysteroscopy and were thus not assessible regarding the primary study endpoint. One (1) patient was excluded from the analysis due to an unevaluable hysteroscopy video. None of the remaining 34 patients (97.1%) with evaluable hysteroscopies at 6 weeks showed signs of de novo adhesiogenesis after transcervical RF

Table 1
Summary of Intrauterine Procedures.

Procedure Parameter	Patients (N = 37)
Ablated Fibroid Diameter (N = 50 fibroids)	Number of Fibroids Ablated, (%)
< 1 cm	0 (0.0)
1-2 cm	14 (28.0)
> 2 - 3 cm	14 (28.0)
> 3 - 4 cm	7(14.0)
> 4 cm	15 (30.0)
Number of Fibroids/Patient (N = 37 Patients)	
Mean ± SD	1.5 ± 0.80
Median	1.0
Min, Max	1, 4
Number of Ablated Fibroids/Patient (N = 37 Patients)	
Mean ± SD	1.4 ± 0.63
Median	1.0
Min, Max	1, 3
Number of Ablations/Treated Fibroid (N = 50 Fibroids)	
Mean ± SD	1.5 ± 0.61
Median	1.0
Min, Max	1, 3
Number of Ablations/Patient (N = 37 Patients)	
Mean ± SD	2.0 ± 1.09
Median	2.0
Min, Max	1, 5
Visualized Fibroid Diameter (cm) (N = 56 Fibroids)	
Mean ± SD	3.3 ± 1.71
Median	3.0
Min, Max	1.0, 8.0
Ablated Fibroid Diameter (cm) (N = 50 Fibroids)	
Mean ± SD	3.4 ± 1.76
Median	3.0
Min, Max	1.0, 8.0

ablation. Six out of 34 patients had apposing endometrial cavity-indenting fibroids that were treated.

There were no reinterventions reported in the trial. One patient (2.7%) had a serious adverse event deemed by the investigator to have been unrelated to the Sonata device or procedure. This patient was admitted 18 days post-ablation with nonspecific abdominal pain. Computed tomography scan and sonography were both normal, and the event was assessed as not gynecological in origin. No other adverse events were reported. Patients were able to return to their normal daily activities in under 4 days while tolerating a normal diet with normal sleep and normal bowel and bladder functions much earlier (Table 2).

Table 2
Return to Normal Functions.

Parameter (Days)	Patients (N = 37)
Activities	N = 31
Mean ± Sd	3.8 ± 3.13
Median	3.0
Min, Max	0, 13
Diet	N = 33
Mean ± Sd	0.6 ± 0.66
Median	1.0
Min, Max	0, 2
Sleep	N = 33
Mean ± Sd	0.8 ± 1.39
Median	0.0
Min, Max	0, 6
Urinary function	N-32
Mean ± Sd	0.4 ± 0.80
Median	0.0
Min, Max	0, 4
Occurrence of Bowel Movement	N = 33
Mean ± Sd	1.2 ± 1.82
Median	1.0
Min, Max	0, 7

Comment

The OPEN trial did not identify de novo adhesions in 34 women with evaluable baseline and post-ablation diagnostic hysteroscopies after treatment. Obliteration of the endometrial cavity by adhesions (Asherman syndrome) can result in amenorrhea, but lesser degrees of synechiae can impair fertility. The pathophysiology involves mechanical disruption of the basalis layer of the endometrium (as after vigorous curettage), preventing endometrial regeneration; local infection may also predispose to intrauterine adhesiogenesis.

Unlike endometrial ablation, in which there is intentional obliteration/resection of nearly all endometrium and that can incite significant intrauterine adhesions, the Sonata system delivers RF energy focally to ablate fibroids beneath the endometrium and does not target significant areas of endometrium. Anecdotal experience from the use of the Sonata and occasional second-look hysteroscopy had not detected adhesiogenesis, and the OPEN clinical trial was initiated to formally and objectively investigate the potential for intrauterine adhesions in women undergoing elective treatment with Sonata as per its labelling in Europe.

In OPEN, patients returned to their activities of normal daily life in a mean 3.8 ± 3.13 days, although they were tolerating a normal diet with normal sleep and normal bowel and bladder functions much earlier. In contrast, during the SONATA Clinical Trial of 147 patients in the United States and Mexico, patients reported having returned to their normal activities by 2.2 days on average, with more than half of the patients returning to normal activity within 1 day of their treatment. This difference in overall return to normal activity between the two studies likely reflects differences in locoregional clinical practices regarding length of hospital stay as well as culture. In SONATA, mean length of stay (including procedure time) was 2.5 h, with 74.1% of patients having a length of stay $\leq$3 h, whereas in OPEN, the mean length of stay was longer: 22.1 h. The greater mean length of stay in the OPEN clinical trial reflects country-specific reimbursement policies that favor overnight and longer admission after outpatient treatment, in contrast to the US, in which outpatient procedures do not incur greater reimbursement for a medically unnecessary inpatient stay.

Strengths of the study design include the use of independent reviewers for the assessment of baseline and post-treatment hysteroscopy videos and the requirement for at least one indenting myoma in each patient. The lack of adhesion formation among the 34 patients and particularly in the 6 women with apposing fibroids that were ablated suggests that the Sonata system is not as adhesiogenic as hysteroscopic myomectomy.

Conclusions

Intrauterine adhesiogenesis was not seen post-treatment with the Sonata system. These results suggest the potential for adhesiogenesis after transcervical fibroid ablation, including in women with apposing submucous and/or transmural myomata, may be minimal.

Author disclosure statement

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.09.013.

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ORIGINAL RESEARCH

The INSPIRE Comparative Cost Study: 12-Month Health Economic and Clinical Outcomes Associated with Hysterectomy, Myomectomy, and Treatment with the Sonata System

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Purpose: The INSPIRE study compared perioperative and 12-month health economic and clinical outcomes associated with hysterectomy, myomectomy, and sonography-guided transcervical fibroid ablation (TFA) using the Sonata® system.

Patients and Methods: Cost and health care resource utilization (HCRU) data for TFA were obtained from a prospective, multicenter, single-arm clinical trial. Data for hysterectomy and myomectomy arms were derived from the Truven Health MarketScan commercial payer claims database. The Truven data was used to determine health economic outcomes and costs for the hysterectomy and myomectomy arms. For each arm, payer perspective costs were estimated from the available charge and HCRU data.

Results: TFA with Sonata had significantly lower mean length of stay (LOS) of 5 hrs versus hysterectomy (73 hrs) or myomectomy (79 hrs; all $p< 0.001$). The average payer cost for TFA treatment, including the associated postoperative HCRU was $8,941. This was significantly lower compared to hysterectomy ($24,156) and myomectomy ($22,784; all $p< 0.001$). In the TFA arm, there were no device- or procedure-related costs associated with complications during the peri- or postoperative time frame. TFA subjects had significantly lower costs associated with complications, prescription medications, and radiology.

Conclusion: Compared to hysterectomy and myomectomy, TFA treatment with the Sonata system was associated with significantly lower index procedure cost, complication cost, and LOS, contributing to a lower total payer cost through 12 months.

Keywords: uterine fibroids, health care resource utilization, payer perspective analysis, transcervical fibroid ablation, TFA, uterine preserving treatment

Introduction

Uterine fibroids, also known as leiomyomata uteri, are benign tumors of the uterus that frequently occur in women of reproductive age. Uterine fibroids may be associated with heavy menstrual bleeding, dysmenorrhea, pelvic pain, decreased quality of life, and subfertility.[1] Uterine fibroids are highly prevalent, with approximately 70% to 80% of premenopausal women likely to develop uterine fibroids prior to menopause.[1,2] Among premenopausal women aged 40–49 years with uterine fibroids, 25% to 50% will develop clinical symptoms.[2] Causal factors are not fully understood. However, certain risk factors are known, including epigenetic factors, concentrations of steroid hormones and growth factors, obesity, and being of Afro-Caribbean descent.[3]

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Hysterectomy and myomectomy are the most commonly performed surgical interventions for the treatment of uterine fibroids.[4] Hysterectomy involves extirpation of the uterus (and generally, the cervix), with or without ovarian conservation. Myomectomy is an operation in which individual fibroids are removed, retaining the uterus and the potential for pregnancy. According to a report from the Healthcare Cost and Utilization Project, myomectomies represented about 22% of operations for uterine fibroid treatment in the US during 2013 in both inpatient and ambulatory settings, while hysterectomies constituted more than 75% of the inpatient surgeries and 67% of the hospital-based ambulatory operations.[4–6] One cost-effectiveness study estimated that major complications within 30 days of surgery averaged $2,094 for either hysterectomy or myomectomy.[7] Recent studies estimated average payer costs for hysterectomy ranging from $16,184–$25,499 (2016 dollars), depending upon the procedure setting and route of surgery.[8,9] A 2014 comparative effectiveness study of uterine fibroid treatments estimated the combined payer and patient direct cost per myomectomy to be $23,983.[10] With over two hundred thousand combined procedures performed per year, this would equate to nearly five hundred million dollars in complication costs per year for hysterectomies and myomectomies in the United States alone.[11]

It is useful to understand both the clinical outcomes and the related payer costs associated with emerging treatment options compared to current standards of care such as hysterectomy and myomectomy. The Sonata® system provides a transcervical fibroid treatment (TFA) for symptomatic uterine fibroids. It is a sonography-guided, incisionless, and uterus-preserving radiofrequency ablation treatment and is approved and commercially available in Europe and the United States. Sonata utilizes a single-use radiofrequency ablation handpiece connected to a reusable intrauterine ultrasound probe, forming a single integrated treatment device designed to ablate uterine fibroids. This integration of real-time ultrasound (for imaging) with radiofrequency ablation (for treatment) in a single device, enables a gynecologist to visualize, target and ablate a greater range of fibroid types transcervically than can be approached via operative hysteroscopy. Operative hysteroscopy is limited to the treatment of intracavitary and smaller submucosal fibroids; at least in the case of submucosal fibroid, it represents a gold standard for treatment.[12] However, Sonata uses intrauterine ultrasound to image and treat all non-pedunculated fibroids.

To better understand health care resource utilization (HCRU), procedure outcomes, and associated costs, we undertook a combined prospective and retrospective cohort study comparing TFA with Sonata to hysterectomy and myomectomy.

Materials and Methods

For the TFA procedure (Sonata® System, Gynesonics, Inc. Redwood City, CA, USA), HCRU, along with procedural and 12-month postoperative charges, were obtained from a subset of sites participating in the SONATA pivotal Investigational Device Exemption (IDE) clinical trial. SONATA was a prospective, longitudinal, multicenter, single-arm cohort clinical trial to assess the safety and efficacy of the Sonata system in the treatment of symptomatic uterine fibroids and enrolled patients between April 2015 and October 2016.[13] Procedural and 12-month postoperative cost and outcomes data for the hysterectomy and myomectomy arms were obtained from a nationally representative administrative claims database (the Truven Health MarketScan commercial payer claims database) for the period from July 1, 2012 to June 30, 2014 as it was the most recent data available from Truven at the time of the data request. There were no specific sample size calculations due to the need to retrospectively obtain charge data from sites that had already participated in the prospective SONATA trial. It was anticipated that only some of those sites would be able to participate and that sample size for the Sonata group would be limited in this way.

Study Population

TFA arm included patients who were enrolled in the prospective clinical trial of the Sonata procedure (SONATA pivotal IDE trial) and consisted of premenopausal women 25–50 years of age, with heavy menstrual bleeding (HMB) associated with up to 10 fibroids from 1–5 cm in maximal diameter.[13]

The hysterectomy and myomectomy patients included in the claims database analysis were women 25–50 years of age who reported one of the following: a claim with a uterine fibroid diagnosis on the same day as the index procedure; an inpatient claim with a uterine fibroid diagnosis at any time in the 12-month pre-index period; or at least two outpatient claims, occurring 30 days apart or more, with a uterine fibroid diagnosis at any time in the 12-month pre-index period. Hysterectomy and myomectomy procedures of interest were identified using appropriate International Classification of Diseases, Ninth Revision, Clinical

Modification (ICD-9-CM), International Classification of Disease, Tenth Revision, and Current Procedural Terminology (CPT) codes describing the procedures (Table 1). Patients included met the additional criteria of having had no uterine fibroid treatment procedure in the 42-month pre-index period; no diagnosis associated with post-menopause in either the 42-month pre-index period or the 24-month post-index period; no diagnosis for an extrauterine pelvic mass or abdominal/pelvic malignancy in the 24-month post-index period; and 42 months of pre-index and 24 months of post-index continuous medical and pharmacy enrollment.

The Western IRB (WIRB) determined that this research was exempt from IRB approval on 9/11/2017, finding that it did not involve human subjects under 45 CFR 46.102(f). The finding was based on both the research not involving data collected specifically for the current project and the researchers not being able to ascertain the identity of individual participants.

Outcomes

The primary outcomes of interest for the Initial Comparison of Payer Costs for Sonata Relative to Standard of Care (INSPIRE) study were payer costs associated with the index procedure and the postoperative HCRUs through 12-months. The perioperative period was defined as the hospital stay for the index procedure. The postoperative period was defined as the period after discharge through 1 year. Postoperative HCRU categories included complication related HCRU, medications including opioid usage, radiology, office visits, supply costs, procedure-related complications, and subsequent procedures.

Table 1 Codes Used for Procedure Identification

Procedure	ICD-9	CPT
Hysterectomy		
Hysterectomy - abdominal	68.39, 68.49	58150, 58152, 58180
Hysterectomy - vaginal	68.59	58260, 58262, 58263, 58267, 58270, 58275, 58280, 58290, 58291, 58292, 58293, 58294
Hysterectomy - laparoscopic	68.31, 68.41	58541, 58542, 58543, 58544, 58570, 58571, 58572, 58573
Hysterectomy – laparoscopic vaginal	68.51	58550, 58552, 58553, 58554
Myomectomy		
Myomectomy	68.29	58140, 58145, 58146
Myomectomy - laproscopic		58545, 58546
Myomectomy - hysterscopic		58561
Codes used if robotic assistance was used		
Robotic assistance	17.41, 17.42, 17.49	S2900

As part of the SONATA trial protocol, participating sites submitted institution billing form (UB-04) and/or provider billing form (HCFA-1500) for all charges accrued during the enrolled patients' Sonata procedure. The associated hospital outpatient payment is estimated based on Medicare 2016 Outpatient Prospective Payment System rates that would be associated with the Sonata procedure code 0404T ($5,699), which was effective January 1, 2016; all hospital outpatient services provided on the day of the procedure were bundled into one payment, as the code is a J1 status indicator. The physician payment for the TFA was based on average 2017 Medicare rates, which includes surgeon and anesthesiologist, and payments. We estimated for this study the surgeon payment (CPT code 0404T) would be comparable to that of laparoscopic radiofrequency ablation (CPT code 58674) and assigned the corresponding Medicare 2017 national payment. The anesthesiologist payment (CPT code 00852) was based on the 2016 Medicare base anesthesia unit payment (4.0). Five (5) time units (15 min increments per time unit), or 75 mins, were used to estimate the average anesthesia duration. This estimate is a conservative assessment based on the average operating room time of 77 mins for the TFA patients. This was then multiplied by the anesthesia 2016 conversion factor of $22.4426, to arrive at the total estimated payment for the anesthesiologist services. Office visits were assumed to be coded as established patients, and CPT code 99213 was used. As the Sonata procedure reimbursement is carrier dependent, payments for all hospital and physician fees were then adjusted by a Medicare-to-commercial payer ratio of 125%.[14] Prescription costs were based on RED BOOK Online (Truven Health Analytics, accessed December 2017).[15]

For the hysterectomy and myomectomy arms, patient-level charge data associated with the index procedure and 12-month postoperative HCRU data from the Truven dataset were converted to payments using a 70% charge-to-payment adjustment.[16] The robustness of the result was assessed by varying this parameter in several sensitivity analyses. For each procedure, the following were collected: inpatient and outpatient facility charges, professional service charges, complication-related charges, postoperative outpatient office visits, prescription medications including opioids, ED visits,

inpatient hospitalizations, length of stay, subsequent procedures, and radiology.

Several sensitivity analyses were conducted around the procedural and 12-month postoperative HCRU payment estimates. The Medicare-to-commercial payer adjustment used to estimate payments for TFA was increased to as much as 188% (from the base case of 125%) to reflect Medicare-to-commercial payer ratios reported in the literature,[17,18] while the charge-to-payment adjustment for hysterectomy and myomectomy arms was also decreased down to 50% (from the base case of 70%), to assess the robustness of results. Payer costs for the hysterectomy and myomectomy arms were stratified by inpatient or outpatient setting, as well as by robotic-assisted status, to explore how these factors affect costs. Finally, sensitivity analyses were conducted in which the high-cost outliers, or those costs that were more than 1.5 times median, were removed from the hysterectomy and myomectomy arms.

Analysis

All analyses were conducted in Stata (version 13; StataCorp LLC, College Station, Texas). Patient characteristics were reported, and a chi-square analysis was used to determine the difference between groups. Means for total payments, payments for the index procedure and length of stay (LOS, defined as time of admission to time of discharge or time eligible to be discharged), and payments for postoperative HCRU were reported for the TFA, hysterectomy, and myomectomy procedures. The Welch *t*-test for unequal variances were used to compare mean facility costs between TFA and the comparators. For all comparisons, a p-value <0.05 was considered statistically significant.

Results

Patient Characteristics and LOS

In the TFA arm, 6 outpatient hospital sites from the SONATA trial participated in INSPIRE and provided billing data on 51 patients. For the comparator arms, a total of 35,463 patients who underwent hysterectomy and 8,548 patients who underwent myomectomy were included.

Table 2 describes the characteristics of patients included in the study. Women undergoing treatment with the Sonata system, with a mean age of 44 (CI: 43.0–45.0) years, were older than those undergoing either a hysterectomy (42; CI:

Table 2 Characteristics of Study Patients

Parameter Mean ± SD	TFA n=51	95% CI	Hysterectomy n=35,463	95% CI	Myomectomy n=8,548	95% CI	*p*-value
Age in years	44 ± 3.7	43.0–45.0	42 ± 5.0	41.9–42.1	39 ± 5.9	38.9–39.1	<0.001
LOS in hours*	5 ± 1.7	4.4–5.6	73 ± 39.1	72.6–73.4	79 ± 34.6	78.2–79.8	<0.001
Region n (%)							
Northeast	11 (21.6%)		4,165 (11.7%)		1,861 (21.8%)		<0.001
North central	22 (43.1%)		6,992 (19.7%)		1,349 (15.8%)		
South	9 (17.7%)		18,925 (53.4%)		4,007 (46.9%)		
West	9 (17.7%)		5,134 (14.5%)		1,278 (15.0%)		
Unknown	-		247 (0.7%)		53 (0.6%)		

Notes: *p*-values for age and LOS was calculated using *t*-test assuming unequal variances, and for region calculated using chi-square test. *LOS was only available for inpatient hysterectomy (n=11,166) and myomectomy (n=2,259) patients. All other measurements were captured for all patients.
Abbreviations: TFA, transcervical fibroid ablation; LOS, Length of stay.

Table 3 Postoperative Health Care Resource Utilization (HCRU)

HCRU Frequency (%)	TFA n= 51	Hysterectomy n=35,463	*p*-value	Myomectomy n=8,548	*p*-value
Subsequent Procedure†	1 (2.0)	2,201 (6.2)	0.209	493 (5.8)	0.244
Prescriptions					
Opioids	16 (31. 4)	15,757 (44.4)	0.061	3,212 (37.6)	0.362
NSAID	21 (41.2)	12,752 (36.0)	0.438	2,650 (31.0)	0.117
Outpatient office visits (total)	5 (9.8)	1,203 (3.4)	0.012	4,278 (50.1)	<0.001

Notes: *p*-value: test of proportions (z-test), each comparator versus Sonata. †Subsequent procedures (following the initial procedure) included myomectomy, hysterectomy, uterine artery embolization, MR-guided focused ultrasound, endometrial ablation, or trachelectomy.
Abbreviation: TFA, transcervical fibroid ablation.

Table 4 Payments Through the 1-Year Postoperative Period

Total Payments Mean (SD)	TFA	95% CI	Hysterectomy	95% CI	*p*-value	Myomectomy	95% CI	*p*-value
	n= 51		n=35,463			n=8,548		
Total payments ($)	8,941 (448.9)	8,815–9,067	24,156 (16,695.3)	23,982–24,330	<0.001	22,784 (19,341.7)	22,374–23,194	<0.001
Index procedure	8,797 (184.8)	8,745–8,849	23,457 (15,753.5)	23,293–23,621	<0.001	21,340 (18,499.0)	20,948–21,732	<0.001
Postoperative	143 (427.1)	23–263	699 (4,983.10)	647–751	<0.001	1,444 (5,283.5)	1,332–1,556	<0.001
Complication-related	0 (0.0)	0-0	289 (4,640.4)	241–337	<0.001	14 (506.3)	3–25	0.011
Office Visits†	9 (27. 8)	1–17	4 (66.5)	3–5	0.210	99 (1,443.6)	68–130	<0.001
Subsequent Procedure	59 (417.8)	−59-177	117 (710.8)	110–124	0.224	135 (868.6)	117–153	0.206
Medications	75 (207.3)	17–133	236 (1,548.6)	220–252	<0.001	881 (4,453.4)	787–975	<0.001
Radiology	6 (46.2)	−7-19	52 (291.4)	49–55	<0.001	314 (935.3)	294–334	<0.001

Notes: *p*-value: *t*-test assuming unequal variances was used to determine statistical significance, each comparator versus Sonata. †Defined differently for TFA vs Hysterectomy and Myomectomy; TFA=office visits other than SONATA protocol defined visits; Hysterectomy/Myomectomy=office visit specific to UF.
Abbreviation: TFA, transcervical fibroid ablation.

41.9–42.1) or myomectomy (39; all $p<0.001$; CI: 38.9–39.1). Additionally, patients in the Sonata arm had a significantly shorter mean LOS for their procedure (5 ± 1.7 hrs; CI: 4.4–5.6), compared to those who underwent either hysterectomy or myomectomy (>3 days; $p<0.001$; CI: 72.6–73.4 and CI: 78.2–79.8).

HCRU

Table 3 shows the results from the 12-month postoperative HCRU review. HCRU categories included total outpatient office visits, subsequent procedure, and prescription medications (opioids and NSAIDs). As a determinant of pain control costing, 31.4% of TFA, 44.4% of hysterectomy, and 37.6% of myomectomy patients received an opioid prescription, although differences were not statistically significant. To gain further understanding of procedural outcomes and associated cost, total payments were broken down by index procedure and postoperative HCRU (Table 4).

Index procedure payments were significantly lower for TFA in comparison to both hysterectomy and myomectomy ($p<0.001$). For total postoperative costs, Sonata

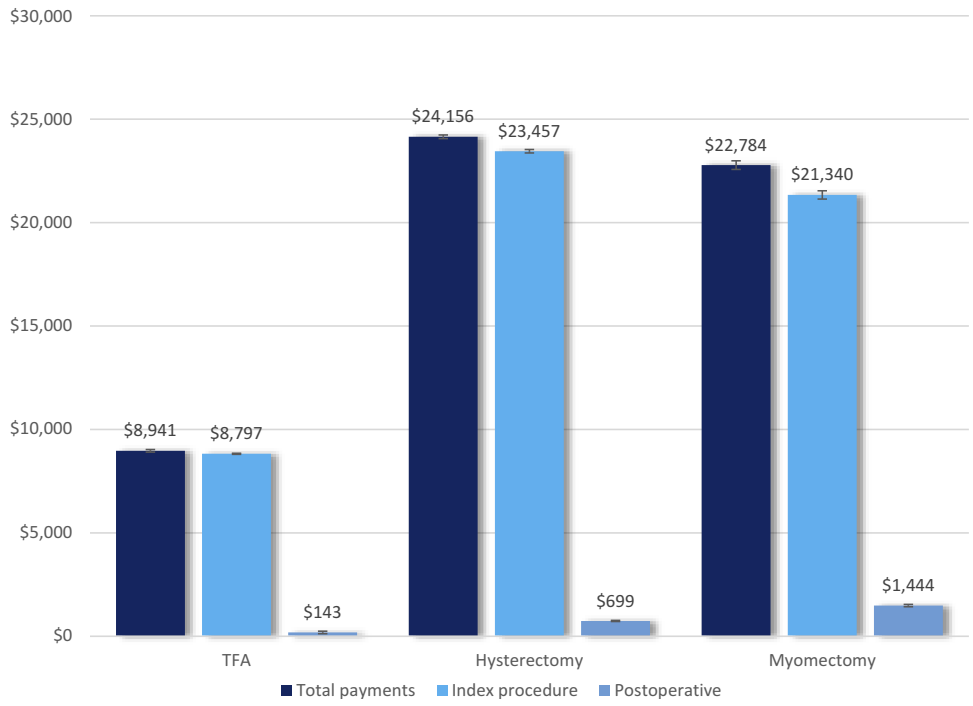

Figure 1 Mean payments per procedure (±SE). Each payment category for Transcervical Fibroid Ablation was significantly less costly than the corresponding Hysterectomy or Myomectomy payment category.
Abbreviations: SE, standard error; TFA, transcervical fibroid ablation.

patients, on average, had significantly lower total postoperative costs than both hysterectomy and myomectomy patients (p <0.001). As shown in Table 4, the mean costs of complications across all patients by study arm were $0 (no complications) for TFA, $289 for hysterectomy ($p$ <0.001; CI: $241–$337), and $14 for myomectomy patients (p= 0.011; CI: $3–$25). The mean cost associated with postoperative prescription use for TFA was $75 (CI: $17–$133), which was significantly lower in comparison to both hysterectomy patients ($236, p<0.001; CI: $220–$252) and myomectomy patients ($881, p<0.001; CI: $787–$975). TFA patients had mean outpatient office visit costs ($9; CI: $1–$17) comparable to those of hysterectomy patients ($4, non-significant; CI: $3–$5), but significantly different from myomectomy patients ($99, p<0.001; CI: $68–$130). TFA patients had a mean cost of $6 (CI: $7–$19) for radiology, with hysterectomy and myomectomy mean costs both significantly higher at $52 ($p$<0.001; CI: $49–$55) and $314 ($p$<0.001; CI: $294–$334), respectively.

Payer Costs

Procedure Costs

Results from the overall payer cost analysis are presented in Figure 1. The mean cost to the payer for TFA with Sonata and the associated 12-month postoperative HCRU was $8,941 (CI: $8,815–$9,067), compared to $24,156

Table 5 Breakdown of Hysterectomy and Myomectomy Payments by Robotic Assisted/Not Robotic Assisted and Inpatient/Outpatient Status

Technology	Setting	Robotic Assisted Status	Variable	Mean ($)	SD ($)	95% CI	*p*-value
TFA‡	Outpatient	Non-robotic assisted (n=51)	Total payments Index procedure Postoperative	8,941 8,797 143	448.9 184.8 427.1	8,815–9,067 8,745–8,849 23–263	Ref Ref Ref
Hysterectomy	Inpatient	Robotic assisted (n=142)	Total payments Index procedure Postoperative	32,547 31,864 682	19,166.5 18,321.4 4,490.4	29,367–35,727 28,825–34,903 −62-1,428	<0.001 <0.001 0.160
		Non-robotic assisted (n=11,024)	Total payments Index procedure Postoperative	28,144 27,161 983	19,421.0 17,285.9 8,078.8	27,781–28,507 26,838–27,484 832–1,134	<0.001 <0.001 <0.001
	Outpatient	Robotic assisted (n=2,362)	Total payments Index procedure Postoperative	31,219 30,633 586	19,674.1 19,498.4 1,728.4	30,425–32,013 29,846–31,420 516–656	<0.001 <0.001 <0.001
		Non-robotic assisted (n=21,935)	Total payments Index procedure Postoperative	21,337 20,769 568	13,975.0 13,706.3 2,614.5	21,152–21,512 20,588–20,950 533–603	<0.001 <0.001 <0.001
Myomectomy	Inpatient	Robotic assisted (n=11)	Total payments Index procedure Postoperative	31,720 30,966 754	11,929.9 11,737.3 1,056.4	23,705–39,735 23,041–38,891 45–1,463	<0.001 <0.001 0.087
		Non-robotic assisted (n=2,248)	Total payments Index procedure Postoperative	30,814 29,794 1,020	21,702.2 21,416.7 3,448.4	29,916–31,712 28,908–30,680 877–1,163	<0.001 <0.001 <0.001
	Outpatient	Robotic assisted (n=287)	Total payments Index procedure Postoperative	40,875 38,810 2,065	29,556.7 28,056.8 7,614.7	37,441–44,309 35,550–42,070 1,180–2,950	<0.001 <0.001 <0.001
		Non-robotic assisted (n=6,002)	Total payments Index procedure Postoperative	18,896 17,321 1,574	16,109.5 14,839.7 5,695.4	18,488–19,304 16,945–17,697 1,430–1,718	<0.001 <0.001 <0.001

Notes: p-value: *t*-test assuming unequal variances was used to determine statistical significance. ‡ TFA with Sonata does not utilize robotic assistance, laparoscopic, or hysteroscopic guidance.

Abbreviation: TFA, transcervical fibroid ablation.

Table 6 Sensitivity Analysis

Charge to Payment Ratio	Technology	Variable	Mean ($)	SD ($)	95% CI ($)	p-value
Site-specific	TFA (125% Medicare to commercial ratio)	Total payments Index procedure Postoperative	8,941 8,797 143	448.9 184.8 427.1	8,815–9,067 8,745–8,849 23–263	Ref Ref Ref
70% Base case	Hysterectomy	Total payments Index procedure Postoperative	24,156 23,457 699	16,695.3 15,753.5 4,983.1	24,154–24,158 23,293–23,621 647–751	<0.001 <0.001 <0.001
	Myomectomy	Total payments Index procedure Postoperative	22,784 21,340 1,444	19,341.7 18,499.0 5,283.5	22,374–23,194 20,948–21,732 1,332–1,556	<0.001 <0.001 <0.001
60%	Hysterectomy	Total payments Index procedure Postoperative	20,705 20,106 599	14,310.3 13,503.0 4,271.2	20,556–20,854 19,965–20,247 555–643	<0.001 <0.001 <0.001
	Myomectomy	Total payments Index procedure Postoperative	19,529 18,291 1,238	16,578.6 15,856.3 4,528.7	19,177–19,881 17,955–18,627 1,142–1,334	<0.001 <0.001 <0.001
50%	Hysterectomy	Total payments Index procedure Postoperative	17,254 16,755 499	11,925.2 11,252.5 3,559.3	17,130–17,378 16,638–16,872 462–536	<0.001 <0.001 <0.001
	Myomectomy	Total payments Index procedure Postoperative	16,274 15,243 1,031	13,815.5 13,213.6 3,773.9	15,981–16,567 14,963–15,523 951–1,111	<0.001 <0.001 <0.001
Site-specific	TFA (140% Medicare to commercial ratio)	Total payments Index procedure Postoperative	10,014 9,853 160	502.8 207.0 478.4	9,873–10,155 9,795–9,911 26–294	Ref Ref Ref
70% Base case	Hysterectomy	Total payments Index procedure Postoperative	24,156 23,457 699	16,695.3 15,753.5 4,983.1	24,154–24,158 23,293–23,621 647–751	<0.001 <0.001 <0.001
	Myomectomy	Total payments Index procedure Postoperative	22,784 21,340 1,444	19,341.7 18,499.0 5,283.5	22,374–23,194 20,948–21,732 1,332–1,556	<0.001 <0.001 <0.001
60%	Hysterectomy	Total payments Index procedure Postoperative	20,705 20,106 599	14,310.3 13,503.0 4,271.2	20,556–20,854 19,965–20,247 555–643	<0.001 <0.001 <0.001
	Myomectomy	Total payments Index procedure Postoperative	19,529 18,291 1,238	16,578.6 15,856.3 4,528.7	19,177–19,881 17,955–18,627 1,142–1,334	<0.001 <0.001 <0.001
50%	Hysterectomy	Total payments Index procedure Postoperative	17,254 16,755 499	11,925.2 11,252.5 3,559.3	17,130–17,378 16,638–16,872 462–536	<0.001 <0.001 <0.001
	Myomectomy	Total payments Index procedure Postoperative	16,274 15,243 1,031	13,815.5 13,213.6 3,773.9	15,981–16,567 14,963–15,523 951–1,111	<0.001 <0.001 <0.001

(*Continued*)

Table 6 (Continued).

Charge to Payment Ratio	Technology	Variable	Mean ($)	SD ($)	95% CI ($)	p-value
Site-specific	TFA (188% Medicare to commercial ratio)	Total payments Index procedure Postoperative	13,447 13,231 215	675.2 278.0 642.4	13,257–13,637 13,153–13,309 34–396	Ref Ref Ref
70% Base case	Hysterectomy	Total payments Index procedure Postoperative	24,156 23,457 699	16,695.3 15,753.5 4,983.1	24,154–24,158 23,293–23,621 647–751	<0.001 <0.001 <0.001
	Myomectomy	Total payments Index procedure Postoperative	22,784 21,340 1,444	19,341.7 18,499.0 5,283.5	22,374–23,194 20,948–21,732 1,332–1,556	<0.001 <0.001 <0.001
60%	Hysterectomy	Total payments Index procedure Postoperative	20,705 20,106 599	14,310.3 13,503.0 4,271.2	20,556–20,854 19,965–20,247 555–643	<0.001 <0.001 <0.001
	Myomectomy	Total payments Index procedure Postoperative	19,529 18,291 1,238	16,578.6 15,856.3 4,528.7	19,177–19,881 17,955–18,627 1,142–1,334	<0.001 <0.001 <0.001
50%	Hysterectomy	Total payments Index procedure Postoperative	17,254 16,755 499	11,925.2 11,252.5 3,559.3	17,130–17,378 16,638–16,872 462–536	<0.001 <0.001 0.003
	Myomectomy	Total payments Index procedure Postoperative	16,274 15,243 1,031	13,815.5 13,213.6 3,773.9	15,981–16,567 14,963–15,523 951–1,111	<0.001 <0.001 <0.001

Notes: p-value: *t*-test assuming unequal variances was used to determine statistical significance, each comparator versus Sonata.
Abbreviation: TFA, transcervical fibroid ablation.

(CI: $23,982–$24,330) for hysterectomy and $22,784 (CI: $22,374–$23,194) for myomectomy. When compared to TFA, both hysterectomy and myomectomy incurred significantly higher payer costs (p <0.001).

Payment Sub-Analyses

Table 5 presents payer costs stratified by both the use of robotic-assistance and the site of service (inpatient or outpatient). The least-costly hysterectomy procedures are those conducted in the outpatient setting without robotic assistance (mean cost of $21,337; CI: $21,152–$21,512), while the least costly myomectomy procedures are also conducted in the outpatient setting, again without robotic assistance (mean cost of $18,896; CI: $18,488–$19,304). However, TFA continued to have significantly lower payer costs compared to these least costly comparator procedures (p <0.001).

Sensitivity Analyses

A variety of one-way and two-way sensitivity analyses altered the Medicare-to-commercial payment ratios (ranging from the base case of 125% up to 188%) and charge-to-payment ratios (ranging from the base case of 70% down to 50%) to explore how market changes affect payer costs of uterine fibroid treatment (Table 6). The mean payer cost for TFA rose to $13,447 (CI: $13,257–$13,637) when the Medicare-to-commercial payment ratio increased to 188%. Mean payer costs for hysterectomy and myomectomy fell to $17,254 (CI: $17,130–$17,378) and $16,274 (CI: $15,981–$16,567), respectively, when the charge-to-payment ratio for the comparator arms is reduced from 70% to 50%. However, the mean total cost difference between TFA and both hysterectomy and myomectomy remained statistically significant in each of these analyses (p <0.001), demonstrating significantly lower costs associated with TFA.

Consideration of High Cost Outliers

Figure 2 presents payer costs when high-cost outliers are removed from the hysterectomy and myomectomy cohorts. High-cost outliers for comparator arms were identified as procedures with total costs more than 1.5 times the median, resulting in thresholds of $48,541 and $51,840 for

hysterectomy and myomectomy, respectively. With high-cost outliers removed, the mean total payments associated with hysterectomy decreased to $21,268 (CI: $21,152–$21,384) and the mean total payments associated with myomectomy decreased to $19,388 (CI: $19,129–$19,647). With high-cost outliers removed from the comparator arms, TFA continued to maintain significantly lower mean total payer costs ($8,941, p <0.001; CI: $8,815–$9,067).

Discussion

The results of the INSPIRE study, which examined the health economic outcomes and costs of TFA using the Sonata system compared to hysterectomy and myomectomy, showed that the cost of TFA to payers is significantly less than that of hysterectomy and myomectomy. Based on the current analysis, the adoption of the TFA procedure may lead to a 60% reduction in payer costs when compared to the current prevalent surgical treatments for uterine fibroids. In an environment of increasing health care costs, it is important to understand the outcomes and costs associated with innovative new treatment options relative to the current standard(s) of care. While the safety and effectiveness of the Sonata procedure has been verified,[13] there have yet to be published data comparing health economic outcomes, medical resource utilization, and payer costs of the procedure to the current standard treatments of hysterectomy and myomectomy.

This is the first study to examine 12-month payer costs and HCRU for TFA using the Sonata system and compared to those for hysterectomy and myomectomy for treatment of uterine fibroids. One important strength of the study is that a well-defined methodology for estimating payments was utilized, with extensive sensitivity analyses performed around estimation parameters. Additionally, the hysterectomy and myomectomy populations are well represented in the study, as evidenced by the large sample sizes in these arms.

Despite these strengths, some notable limitations must be acknowledged. Because Sonata payment data were obtained from a subset of sites that participated in the clinical trial, the sample size was small. Also, as described previously, several assumptions had to be made about payments. However, it should be noted that hysterectomy and myomectomy payer costs identified in this study were consistent with other studies in the literature. Research published by O'Sullivan et al found that hysterectomy results in mean payer-perspective costs of $19,800 (in 2005 dollars);[19] this is equivalent to $26,266 in 2016 dollars and similar to the results noted here.[20] Other US

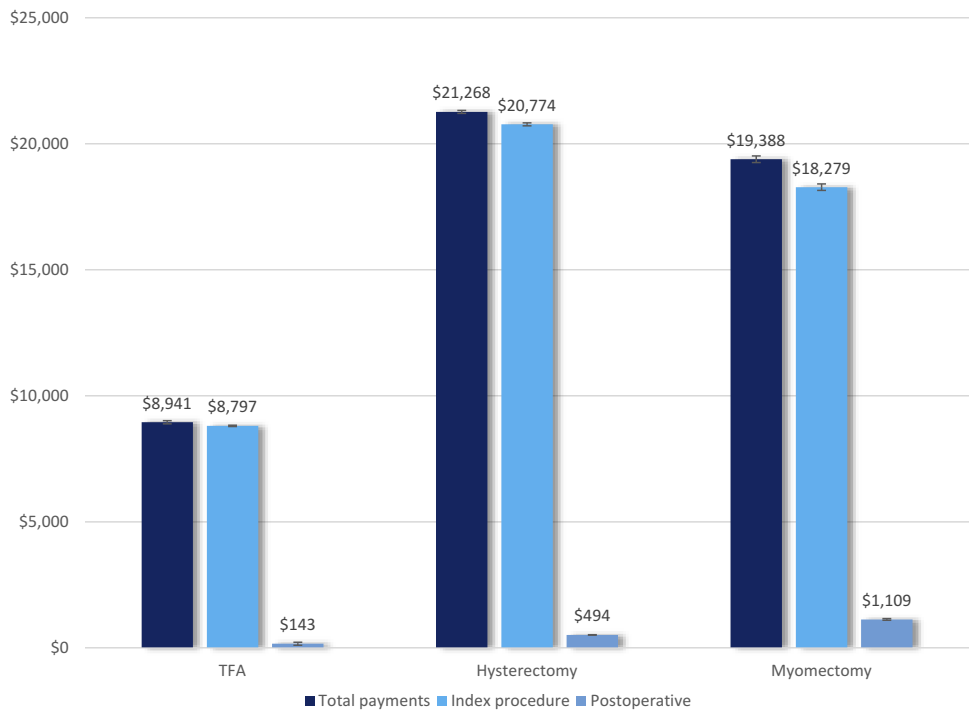

Figure 2 Mean payments per procedure with high cost outliers excluded from hysterectomy and myomectomy arms (±SE). Each payment category for Transcervical Fibroid Ablation was significantly less costly than the corresponding Hysterectomy or Myomectomy payment category. Hysterectomy: Total payments> $48,541.21 excluded. Myomectomy: Total payments> $51,839.99 excluded.
Abbreviations: SE, standard error; TFA, transcervical fibroid ablation.

studies from 2000 and 2013 reviewed by Soliman produced similar 12-month payer costs, ranging from $19,000–$20,000 ($20,588–$21,649 in 2016 dollars) for hysterectomy and $17,500–$19,300 ($18,996–$20,907 in 2016 dollars) for myomectomy.[21]

Fitch and colleagues found that hysterectomy costs ranged from $13,000 to $18,000, which are lower than we estimated for hysterectomy. However, their analyses only looked at costs up to 30 days, while we examined costs through 12-months.[8] They also capped readmission costs at $100,000. Our costs were closer to Bonafede et al, who found one-year hysterectomy costs to be up to $24,000.[9] Bonafede also looked at hysteroscopic myomectomy, which carried a mean cost of $17,300, considerably higher than the cost associated with TFA ($8,914).[9]

Conclusion

Compared to hysterectomy and myomectomy, TFA treatment with the Sonata system was associated with significantly lower index procedure cost, complication cost, and LOS, contributing to a significantly lower total payer cost through 12 months.

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The COMPARE Study: Facility Costs Associated With Hysterectomy, Myomectomy, and the Sonata Procedure for Treatment of Uterine Fibroids

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ABSTRACT

Purpose: The COMPARE study examined facility costs of sonography-guided transcervical fibroid ablation (TFA) using the Sonata System, hysterectomy, and myomectomy for the treatment of symptomatic uterine fibroids.

Design and methodology: A facility-perspective cost analysis of hospital charge data in the perioperative and the 30-day postoperative period was conducted. Length of stay (LOS) and charge data for the TFA arm were collected in the SONATA trial. Hospital-specific cost-to-charge ratios (CCRs) were used to convert charges to facility costs. Charge data and LOS for comparator arms were collected retrospectively from the IBM MarketScan Commercial Database and converted to costs using Medicare national average CCRs.

Results: TFA patients had a statistically significant shorter mean LOS (5.1 hours) compared with hysterectomy (73 hours) or myomectomy (80 hours; all $P<.001$) patients. The mean facility cost of TFA was $7,701, lower than the $10,353 for hysterectomy and the $12,003 for myomectomy (all $P<.001$). TFA facility costs were also statistically significantly lower across all stratifications ($P<.01$) compared with hysterectomy and myomectomy subgroups for site of service (inpatient or outpatient), and/or use of robotic assistance. The lower facility costs were preserved in follow-up analyses that included route subtypes (e.g., laparoscopic, open, vaginal) and removal of high-cost outliers from comparator arms.

Conclusion: TFA using the Sonata System had a shorter LOS than either comparator arms regardless of the procedure route. Sonata was also associated with considerably lower facility costs compared with either hysterectomy or myomectomy regardless of procedure route, site of service, or use of robotic assistance.

Keywords: Uterine fibroids; Sonata; health care resource utilization; facility perspective; database analysis; transcervical fibroid ablation; TFA, uterine preserving; cost analysis; radiofrequency ablation.

INTRODUCTION

Uterine fibroids are benign smooth muscle tumors that are seen in more than 70% of women of childbearing age. While many women with uterine fibroids are asymptomatic, between 20% and 50% of women with uterine fibroids experience symptoms such as abnormal uterine bleeding, pelvic pressure, and subfertility (Wallach 1981, Evans 2007, Pritts 2001). Uterine fibroids place a substantial burden on the U.S. health care system and society — an estimated $4.1 billion to $9.4 billion annually in direct medical costs (2010 dollars) and further losses in work productivity (Cardozo 2012, Côté 2002).

The most common treatments for symptomatic uterine fibroids involve major surgical approaches. Hysterectomy is the most common. It is curative but involves the removal of the uterus and therefore childbearing potential. Myomectomy, the surgical removal of individual uterine fibroids, preserves the uterus (Lethaby 2001).

The adoption of new treatments no longer depends just on safety and effectiveness data. The net impact on health care resource utilization is becoming a large factor and is being scrutinized by payers and providers.

A new treatment alternative for symptomatic uterine fibroids is the Sonata procedure (Sonata System, Gynesonics Inc., Redwood City, Calif.), a minimally invasive, incisionless, transcervical fibroid ablation (TFA) treatment that preserves the uterus. The heat-induced coagulative necrosis that results from the targeted ablation causes fibroids to shrink over time and is associated with symptom relief (Garza-Leal 2011, Bongers 2015). The pivotal SONATA investigational device exemption (IDE) trial demonstrated statistically significant symptom relief, improved quality of health outcomes, zero device-related adverse events, and high patient satisfaction with a low rate of surgical re-intervention (Chudnoff 2019).

The FDA granted the Sonata

System 510(k) clearance in August 2018. Because cost considerations are increasingly important factors in a new treatment's adoption, a cost analysis (the COMPARE study) was conducted to compare facility costs of TFA with those of hysterectomy and myomectomy, using a combined prospective and retrospective cohort study design.

METHODS

Data sources and study population

COMPARE is a mixed-mode (study data were obtained from clinical trial and Truven claims databases), short-term (30-day), facility-perspective cost analysis of uterine fibroid treatment procedure costs. Length of stay (LOS) and charge data for the TFA arm were collected during the SONATA pivotal IDE clinical trial, a prospective, longitudinal, multicenter, interventional trial that enrolled patients between April 2015 and October 2016.

For the hysterectomy and myomectomy arms, LOS and charge data were collected retrospectively for a commercially insured population from a nationally representative claims database (Truven Health MarketScan Commercial Database) for the period from July 1, 2012, to June 30, 2014.

Criteria for participation in the SONATA clinical trial (the TFA arm of COMPARE) have been previously detailed (Chudnoff 2019). For the hysterectomy and myomectomy arms, the claims database analysis consisted of women, ages 25 to 50, who had one of the following: a claim with a uterine fibroid diagnosis on the same day as the index procedure; an inpatient claim with a uterine fibroid diagnosis at any time in the 12-month pre-index period; or at least two outpatient claims, occurring 30 days apart or more, with a uterine fibroid diagnosis at any time in the 12-month pre-index period. Hysterectomy and myomectomy procedures of interest were identified and categorized into procedure route subtypes using appropriate ICD-9-CM and CPT codes (Table 1). Patients who were included must have had no uterine fibroid treatment procedure in the 42-month pre-index period, no diagnosis associated with post-menopause in either the 42-month pre-index period or the 24-month post-index period, no diagnosis for an extrauterine pelvic mass or abdominal/pelvic malignancy in the 24-month post-index period, and 42 months of pre-index and 24 months of post-index continuous medical and pharmacy enrollment.

The hysterectomy arm included data from patients who underwent abdominal and laparoscopic procedures, both supracervical or total hysterectomies; or vaginal hysterectomies.

The myomectomy arm included data from patients who underwent laparoscopic or open myomectomies.

Outcomes

The primary outcomes of interest were LOS and the facility costs associated with the index procedure (i.e., TFA, hysterectomy, or myomectomy) and the index procedure-related hospitalization. As part of the SONATA trial protocol, participating sites submitted institution billing forms (UB-04) and/or provider billing forms (CMS 1500) for all charges accrued during the enrolled patients' index procedure and hospitalization. The charges were converted into facility costs using the Medicare cost-to-charge ratio (CCR) for the facility where each patient's procedure was performed. The CCRs were obtained from the American Hospital Directory (American Hospital Directory).

The CCRs of participating sites ranged from 0.07 to 1.05. For the hysterectomy and myomectomy arms,

TABLE 1
Codes used for procedure identification

Procedure	ICD-9	CPT
Myomectomy codes		
Myomectomy, unspecified	68.29	58140, 58145, 58146
Laparoscopic		58545, 58546
Hysterectomy codes		
Laparoscopic-assisted vaginal	68.51	58550, 58552, 58553, 58554
Abdominal supracervical	68.39	58180
Vaginal	68.59	58260, 58262, 58263, 58267, 58270, 58275, 58280, 58290, 58291, 58292, 58293, 58294
Laparoscopic supracervical	68.31	58541, 58542, 58543, 58544
Total abdominal	68.49	58150, 58152
Total laparoscopic	68.41	58570, 58571, 58572, 58573
Use of robotic assistance		
Any	17.41, 17.42, 17.49	S2900

LOS and charges associated with the index procedure and the index procedure hospitalization were obtained from Truven Health Analytics as patient-level charge data. Charges were then converted into costs using the national average Medicare CCR of 0.30 (National Nurses United). All costs are presented in 2016 U.S. dollars.

Analyses

All analyses were conducted in Stata (version 13; StataCorp LLC, College Station, Texas). Patient characteristics were reported. A chi-square analysis was used to determine the difference between groups. Means for total payments, payments for the index procedure and LOS (defined as time of admission to time of discharge or time eligible to be discharged), and payments for post-operative health care resource utilization were reported for all study arms. The Welch t-test for unequal variances was used to compare mean facility costs between TFA and the comparator arms. For comparisons, a *P* value of <.05 was considered statistically significant. Additionally, the Bonferroni correction was made to account for multiple comparisons. For statistical comparisons where the Bonferroni correction was applied, the new significance level is indicated in the table footnote. For sensitivity analysis, high-cost outliers were removed from the hysterectomy and myomectomy arms. High-cost outliers were defined as procedures with costs more than 1.25 times the interquartile range (IQR).

Patient characteristics

Of the original 22 sites in the pivotal SONATA trial, five that had treated 45 patients in the IDE were able to participate in COMPARE. For the comparator arms, 35,463 patients who underwent hysterectomy and 5,228 patients who underwent myomectomy were included. Table 2 describes the characteristics of study patients. Women in the TFA arm were older (mean age, 45 ± 3.8 years) than those undergoing other procedures (*P*<.001). There were also statistically significant differences in the regions between TFA and the comparator arms.

RESULTS

As summarized in Table 3 (page 43), patients treated with TFA had statistically significantly shorter mean LOS (5 ± 1.5 hours), compared with patients treated with hysterectomy (73 ± 39.1 hours) or myomectomy (80 ± 34.3 hours) (both *P*<.001). Furthermore, the mean LOS of TFA with Sonata was statistically significantly less than mean LOS for hysterectomy and myomectomy route subtypes with the shortest LOS. The hysterectomy route subtype with the shortest LOS was laparoscopic supracervical hysterectomy (57 ± 26.6 hours; *P*<.001). The myomectomy route subtype with the shortest LOS was laparoscopic myomectomy (67 ± 39.5 hours; *P*<.001).

Facility costs

Results from the primary analysis are presented in Figure 1 (page 43). Mean costs for the facility to treat uterine fibroids were statistically significantly lower for TFA ($7,701 ± 2,558) than either hysterectomy ($10,353 ± 7,155; *P*<.001) or myomectomy ($12,003 ± 9,344; *P*<.001). Table 4 (page 43) provides an additional breakdown of procedure costs by site of service or use of robotic assistance. Regardless of stratification, the hysterectomy and myomectomy arms were associated with statistically significantly higher mean facility costs (*P*<.001) as compared with TFA.

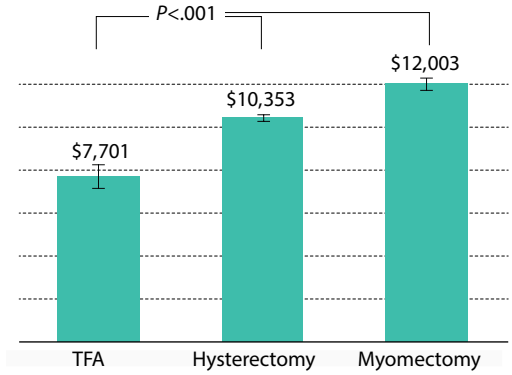
When the combination of site of service *and* use of robotic assistance was used to stratify and compare, the costs of TFA remained statistically lower than either hysterectomy or myomectomy arms (*P*<.05) (Table 5, page 44). As expected, the least costly subgroups in hysterectomy and myo-

TABLE 2
Characteristics of study participants

Characteristic	TFA (n=45)	Hysterectomy (n=35,463)	Myomectomy (n=5,228)	*P* value[a]
Age (years)[b]	45 ± 3.8	42 ± 5.0	37 ± 5.5	<.001
Region, *n* (%)				
Northeast	11 (24.4%)	4,165 (11.7%)	1,063 (20.3%)	<.001
North Central	22 (48.9%)	6,992 (19.7%)	691 (13.2%)	
South	3 (6.7%)	18,925 (53.4%)	2,724 (52.1%)	
West	9 (20.0%)	5,134 (14.5%)	721 (13.8%)	
Unknown	—	247 (0.7%)	29 (0.6%)	

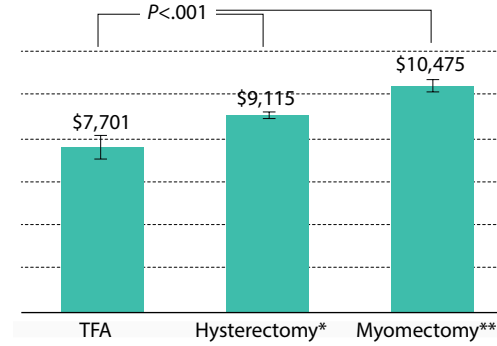
[a]*P* value for age and LOS=t-test, assuming unequal variances; for region=chi-square test
[b]Values presented as mean ± standard deviation
TFA=transcervical fibroid ablation.

FIGURE 1
Mean facility cost per procedure



Error bars=standard error
TFA=transcervical fibroid ablation.

FIGURE 2
Mean facility cost per procedure with high-cost outliers excluded in hysterectomy and myomectomy groups



*Index costs >$20,803 omitted
**Index costs >$25,475 omitted
Error bars=standard error
TFA=transcervical fibroid ablation.

TABLE 3
Length of hospital stay

Index procedure	Mean LOS (hours)[a]	*P* value[b]
TFA (n=45)	5 ± 1.5	(Ref)
Hysterectomy (n=35,463)	73 ± 39.1	<.001
Abdominal supracervical hysterectomy (n=190)	80 ± 34.2	<.001
Laparoscopic supracervical hysterectomy (n=4,991)	57 ± 26.6	<.001
Total abdominal hysterectomy (n=5,975)	81 ± 42.1	<.001
Total laparoscopic hysterectomy (n=12,143)	58 ± 31.3	<.001
Vaginal hysterectomy (n=10,719)	57 ± 27.1	<.001
Hysterectomy, unspecified (n=1,445)	82 ± 38.3	<.001
Myomectomy (laparoscopic and unspecified) (n=5,228)	80 ± 34.3	<.001
Laparoscopic myomectomy (n=2,186)	67 ± 39.5	<.001
Myomectomy, unspecified (n=3,042)	80 ± 33.9	<.001

[a]Values presented as mean ± standard deviation
[b]t-test, assuming unequal variances
LOS=length of stay, TFA=transcervical fibroid ablation.

TABLE 4
Breakdown of mean total costs by site of service or use of robotic assistance[a]

		TFA ($)	Hysterectomy ($)	Myomectomy ($)
Site of service	**Outpatient**	7,701 ± 2,558 (n=45)	9,556 ± 6,393 (n=24,297)	11,103 ± 9,284 (n=3,007)
	Inpatient	—	12,086 ± 8,324 (n=11,166)	13,221 ± 9,289 (n=2,221)
Robotic assistance	**None**	7,701 ± 2,558 (n=45)	10,120 ± 6,996 (n=32,959)	11,683 ± 9,016 (n=4,936)
	Assisted	—	13,412 ± 8,419 (n=2,504)	17,413 ± 12,597 (n=292)

[a]Values presented as mean ± standard deviation
Note: All *P* values for comparing hysterectomy and myomectomy subgroups to TFA <.001, using t-test, assuming unequal variances.
TFA=transcervical fibroid ablation.

mectomy arms were the outpatient non–robotic-assisted procedures (mean of $9,144 and $10,437, respectively), which were statistically significantly higher than the mean cost of the TFA treatment ($7,701, all *P*<.001).

Removing high-cost outliers from hysterectomy and myomectomy arms verified the robustness of these findings (Figure 2). High-cost outliers were identified as hysterectomy and myomectomy procedures with greater than $20,803 or $25,475, respectively (i.e., costs >1.25 x IQR). When high-cost outliers were omitted, the mean facility cost for the index procedure decreased to $9,115 for hysterectomy and $10,475 for myomectomy. Even with high-cost outliers removed, TFA continued to have statistically significantly lower facility costs than hysterectomy and myomectomy procedures (*P*<.001).

Table 6 summarizes facility costs stratified by procedure route. TFA was associated with statistically significantly lower mean facility costs ($7,701) across all stratifications of hysterectomy and myomectomy procedures (all *P*<.001).

DISCUSSION

This is the first study to compare the facility costs of the Sonata procedure with those of hysterectomy and myomectomy. The Sonata System has European Union and FDA clearance, and the multisite, longitudinal, prospective SONATA IDE pivotal trial provides the first cost data source for this treatment (Garza-Leal 2011, Bongers 2015, Chudnoff 2019). The use of the Truven Health MarketScan Commercial Database gave this study

TABLE 5
Breakdown of mean total costs by site of service and use of robotic assistance

Index procedure	Site of service	Robotic assistance	Mean cost ($)[a]	*P* value[b]
TFA	**Outpatient**	**None** (n=45)	7,701 ± 2,558	(Ref)
Hysterectomy	**Inpatient**	**Assisted** (n=142)	13,949 ± 8,214	<.001
		None (n=11,024)	12,062 ± 8,323	<.001
	Outpatient	**Assisted** (n=2,362)	13,380 ± 8,432	<.001
		None (n=21,935)	9,144 ± 5,989	<.001
Myomectomy	**Inpatient**	**Assisted** (n=11)	13,594 ± 5,113	.003
		None (n=2,210)	13,219 ± 9,305	<.001
	Outpatient	**Assisted** (n=281)	17,563 ± 12,782	<.001
		None (n=2,726)	10,437 ± 8,576	<.001

[a]values presented as mean ± standard deviation
[b]t-test, assuming unequal variances; statistical significance based on Bonferroni correction of .005
TFA=Transcervical fibroid ablation

TABLE 6
Comparison of TFA, hysterectomy, and myomectomy costs

Procedure	Mean cost ($)[a]	*P* value[b]
TFA (n=45)	7,701 ± 2,558	(Ref)
Hysterectomy (n=35,463)	10,353 ± 7,155	<.001
Abdominal supracervical hysterectomy (n=190)	12,479 ± 6,655	<.001
Laparoscopic supracervical hysterectomy (n=4,991)	10,228 ± 6,564	<.001
Total abdominal hysterectomy (n=5,975)	11,429 ± 8,360	<.001
Total laparoscopic hysterectomy (n=12,143)	10,821 ± 7,031	<.001
Vaginal hysterectomy (n=10,719)	9,139 ± 6,527	<.001
Hysterectomy, unspecified (n=1,445)	11,116 ± 7,920	<.001
Myomectomy (n=5,228)	12,003 ± 9,344	<.001
Laparoscopic myomectomy (n=2,186)	13,245 ± 9,727	<.001
Myomectomy, unspecified (n=3,042)	11,110 ± 8,955	<.001

*Values presented as mean ± standard deviation
**t-test, assuming unequal variances
TFA=transcervical fibroid ablation.

a higher statistical power with larger sample sizes. Using claims databases for outcomes comparisons has some drawbacks (Koch 2012). For example, with the comparator arms, certain demographic characteristics that may affect outcomes, such as race, socioeconomic status, education level, and health behaviors, (e.g., tobacco use), could not be collected. Additionally, Heisler (2009) showed that administrative claims data can be inconsistent, an issue that could have an effect on the results of this study. However, despite the potential shortfalls of administrative claims data, the results found in this analysis were similar to those reported in the peer-reviewed literature (Becker 2007). The hysterectomy and myomectomy results obtained in this analysis are consistent with studies that reported hysterectomy and myomectomy patient LOS ranging from two to three days (Becker 2007, Siskin 2006, Song 2017). The costs reported in these studies were also similar for total abdominal hysterectomy ($10,236), supracervical hysterectomies ($11,009), and myomectomies ($10,844) when converted from 2003 dollars to the 2016 dollar standard utilized for this analysis (Becker 2007).

CONCLUSION

TFA using the Sonata System had a statistically significant shorter LOS than either comparator arm, irrespective of procedure route. Sonata was also associated with statistically significantly lower facility costs compared with either hysterectomy or surgical myomectomy regardless of procedure route, site of service, or use of robotic assistance. Sonata treatment provided a 26% to 42% reduction in facility costs when compared with hysterectomy and myomectomy, respectively. The primary source of this comparative savings was the reduced usage of hospital resources.

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Full length article

Improvement in health utility after transcervical radiofrequency ablation of uterine fibroids with the sonata system: Health utility after radiofrequency ablation

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ABSTRACT

Objectives: To establish the improvement in patient health utilities following treatment of symptomatic uterine fibroids with the Sonata™ System.
Study design: A prospective, single-arm trial was conducted in which 49 women in the United Kingdom, Netherlands and Mexico with fibroids were treated with transcervical, intrauterine ultrasound- guided radiofrequency ablation. The EQ-5D-3L system was utilized to collect patient health status at baseline, 3, 6, and, 12 months post-procedure. Patient-reported health states at each time point were converted into a health utility value using time-trade off methodology.
Results: In the overall cohort, patient health utility increased from a mean of 0.745 at baseline, to means of 0.838, 0.852, and 0.914 at 3 months, 6 months, and 12 months, respectively. The change from baseline at 12 months was significant. When stratified by country, the 12-month improvement in health utility remained significant for both the Mexican and Dutch cohorts.
Conclusions: Transcervical radiofrequency ablation of uterine fibroids with the Sonata System resulted in statistically significant 12-month improvements in health utility for the overall patient cohort and for the Mexican and Dutch sub-populations.

Introduction

Uterine fibroids, also known as leiomyomata, are noncancerous growths of the uterus. They can vary in size and number and often appear during childbearing years. Uterine fibroids are common; one study of women undergoing pelvic sonography found that over 80% of African-American and almost 70% of Caucasian women will have fibroids by the age of 50 [1]. Whilst the majority of uterine fibroids are asymptomatic [2], 20–50% may produce symptoms [3]; the most common symptom being abnormal uterine bleeding [4]. Fibroids may also cause pelvic pressure and pain [3]. A study of 21,746 women with symptomatic fibroids [5] found that more than half of the patients' symptoms had a negative impact on their lives. Another study found that almost a third of women with symptomatic uterine fibroids reported work absenteeism and over a third reported presenteeism (i.e., reduced work productivity) and impaired general activity [6].

Definitive treatment for uterine fibroids is hysterectomy, with or without removal of the ovaries. However, there are several treatment options for women suffering from fibroids that do not involve surgical removal of the uterus, and these include surgical removal of myomata (myomectomy); uterine artery embolization (UAE); and magnetic resonance-guided focused ultrasound (MRgFUS). With effective treatment, women who had been living with fibroid symptoms can realize improvements in health-related quality of life (HRQOL) [7].

The availability of a variety of treatment options allows women the opportunity to choose an appropriate treatment based on symptom severity, past medical history, and values and preferences (desire for fertility and for uterine preservation). A recent US study found that almost 79% of women would prefer less invasive treatments, with 51% choosing to preserve their uteri, and 43% of women under age 40 desiring fertility preservation [8].

With the goal of providing an incisionless, uterus-preserving alternative to hysterectomy and other treatment options, the Sonata® System (which received CE Mark approval) takes a transcervical approach to treating symptomatic fibroids with

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[1] Locations of study sites: Birmingham, United Kingdom; Haywards Heath, United Kingdom; Amsterdam, Netherlands; Eindhoven, Netherlands; Nieuwegein, Netherlands; Enschede, Netherlands; Monterrey, Mexico.

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radiofrequency energy. Radiofrequency energy heats fibroids to a high temperature and this results in thermal fixation, coagulative necrosis and gradual reduction in fibroid volume. Fibroid ablation with the Sonata® System takes place under real-time visualization provided by an intrauterine sonography probe that is integrated within the device [9] (Fig. 1). The advantage of treatment with the Sonata® System over MRgFUS is that it takes approximately four minutes to ablate a fibroid up to 5 cm, whereas fibroid ablation with MRgFUS requires much longer ablation durations (typically 3 h in total) [10]. One advantage of the Sonata® System over UAE is that postoperative pain and symptoms are more limited and do not typically require hospital admission [11,12].

To evaluate the safety and efficacy of the Sonata® System, the Fibroid Ablation Study-EU (FAST-EU) was undertaken in Europe and Mexico. Efficacy and safety endpoints at 3, 6, and 12 months were very promising; both fibroid perfusion and fibroid volume reductions were statistically significant at 6 and 12 months compared to baseline. The detailed results were previously published in gynecologic surgical journals [11,12] In summary, mean perfused fibroid volume was reduced by 68 and 67.4% at 6 and 12 months, respectively. Similarly, mean fibroid volume was reduced by 55 and 67% at the same time intervals. The mean symptom severity score improved by more than 50% at 12 months. The number of post-procedural complications was low and these were typically minor and anticipated. There were four surgical reinterventions (8%) within 12 months.

An additional objective of the study was to obtain a descriptive profile of patient health status at baseline, 3, 6, and 12 months post treatment, to enable assessment of patient health utility and calculation of total quality-adjusted life years (QALYs) experienced by patients during the 12 months post- procedure. These data were not included in the previously published papers as these focused on traditional clinical safety and efficacy outcomes. The current paper focuses on the health utility and quality of life outcomes for women who were treated with transcervical radiofrequency ablation in the FAST-EU study.

Materials and methods

The FAST-EU study, a prospective, longitudinal, multicenter, single-arm trial, was conducted in Mexico, the United Kingdom, and the Netherlands. Given the early phase of implementation of this new technique, the chosen study design was in line with guidance on research of innovative interventions of the IDEAL collaboration (Idea, Development, Exploration, Assessment, and Long-term study) [13]. In particular, the IDEAL collaboration notes that immediate execution of comparative studies may result in the underestimation of the potential effect of a new technique.

Fig. 1. Intrauterine sonography probe.

In this study, 50 consecutive women with symptomatic fibroids meeting eligibility requirements [11,12] received treatment using the Sonata® System (Gynesonics, Redwood City, CA, USA). The procedure involved transcervical, intrauterine ultrasound-guided radiofrequency ablation. The Sonata System consists of a reusable intrauterine ultrasound (IUUS) probe and a single-use disposable RFA handpiece with proprietary graphical guidance software (SMART Guide™) for fibroid targeting and ablation (Fig. 1). Through the use of the SMART Guide, each ablation with a targeted fibroid is placed to encompass as much of the fibroid as possible while keeping thermal energy within the uterine serosal margin (Fig. 2). This permits the safe and predictable delivery of RF energy to the fibroid. Treatment parameters, such as time at temperature (105° C) and power, are set by the Sonata System based on the ablation dimensions that the gynecologist has selected via the SMART Guide. The Sonata System can create a continuous range of ablation sizes up to 4.0 cm wide and up to 5.0 cm long. Multiple ablations may be created within a single fibroid and several fibroids may be treated within a single session; there is no need for staged treatment, unlike some cases of hysteroscopic myomectomy. The Sonata System is also capable of ablating a broader repertoire of fibroids than is possible with operative hysteroscopy, including intramural and selected subserous fibroids.

Patients were included in one of the participating hospitals in Mexico (one site), United Kingdom (2 sites) and The Netherlands (3 sites) between January 2011 and March 2014. Inclusion criteria included women with up to 5 fibroids of International Federation of Gynecology and Obstetrics (FIGO) types 1,2,3,4 and 2–5 (transmural) [14] with individual maximum diameter of 1–5 cm. At least one fibroid was required to indent the endometrial cavity. Patients were 28 years of age or older and not pregnant, with regular, predictable menstrual cycles and heavy menstrual bleeding for at least 3 months, with a Menstrual Pictogram score $\geq$120 and a Uterine Fibroid Symptom-Quality of Life (UFS-QOL) Symptom Severity Score (SSS) $\geq$20 for one cycle [15,16]. Exclusions included a desire for future fertility, the presence of one or more type 0 fibroids, cervical dysplasia, endometrial hyperplasia, active pelvic infection, clinically significant adenomyosis (>10% of the junctional zone measuring more than 10 mm in thickness as measured by MRI), and the presence of one or more treatable fibroids that were significantly calcified (defined as <75% fibroid enhancement by volume on contrast-enhanced MRI). MRI scans were all assessed by an independent core laboratory.

Patients were followed at 3, 6, and 12 months post-treatment. The primary study endpoint was percentage change in target fibroid perfused volume assessed at 3 months; the reduction was statistically significant at 3 months, and also at 12 months, with a nearly 70% reduction in volume ($P < 0.001$) [12]. Secondary endpoints, evaluated at 6 and 12 months, included safety outcomes, symptom severity, Health-related Quality of Life (HRQOL) and reintervention. Of note, symptom severity and HRQOL were assessed using the SSS and HRQOL subscales of the UFS −QOL questionnaire, which is a tool that has been validated in women with uterine fibroids and compared with a cohort of women without uterine fibroids [17].

While not reported previously, the EuroQol-5D-3L (EQ-5D-3L) instrument [18,19] was also utilized in FAST-EU to obtain a descriptive profile of patient health status at baseline, and at 3 months, 6 months and 12 months post-procedure.

In this study, the TTO value sets specific to the Dutch and UK populations were applied to the FAST-EU patient populations from the Netherlands and UK, respectively. As neither VAS nor TTO value sets were available for Mexico, the UK TTO value sets were also applied to the Mexican patient population (as it is the largest, most

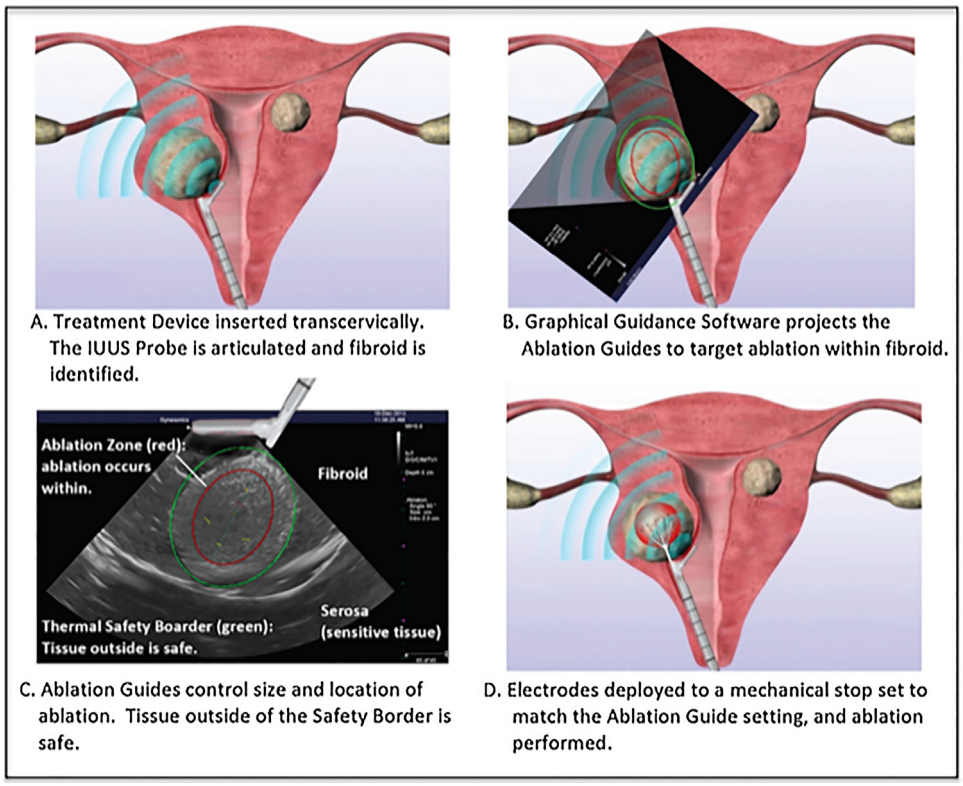

Fig. 2. Method of Intrauterine US (IUUS) guided ablation using the Sonata System.

robust TTO value set available). Six missing values were imputed using the method of last observation carried forward (LOCF). Improvement in health utility from baseline to 12 months was calculated using the Wilcoxon matched-pairs signed-rank test. All statistical analysis was completed using Stata 13 (StataCorp LP, College Station, TX). Quality- adjusted life years (QALYs) were then calculated from health utility values using area under the curve methodology (trapezoidal rule) [21,22].

Results

Of the 49 women who provided responses to the EQ-5D-3L (data from one patient who conceived three months post-ablation and delivered at term was not imputed), 22 were from Mexico, 21 were from the Netherlands, and 6 were from the United Kingdom. Among the Mexican participants, all were Latinas. In the European cohort, 46 participants were white, with two participants of African descent, and one participant each of Mediterranean, Turkish, and mixed race The majority of the participants were between the ages of 35–40 years of age, with 31% younger than 35 years and 26% older than 40 years. At baseline, women from the UK tended to report more severe symptoms, while participants from the Netherlands reported the lowest health-related quality of life (Table 1).

In the overall cohort, patient health utility increased from a mean of 0.75 at baseline, to means of 0.84, 0.85, and 0.91 at 3

Table 1
Baseline participant demographics and quality of life Indicators.

Country	Age[a]	Number (%)	*Baseline Measures*	
			Symptom Severity[b]	Health-Related Quality of Life[c]
Mexico	25–30	1 (4.5)	28.00	73.00
	30–35	8 (36.4)	27.13	100.88
	35–40	9 (40.9)	29.10	121.89
	40–45	4 (18.2)	28.25	114.25
	45–50	0	n/a	n/a
Netherlands	25–30	1 (4.8)	24.00	106.00
	30–35	3 (14.3)	21.67	87.00
	35–40	9 (42.9)	30.11	97.22
	40–45	6 (28.5)	24.64	93.50
	45–50	2 (9.5)	26.00	84.00
UK	25–30	1 (16.7)	30.00	120.00
	30–35	1 (16.7)	19.00	71.00
	35–40	3 (49.9)	32.67	128.67
	40–45	1 (16.7)	35.00	113.00
	45–50	0	n/a	n/a

[a] Subject ages were specified as a range by each site to protect subject privacy.
[b] Symptom severity as measured by the Symptom Severity Score (SSS) subscale of the Uterine Fibroid Symptom-Quality of Life (UFS-QOL) questionnaire. Higher scores indicate greater severity.
[c] Health-related quality of life (HRQOL) as measured by the HRQOL subscale of the UFS-QOL). Lower scores indicate lower HRQOL.

Table 2
Change in health utilities from baseline to 12 months

	Baseline		3-month		6-month		12-month		p-value*
COHORT GROUP	*MEAN*	*MEDIAN*	*MEAN*	*MEDIAN*	*MEAN*	*MEDIAN*	*MEAN*	*MEDIAN*	
Overall (N = 49)	0.745	0.811	0.838	0.848	0.852	0.848	0.914	1.000	<**0.001**
Mexico and Netherlands (N = 43)	0.747	0.811	0.864	0.897	0.859	0.848	0.935	1.000	<**0.001**
Mexico (N = 22)	0.739	0.769	0.869	0.848	0.862	0.848	0.944	1.000	**0.004**
Netherlands (N = 21)	0.755	0.811	0.858	1.000	0.855	0.897	0.925	1.000	**0.003**
UK (N = 6)	0.737	0.898	0.650	0.778	0.802	0.898	0.762	0.796	**0.75**

* Wilcoxon matched-pairs signed-rank test comparison of baseline with 12-month health utility scores.

months, 6 months, and 12 months, respectively. Because the UK cohort had a small sample size (n = 6) and because three of the six missing values were from the UK cohort, an analysis with only the Mexican and Netherlands cohorts was also conducted. In this limited cohort, patient health utility increased from a mean of 0.75 at baseline, to means of 0.86, 0.86, and 0.94 at 3 months, 6 months, and 12 months respectively. At twelve months overall health utility improvements from baseline were statistically significant ($P < 0.001$), as well as combined and individually in Mexico and the Netherlands (Table 2).

After translating health utility values into quality-adjusted life years (QALYs), it was found that in the one-year period from baseline to the 12-month follow-up visit, the overall cohort experienced, on average, 0.85 quality-adjusted life years (QALYs). Because six missing utility values were imputed utilizing the LOCF methodology, the analysis was repeated using only those patients with complete utility measurements. When the patients with missing utility values were removed, the average QALYs experienced increased from 0.85 to 0.87; therefore, the introduction of LOCF methodology did not introduce upward bias. Similarly, when the UK sample was excluded, the mean QALYs experienced increased to 0.87 QALYs. After stratifying by country, QALYs for the Mexican, Dutch, and British cohorts were 0.87, 0.86, and 0.75, respectively (Fig. 3).

Comment

Transcervical radiofrequency ablation of uterine fibroids resulted in statistically significant 12-month improvements in health utility for the overall patient cohort, for the combined Mexican and Dutch population cohort, and for the individual Mexican and Dutch sub-populations. The UK cohort also demonstrated a trend for 12-month improvement in health utility; the small sample size (n = 6) for the UK population combined with 50% of patients having missing health utility values may explain the lack of statistically significant findings in this subpopulation. The study had several key strengths. Though the sample size was small, the study was a multicenter, international study, which increases its generalizability. The study also utilized a validated, standardized instrument (EQ-5D-3L) and country-specific TTO value sets wherever possible (for the UK and Netherland populations) for assigning health utility to collected health states. The EQ-5D-3L is a well-published, frequently used instrument, with a 2014 systematic review reporting it as the most widely used tool for measuring health-related quality of life in cost-utility analysis [23]. The EQ-5D-3L has previously been used successfully to evaluate treatments for menorrhagia, and is especially valuable in cost-effectiveness analysis of uterine fibroid treatments [24].

There are also several limitations to the study. FAST-EU was a single-arm study, so direct comparisons to alternative uterine fibroid treatments cannot yet be made. Other potential confounders cannot be entirely excluded. For example, accommodation is sometimes used as a proxy for socioeconomic class [25]. While it is possible there were covariates that was not controlled for, accommodation and potential impacts on health utility are not reported in other studies of fibroid treatments [26,27]. The effect of selection bias may also be limited as patients served as their own controls. There is a possibility of control evaluation bias, since women with persisting symptoms may have had additional therapies (n = 4) or may have been lost to follow-up with regard

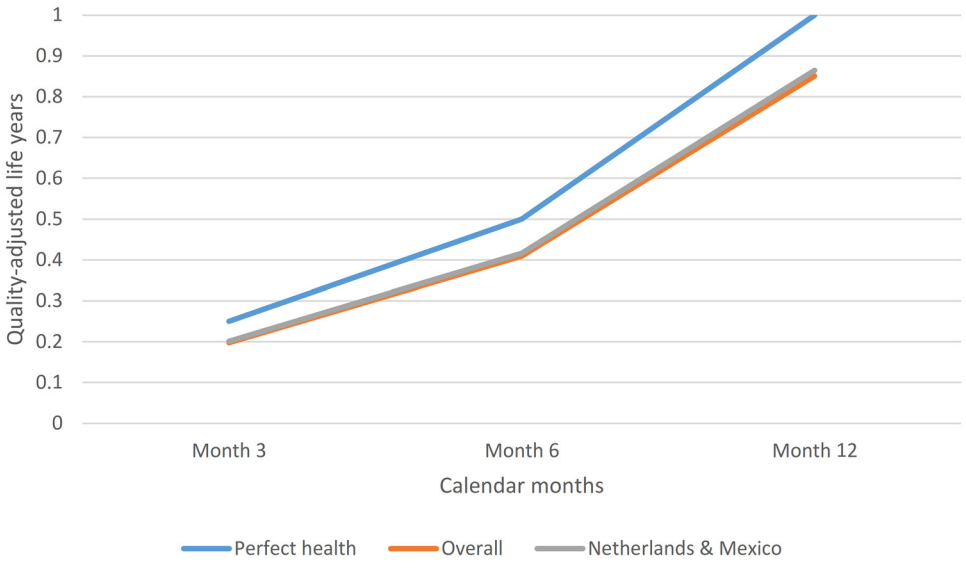

Fig. 3. Quality adjusted life years after treatment.

to the EQ-5D-3L questionnaire (n = 1). The follow-up time was also limited to one year, so long-term impact on patient health utility and on the QALYs experienced requires further research.

In the overall cohort, health utility did improve at each 3-month time point, but the difference may not have been statistically significant, possibly due to sample size. When stratified by nation, the sample sizes were much smaller, allowing outliers to have a stronger effect.

The UK cohort had a particularly small sample size (n = 6), which likely led the cohort to be underpowered to detect a statistically significant difference in health utility from baseline to 12-months follow-up. Additionally, the UK cohort had a preponderance of missing data, with 3 of the 6 missing health states occurring within this small sample. For this reason, we analyzed patient health utilities and QALYs both with and without the six UK participants. Given the lack of the availability of the Mexican value set we used the UK value set in the Mexican population. This is not optimal but was chosen because we there was no comparable country to Mexico that had a value set available. As recommended by EuroQoL, we used the UK value set as it is the most robust [28].

Clinical implications

It has been demonstrated that patient health utility improves following other available alternatives for treating uterine fibroids, ranging from treatments that are invasive (abdominal hysterectomy, abdominal myomectomy) to minimally invasive (laparoscopic hysterectomy, UAE) to noninvasive (MRgFUS). Based on an informal comparison, QALYs experienced by patients in the FAST-EU study are similar compared to those reported for these alternative treatments. For a one-year period, the QALYs for alternative treatments were 0.92, 0.93, and 0.91 (representing hysterectomy, UAE, and myomectomy, respectively) [29]. While the cohort in the FAST-EU trial experienced 0.85 QALYs in a one-year period, it must be noted that QALYs experienced by patients in the FAST-EU trial are likely lower due to lower baseline health utility index values (i.e., due to patients with lower HRQOL at baseline). The ongoing increase in health utilities to levels nearing "perfect health" after 1 year indicates that even after 6 months follow-up an additional positive effect can be expected, and demonstrates that this technology may be an effective alternative to traditional treatments. QALYs, a population-based measure, are an extremely valuable tool used to inform policy-makers and payers about the cost-effectiveness of interventions and treatments.

Multi-year longitudinal studies will be required to assess longer-term impact of treatment on patient health utility and QALYs experienced. Studies comparing the safety, effectiveness, and patient-reported outcomes associated with the Sonata® System to those of hysterectomy, myomectomy, or UAE would be particularly informative. While radiofrequency ablation is comparable to other fibroid treatment options, it also has many benefits in terms of patient satisfaction and costs. For example, when compared to uterine artery embolization, radiofrequency ablation has both a shorter procedural time and a faster return to normal activities [30,31]. The FAST-EU study, however, demonstrates that for appropriately selected patient populations, such as those without type 0 or significantly calcified fibroids, the Sonata System may significantly improve patient health utility over a one-year period.

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