NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids

Uterine fibroids are non-cancerous growths on the inside or outside of the womb (uterus). In this procedure, a device is put into the womb through the vagina (transcervical). It uses ultrasound waves to locate the fibroid, and then delivers heat (radiofrequency) energy to destroy it (ablation). The aim is to shrink the fibroid and reduce symptoms.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in January 2020 and updated in January 2021.

Procedure name

- Transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids

Professional societies

- Royal College of Obstetrics and Gynaecology
- British Society for Gynaecological Endoscopy

Description of the procedure

Indications and current treatment

Uterine fibroids (also known as uterine leiomyomas or myomas) are benign tumours of the uterine wall. They can be asymptomatic or cause symptoms including menorrhagia, intermenstrual bleeding, pelvic pressure or pain, and urinary incontinence. They can be associated with fertility problems and miscarriage.

Treatment depends on whether the fibroids cause symptoms, and if the person would like to become pregnant in the future. For symptomatic fibroids, treatment options include medications, interventional radiology and surgery. Interventional radiology treatments include uterine artery embolisation and MRI-guided focused ultrasound. Surgery includes hysterectomy, myomectomy, endometrial ablation techniques and myolysis.

What the procedure involves

Transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids is done under general or regional anaesthesia, or sedation. A radiofrequency ablation device with an ultrasound probe at the tip is inserted through the cervix into the endometrial cavity. The ultrasound probe is used to visualise and target the fibroid, which is then ablated with radiofrequency energy. The aim is to shrink the fibroid and reduce symptoms.

Outcome measures

Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire (UFS-QOL)

The UFS-QOL is a disease-specific questionnaire that assesses symptom severity and health-related quality of life (HRQoL) in patients with uterine fibroids. It consists of an 8-item symptom severity scale and 29 HRQoL items with 6 domains: concern, activities, energy/mood, control, self-consciousness, and sexual function. All items are scored on a 5-point Likert scale, ranging from 'not at all' to 'a very great deal' for symptom severity items and 'none of the time' to 'all of the time' for the HRQoL items. Symptom severity and HRQoL subscale scores are summed and transformed into a 0 to 100 point scale. Higher symptom severity scores indicate worse symptoms and higher HRQoL subscale scores indicate better HRQoL.

Efficacy summary

Reduction in menstrual blood loss

In a cohort study of 147 patients, 95% of patients had reduced menstrual bleeding at 12 months and 65% of patients had 50% or greater reduction in menstrual bleeding. The mean pictorial blood loss assessment chart score reduced from 303.6 at baseline to 159.5 at 6 months and 143.8 at 12 months ($p<0.001$ for both).[1] In a cohort study of 50 patients, the proportion of patients with more than 50% reduction in menstrual pictogram scores was 57% (28/49), 73% (35/48) and 65% (31/48) at 3-month, 6-month and 12-month follow up respectively.[3]

Reduction in symptom severity

In the cohort study of 147 patients, the mean symptom severity score reduced from 54.9 at baseline to 26.9 at 3 months and 22.6 at 12 months ($p<0.001$ for both). Improvement in symptoms at 12 months was reported by 96% (130/135) of

patients.[1] In the 125 patients who were followed up to 2 years, the mean symptom severity score reduced from 55 at baseline to 24 at 2 years (p<0.001) and 88% of patients reported improvement in fibroid symptoms.[2] At 3 years, the mean symptom severity score was 22 (p<0.001).[9] In the cohort study of 50 patients, the proportion of patients with at least a 10-point reduction in symptom severity scores was 82%, 86% and 78% at 3-month, 6-month and 12-month follow up respectively.[3] In a series of 17 patients from the same study with longer follow up, the mean symptom severity score improved from 64.9 at baseline to 27.6 after a mean follow up of 64 months (p=0.002).[5]

Quality of life

In the cohort study of 147 patients, the mean health-related quality of life score improved from 40.3 at baseline to 77.9 at 3 months and 84.2 at 12 months (p<0.001 for both).[1] In the 125 patients who were followed up to 2 years, the mean health-related quality of life score improved from 40 at baseline to 83 at 2 years (p<0.001).[2] At 3 years, the mean score remained at 83 (p<0.001).[9] In the cohort study of 50 patients, the patient health utility increased from a mean of 0.75 at baseline to means of 0.84, 0.85 and 0.91 at 3 months, 6 months and 12 months respectively (p<0.001).[4] In the series of 17 patients, the mean health-related quality of life score improved from 27.2 at baseline to 76.0 after a mean follow up of 64 months (p=0.0001).[5]

Patient satisfaction

In the cohort study of 147 patients, 70% of patients were very satisfied with the procedure at 12 months, 18% were moderately satisfied and 1% were moderately dissatisfied.[1] Patient satisfaction at 2 and 3 years was 94%.[2,9] At 12 months, 82% of patients responded that they would definitely recommend the procedure, 16% would probably recommend it and 3% would probably not recommend it.[1] In the cohort study of 50 patients, overall satisfaction rate at 12 months was 88% (43/49).[3]

Time to return to usual activities

In the cohort study of 147 patients, the mean time to return to normal daily activities was 2.2 days and the mean time to return to work was 3.6 days.[1] In the cohort study of 50 patients, the mean time to return to normal activities of daily life was 4.4 days (range 1 to 14).[3]

Reduced fibroid or uterine volume

In the cohort study of 147 patients, the mean reduction in total uterine volume was 13% after 12 months. The mean maximal reductions in total and perfused

leiomyoma volumes per patient from baseline to 12 months was 62% (n=129) and 64% (n=128) respectively (p<0.001 for both).[1] In the cohort study of 50 patients, perfused fibroid volume reduced from baseline by an average of 68% at 3 months and 67% at 12 months (p<0.001 for both). Total fibroid volume reduced by an average of 55% and 67% respectively (p<0.001 for both).[3]

Surgical reintervention

In the cohort study of 147 patients, 1 patient had an elective hysterectomy for bleeding just before her 12-month visit.[1] The cumulative rate of surgical reintervention for heavy menstrual bleeding through 2 years was 6% (95% confidence interval 2 to 11).[2] In the cohort study of 50 patients, the rate of surgical intervention at 12 months was 8% (4/50).[3] In the series of 17 patients, 2 patients had a hysterectomy for abnormal uterine bleeding: 1 was 3.5 years after the ablation procedure and 1 was about 4 years after the procedure.[5]

Pregnancy

In the cohort study of 147 patients, 2 pregnancies were reported. One patient delivered at term by elective repeat caesarean section 31 months after the procedure. The second patient (aged 40) had a miscarriage 29 months after the procedure.[9] In the cohort study of 50 patients, there was a single pregnancy reported within the first 6 months after ablation. The patient delivered a liveborn male infant at term by elective repeat caesarean section.[3] A case report of a pregnancy confirmed 33 months after the procedure has also been described. The patient had a normal spontaneous vaginal delivery of a liveborn female infant.[7]

Safety summary

Fibroid sloughing

Fibroid sloughing was reported in 31% of patients and fibroid expulsion in 1% of patients in the cohort study of 147 patients. One patient had leucorrhoea, pelvic pain and unconfirmed low-grade fever 28 days after the procedure. The patient was admitted overnight and offered broad-spectrum antibiotics. An independent medical advisory committee concluded that the event was related to fibroid sloughing and leucorrhoea with no evidence of infection.[1] Fibroid expulsion was reported in 1 patient in the cohort study of 50 patients.[3]

Deep venous thrombosis

Deep venous lower extremity thrombus was reported in 1 patient in the cohort study of 147 patients. It was diagnosed 15 days after the procedure and managed on an outpatient basis without sequelae.[1]

Cramping or pain

Cramping or pain was reported in 8% of patients in the cohort study of 147 patients. The overall mean pain score was 0.2 (range 0 to 7) during the procedure (on a scale from 0 to 10) and 2.6 (range 0 to 10) during recovery.[1] Pelvic pain or cramping was reported in 8% (4/49) of patients in the cohort study of 50 patients. The mean pain score during recovery was 3.0 (range 0 to 9).[3]

Nonspecific abdominal pain was reported in 1 patient in a case series of 37 patients. The patient was admitted 18 days after ablation; CT and ultrasound were both normal and the event was assessed as not gynaecological in origin. This event was deemed to be unrelated to the device or procedure.[6]

Leucorrhoea

Leucorrhoea was reported in 6% of patients in the cohort study of 147 patients.[1]

Infection

Uncomplicated genitourinary infection was reported in 5% of patients in the cohort study of 147 patients.[1] Urinary tract infection was reported in 4% (2/49) of patients in the cohort study of 50 patients (both within 30 days of the procedure). One of these patients was admitted overnight on postoperative day 9 for antibiotic treatment. This event was deemed not to be related to the ablation system upon review by an independent medical advisory board.[3]

Flu-like symptoms

Flu-like symptoms were reported in 1% of patients in the cohort study of 147 patients.[1]

Nausea or vomiting

Nausea or vomiting was reported in 1% of patients in the cohort study of 147 patients.[1]

Dysmenorrhoea

Dysmenorrhoea was reported in 14% (7/49) of patients in the cohort study of 50 patients.[3]

Abnormal uterine bleeding

Abnormal uterine bleeding above baseline was reported in 12% (6/49) of patients in the cohort study of 50 patients.[3]

De novo adhesion formation

None of the 34 patients with evaluable hysteroscopies had signs of 'de novo adhesiogenesis' at 6 weeks in the case series of 37 patients.[6]

Other

Bradycardia was reported in 1 patient shortly after the procedure in the cohort study of 50 patients. The patient was kept in hospital overnight for atropine and observation. This event was deemed not to be related to the ablation system upon review by an independent medical advisory board.[3]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events they have heard about) and about theoretical adverse events (events they think might possibly occur, even if they have never happened). For this procedure, professional experts listed minimal pain as an anecdotal adverse event. They did not describe any additional theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids. The following databases were searched, covering the period from their start to 9 November 2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with symptomatic uterine fibroids.
Intervention/test	Transcervical ultrasound-guided radiofrequency ablation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on about 235 patients who had transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids from 2 cohort studies (6 publications), 1 case series, 1 case report and 1 systematic review.[1 to 9]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids

Study 1 Chudnoff S (2019)

Details

Study type	**Cohort study (SONATA trial)**
Country	US and Mexico
Recruitment period	2015 to 2016
Study population and number	**n=147** Women with symptomatic uterine fibroids
Age	Median 43 years (range 31 to 50)
Patient selection criteria	Premenopausal women aged between 25 and 50 years with up to 10 fibroids of International Federation of Gynecology and Obstetrics type 1, 2, 3, 4, 2 to 5 (transmural), or all of these with diameters between 1 cm and 5 cm; at least 1 fibroid that indented or impinged on the endometrial cavity; minimum pictorial blood loss assessment chart score between 150 and 500 at baseline; consistent menstrual cycles that were within normal limits. Exclusion criteria: desire for future pregnancy, the presence of type 0 myomata 1 cm or greater, endometrial polyps 1.5 cm or greater or multiple polyps, bulk symptoms attributable to subserous fibroids, prior endometrial ablation or uterine artery embolisation or uterine artery occlusion or hyperthermic ablation of fibroids, uterine volume 1,000 ml or greater, the presence of tubal implants for sterilisation, and clinically significant adenomyosis. 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.
Technique	The Sonata system, which integrates intrauterine ultrasound imaging with a radiofrequency treatment device, was used. All patients were treated in an outpatient setting. General anaesthesia was used in 74 (50%) patients and 73 (50%) patients had the procedure done under sedation. Prophylactic antibiotics were offered to 57 (39%) patients.
Follow up	**12 months**
Conflict of interest/source of funding	The study was supported by Gynesonics Inc. Of the 6 authors, 4 have served on the Gynesonics advisory board. One author has received expenses and honoraria from Gynesonics. One author has received royalties from Crossbay Medical Inc. and stock options from Channel Medical Inc. and has served as a consultant for Boston Scientific. One author has been a consultant for Gynesonics and a consultant for Aegea Medical. One author has also served on the advisory board for Abbvie. One author has received a stock option grant from Gynesonics. Five authors serve on the Sonography Guided Transcervical Ablation of Uterine Fibroids study steering committee.

Analysis

Follow-up issues: Of the 147 enrolled patients, 4 reached menopause before the 12-month visit and were excluded from the analysis. One patient had surgical reintervention before the 12-month visit and was excluded from the analysis of menstrual bleeding reduction endpoint. Of the 142 remaining patients, 135 (95%) provided a pictorial blood loss assessment chart questionnaire at 12 months.

Study design issues: Prospective, multicentre cohort study. 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 fibroid volume and safety. Reduction in menstrual blood loss was measured by a pictorial blood loss assessment chart, a validated assessment tool that uses icons representing various degrees of saturation of sanitary products. The Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire (UFS-QOL) was used for symptom severity and health-related quality of life and the EuroQoL questionnaire was used to determine change in general health.

For the menstrual blood loss, 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. Success for the surgical reintervention endpoint was defined as the proportion of patients who did not need surgical reintervention for heavy menstrual bleeding with the lower 95% confidence interval (CI) of the percentage of patient success 75% or greater.

Missing values for the pictorial blood loss assessment chart were imputed using last observation carried forward.

Study population issues: The median body mass index at baseline was 28 kg/m^2 (range 18 kg/m^2 to 50 kg/m^2). The mean uterine volume was 268 cm^3 and mean total fibroid volume was 71 cm^3. The mean number of fibroids per patient was 3.5 (range 1 to 10).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **147**

Change in PBAC score by follow-up period (n=142)

Follow up	PBAC score	change	Percent change
Baseline			
Mean±SD	303.6±98.6		
Median	285.9		
Minimum, maximum	150.2, 499.0		
6 months			
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 value		<0.001	<0.001
12 months			
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 value		<0.001	<0.001

95.1% of patients had reduced menstrual bleeding at 12 months.

64.8% (95% CI 56.3 to 72.6) of patients had 50% or greater reduction in menstrual bleeding.

At 12-month follow up, 99.3% (95% CI 95.1 to 99.9) of patients did not have a surgical reintervention for heavy menstrual bleeding. One patient had an elective hysterectomy for bleeding just before her 12-month visit.

Change in symptom severity score by follow-up period

Follow up	Symptom severity score (mean±SD)	Change (mean±SD)	p value
Baseline, n=143	54.9±18.65		
3 months, n=141	26.9±19.0	-27.9±22.85	<0.001
6 months, n=138	22.7±17.47	-31.9±20.98	<0.001
12 months, n=135	22.6±17.75	-32.1±21.03	<0.001

Safety

Tolerability of procedure

- Very tolerable=64.6% (95/147)
- Moderately tolerable=30.6% (45/147)
- Minimally tolerable=2.7% (4/147)
- Intolerable=2.0% (3/147)

Overall mean pain score during procedure (0 to 10 scale)=0.2±1.0 (range 0.0 to 7.0)

Overall mean pain score during recovery (time between procedure completion and discharge, recorded before discharge)=2.6±2.8 (range 0.0 to 10.0)

There were no device-related adverse events.

Procedure-related serious adverse events=1.4% (2/147):

- One patient had deep venous lower extremity thrombus diagnosed 15 days after the procedure, managed as an outpatient without sequelae.
- One patient had leucorrhoea, pelvic pain and unconfirmed low-grade fever 28 days after the procedure. The patient was admitted overnight and offered broad-spectrum antibiotics. An independent medical advisory committee concluded that the event was related to fibroid sloughing and leucorrhoea with no evidence of infection.

Nonserious procedure-related adverse events=50.3% (74/147):

- Fibroid sloughing=30.6%
- Cramping or pain=7.5%
- Leucorrhoea=6.1%
- Uncomplicated genitourinary infections=4.8%
- Nonspecific (constitutional) symptoms=3.4%

Change in HRQoL by follow-up period

Follow up	HRQoL (mean±SD)	Change (mean±SD)	p value
Baseline, n=142	40.3±20.51		
3 months, n=140	77.9±21.90	37.3±24.30	<0.001
6 months, n=137	84.0±17.63	43.3±25.07	<0.001
12 months, n=135	84.2±18.96	43.7±24.25	<0.001

Change in symptoms at 12 months, measured by the Overall Treatment Effect Scale questionnaire

- Improvement in symptoms=96.3% (130/135)
- No change=3.0% (4/135)
- Worsening of symptoms=0.7% (1/135)

Health status measured on the Euro-QoL questionnaire improved from a mean overall score of 0.72 at baseline to 0.89 at 12 months (p<0.001).

Patient satisfaction at 12 months (n=135)

- Very satisfied=70.4%
- Moderately satisfied=17.8%
- Somewhat satisfied=8.9%
- Somewhat dissatisfied=2.2%
- Moderately dissatisfied=0.7%

81.5% of patients would definitely recommend the procedure, 15.6% would probably recommend it and 3.0% would probably not recommend it.

Mean return to normal daily activities=2.2 days

Mean return to work for employed patients=3.6 days

Mean reduction in total uterine volume at 12 months=12.9%

Mean maximal reductions in total and perfused fibroid volumes per patient from baseline to 12 months was 62.4% (n=129) and 63.9% (n=128) respectively (p<0.001 for both).

- Expelled fibroid=1.4%
- Flu-like symptoms=1.4%
- Nausea or vomiting=0.7%
- Other nongynaecological events (constipation, sore throat, atelectasia, high blood pressure)=5.4%

Abbreviations used: CI, confidence interval; HRQoL, health-related quality of life; PBAC, pictorial blood loss assessment chart; SD, standard deviation; UFS-QoL, Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire

Study 2 Miller C (2019)

Details

Study type	**Cohort study (longer term follow up of SONATA trial)**
Country	US and Mexico
Recruitment period	2015 to 2016
Study population and number	**n=147** Women with symptomatic uterine fibroids
Age	Mean 43 years (range 31 to 50)
Patient selection criteria	Premenopausal women aged 25 to 50 years with regular and predictable menstrual cycles, objective evidence of heavy menstrual bleeding, and with up to 10 fibroids of International Federation of Obstetricians and Gynecologists (FIGO) types 1, 2, 3, 4 or 2-5 (transmural), each of 1 cm to 5 cm in diameter. At least 1 fibroid was required to have either indented or abutted the endometrial cavity (FIGO type 1, 2, 3 or 2-5). Women were excluded if they expressed a desire for future pregnancy, had any type 0 fibroids 1.0 cm or larger or endometrial polyps 1.5 cm or larger or multiple polyps of any size, bulk symptoms attributable to subserous fibroids, prior confounding procedures (endometrial ablation, uterine artery embolisation, uterine artery occlusion, or hyperthermic ablation of fibroids), uterine volume 1,000 cm^3 or above, presence of tubal implants for sterilisation or clinically significant adenomyosis.
Technique	The Sonata system (Gynesonics Inc., US), which integrates intrauterine ultrasound imaging with a radiofrequency treatment device, was used. 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.
Follow up	**2 years**
Conflict of interest/source of funding	Gynesonics Inc. provided funding for the study. The institutions of the authors received research support from Gynesonics for participation in the SONATA trial. The first author is a consultant to Gynesonics. The authors have received travel and lodging expenses for attendance at investigator meetings.

Analysis

Follow-up issues: Follow-up data at 2 years were available for 85% (125/147) of patients. Of the 147 enrolled patients, 6 missed the 2-year follow-up visit and 16 patients withdrew from the study before the 2-year visit (none because of adverse events).

Study design issues: Prospective, multicentre cohort study. Follow up remains ongoing in the trial through 3 years. Outcomes at 2 years included changes in symptom severity, health-related quality of life, general health and work or activity limitations, serious adverse events, surgical reinterventions for heavy menstrual bleeding, and occurrence of pregnancy and associated outcomes. The UFS-QOL was used for symptom severity and health-related quality of life and the EuroQoL 5-dimension (EQ-5D) questionnaire was used to determine change in general health. The EQ-5D consists of 5 questions that provide a description of the patient's health state with scores ranging from 0 (death) to 1 (perfect health). Safety analyses included all patients and efficacy analyses excluded patients who reached menopause during follow up.

Study population issues: The mean number of fibroids ablated per patient was 3. At baseline, all patients had a general health status below the 25th percentile compared with sex- and age-matched norms, as measured by the EQ-5D.

IP overview: transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids

Other issues: Patient overlap with Chudnoff S (2019).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **125** **Mean symptom severity score** • Baseline=55±19 • 2-year follow up=24±18; p<0.001 **Mean health-related quality of life scores** • Baseline=40±21 • 2-year follow up=83±19; p<0.001 **Mean EQ-5D scores** • Baseline=0.72±0.21 • 2-year follow up=0.89±0.14; p<0.001 **Patient satisfaction with treatment at 2 years=94%** (75% of patients reported that 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 overall treatment effect questionnaire compared with baseline. **Mean percentage of missed work time** • Baseline=2.9% • 2-year follow up=1.3%; p<0.001 **Mean overall percentage of work impairment** • Baseline=51% • 2-year follow up=14%; p<0.001 **Mean percentage of activity impairment because of fibroid symptoms** • Baseline=58% • 2-year follow up=14%; p<0.001 **Cumulative rate of surgical reintervention for heavy menstrual bleeding through 2 years=5.5% (95% CI 2.2 to 11.0)** **Pregnancy** One singleton pregnancy was reported; the patient conceived 22 months after ablation. The patient delivered a liveborn male infant at term by elective repeat caesarean section. There was no evidence of uterine dehiscence or rupture.	There were no device-related adverse events between the 1- and 2-year follow-up visits.
Abbreviations used: CI, confidence interval; UFS-QoL, Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire.	

Study 3 and 4 Brölmann H (2016), Huirne J (2018)

Details

Study type	**Cohort study (FAST-EU trial)**
Country	UK, the Netherlands, Mexico
Recruitment period	Not reported
Study population and number	**n=50** Women with symptomatic uterine fibroids
Age	Most frequent age range across study centres: 41 to 45 years
Patient selection criteria	Women with 1 to 5 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 because they were believed to be less likely to materially contribute to abnormal uterine bleeding. At least 1 fibroid was required to indent the endometrial cavity. Patients were 28 years old or above and not pregnant, with regular, predictable menstrual cycles and heavy menstrual bleeding for at least 3 months. A Menstrual Pictogram score of 120 or more was also required for inclusion along with a baseline Uterine Fibroid Symptom-Quality of Life (UFS-QOL) symptom severity score 20 or more. Exclusion criteria: desire for future fertility, presence of 1 or more type 0 fibroids, cervical dysplasia, endometrial hyperplasia, active pelvic infection, clinically significant adenomyosis (more than 10% of the junctional zone measuring more than 10 mm in thickness as measured by MRI), and the presence of 1 or more treatable fibroids that were significantly calcified (<75% fibroid enhancement by volume on contrast-enhanced MRI).
Technique	The VizAblate system (Gynesonics Inc., US), which combines radiofrequency ablation with intrauterine sonography in 1 device was used. The method of anaesthesia was chosen by each investigator based on individual patient characteristics in consultation with an anaesthetist. Of the 50 patients, 15 had the procedure under general anaesthesia alone, 15 had conscious sedation alone, 8 had spinal anaesthesia alone, 8 had conscious sedation and epidural anaesthesia, 2 had epidural anaesthesia alone, 1 had paracervical blockade alone and 1 had general anaesthesia and epidural anaesthesia.
Follow up	**12 months**
Conflict of interest/source of funding	The trial was fully sponsored by Gynesonics Inc. One author was a consultant for Gynesonics and another was medical director of Gynesonics.

Analysis

Follow-up issues: One patient was excluded from the analysis of the primary endpoint because of unusable imaging. One patient was pregnant at the 6-month follow up and was thus excluded from the 6- and 12-month analyses. One patient each at 3, 6 and 12 months declined to submit a menstrual pictogram. One patient did not return her baseline HRQOL portion of the UFS-QOL.

Study design issues: Prospective, multicentre cohort study. The primary endpoint was the percentage change in target fibroid perfused volume at 3 months. The primary trial endpoint success criterion was achievement of more than 30% reduction in mean target fibroid perfused volume in at least 50% of patients at 3 months. Patients who had a surgical reintervention were considered treatment failures, and their subsequent data were imputed using the last observation carried forward method. Missing data were not imputed for patients who conceived or who did not

complete a questionnaire. The protocol was amended after several patients had been treated, to include a 12-month MRI study.

Study population issues: The mean number of target fibroids per patient was 2.4 (range 1 to 7). The mean total fibroid volume at baseline was 18.8 cm^3 (range 0.3 to 77.0).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 49

Fibroid volume
At 3 months, 88.8% (79/89) of treated fibroids in all 49 patients with measurable MRI data met the primary trial endpoint criterion. At 12 months, 86.0% (37/43) of fibroids in all 28 patients with imaging data showed >30% reduction in perfused volume.

Patient reported outcomes
Proportion of patients with >50% reduction in menstrual pictogram scores
• 3 months=57.1% (28/49)
• 6 months=72.9% (35/48)
• 12 months=64.6% (31/48)

Proportion of patients with at least a 10-point reduction in symptom severity score
• 3 months=82%
• 6 months=86%
• 12 months=78%

Mean time to return to normal activities of daily life=4.4±3.1 days (range 1 to 14)

Overall satisfaction rate at 12 months=87.8% (43/49)

At 12 months, 49 patients gave a mean score of 8.8±2.4 out of 10 for how likely they would be to recommend the treatment to a friend or relative.

Reduction in mean perfused and total fibroid volumes at 3 months, n=49 (89 ablated fibroids)
<table>
<tr><th></th><th>Baseline</th><th>3 months</th><th>% reduction from baseline</th><th>p value</th></tr>
<tr><td colspan="5">Perfused fibroid volume (cm^3)</td></tr>
<tr><td>Mean±SD</td><td>18.3±20.6</td><td>5.8±9.6</td><td>68.1±28.6</td><td><0.001</td></tr>
<tr><td>Median</td><td>9.5</td><td>1.6</td><td>76.9</td><td></td></tr>
<tr><td>Range</td><td>0.3 to 77.0</td><td>0.0 to 45.7</td><td>-33.3 to 100</td><td></td></tr>
<tr><td colspan="5">Total fibroid volume (cm^3)</td></tr>
<tr><td>Mean±SD</td><td>18.8±21.4</td><td>8.0±12.0</td><td>54.7±37.4</td><td><0.001</td></tr>
<tr><td>Median</td><td>9.5</td><td>1.9</td><td>62.5</td><td></td></tr>
<tr><td>Range</td><td>0.3 to 77.0</td><td>0.0 to 56.3</td><td>-85.7 to 100</td><td></td></tr>
</table>
Reduction in mean perfused and total fibroid volumes at 12 months, n=28 (43 ablated fibroids)
<table>
<tr><th></th><th>Baseline</th><th>12 months</th><th>% reduction from baseline</th><th>p value</th></tr>
<tr><td colspan="5">Perfused fibroid volume (cm^3)</td></tr>
<tr><td>Mean±SD</td><td>18.3±20.6</td><td>6.6±11.3</td><td>67.4±31.9</td><td><0.001</td></tr>
</table>
</td><td>
There were 34 adverse events deemed possibly, probably or definitely related to the ablation system or overall procedure over 12 months. These included:
• Dysmenorrhoea, n=7 patients
• Abnormal uterine bleeding above baseline, n=6 patients
• Pelvic pain or cramping, n=4 patients
• Urinary tract infection, n=2 patients (both within 30 days of procedure)
• Fibroid expulsion, n=1 patient (no significant consequences)
• Readmissions within 30 days, n=2 patients (1 patient was admitted overnight on postoperative day 9 for antibiotic treatment for lower abdominal pain believed to be secondary to cystitis [1 of the 2 instances of urinary tract infection described above] and was discharged the next day. Another patient had bradycardia shortly after the procedure and was kept in hospital overnight for atropine and observation. Neither of these events was deemed to have been related to the ablation system upon review by an independent medical advisory board.)

Mean visual analogue scale pain score (range 0 to 10) during recovery (up to 14 days after treatment)=3.0±1.7 (median 3.0, range 0 to 9).
</td></tr>
</table>

Median	9.5	1.0	73.3	
Range	0.3 to 77.0	0.0 to 56.1	-32.7 to 100	
Total fibroid volume (cm^3)				
Mean±SD	18.8±21.4	6.8±11.4	66.6±32.1	<0.001
Median	9.5	1.2	73.3	
Range	0.3 to 77.0	0.0 to 56.1	-32.7 to 100	

Improvement in patient reported outcomes at 3 months

	Baseline	3 months	% change from baseline	p value
Menstrual Pictogram				
Mean±SD	423±253	202±202	45.2±57.9	<0.001
Symptom severity score (range 0 to 100)				
Mean±SD	61.7±16.9	31.7±20.1	46.7±32.8	<0.001
HRQoL (range 0 to 100)				
Mean±SD	34.3±19.0	76.4±22.2	336±846	<0.001

Improvement in patient reported outcomes at 6 months

	Baseline	6 months	% change from baseline	p value
Menstrual Pictogram				
Mean±SD	423±253	181±209	51.9±59.8	<0.001
Symptom severity score (range 0 to 100)				
Mean±SD	61.7±16.9	25.1±19.3	57.6±31.4	<0.001
HRQoL (range 0 to 100)				
Mean±SD	34.3±19.0	79.5±22.7	266±475	<0.001

Improvement in patient reported outcomes at 12 months

	Baseline	12 months	% change from baseline	p value
Menstrual Pictogram				
Mean±SD	423±253	173±200	53.8±50.5	<0.001
Symptom severity score (range 0 to 100)				
Mean±SD	61.7±16.9	26.6±24.0	55.1±41.0	<0.001
HRQoL (range 0 to 100)				
Mean±SD	34.3±19.0	80.7±24.7	277±483	<0.001

Pregnancy
There was a single pregnancy reported within the first 6 months after ablation. The patient delivered a liveborn male infant at term by elective repeat caesarean section.

Surgical reintervention=8% (4/50)
One patient had hysteroscopy and endometrial ablation at 10 months, 2 had hysteroscopic myomectomies at 6.5 and 7 months respectively, 1 had total abdominal hysterectomy at 11 months (the patient was noted postoperatively to have had an abnormal bleeding duration at baseline that had not been reported in her menstrual history, constituting a protocol violation).

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, 6 and 12 months respectively ($p<0.001$).

Abbreviations used: HRQoL, health-related quality of life; SD, standard deviation.

Study 5 Garza-Leal J (2019)

Details

Study type	**Cohort study (VITALITY trial [long-term follow up of patients included in FAST-EU trial])**
Country	Mexico
Recruitment period	Not reported
Study population and number	**n=17** **Women with heavy menstrual bleeding secondary to fibroids**
Age	Most frequent age range 41 to 45 years
Patient selection criteria	Patients who had been previously enrolled and treated in the FAST-EU clinical trial were eligible for inclusion. Selection criteria included patients with 1 to 5 uterine fibroids of FIGO types 1, 2, 3, 4 and 2-5, between 1 and 5 cm in maximum diameter. All enrolled patients had to have at least 1 myoma that indented the endometrial cavity (type 1, 2 or 2-5).
Technique	The VizAblate system (Gynesonics Inc., US), which combines radiofrequency ablation with intrauterine sonography in 1 device was used.
Follow up	**Mean 64.4 months (range 57 to 73)**
Conflict of interest/source of funding	The author is a consultant to Gynesonics Inc. The study institution received research support from Gynesonics.

Analysis

Follow-up issues: Of the 23 patients treated in the FAST-EU trial at the study site, 17 (74%) were able to be contacted and provided informed consent to be enrolled in the VITALITY study.

Study design issues: Retrospective, single-centre cohort study. The aim of the study was to assess long-term (more than 5 years) clinical outcomes of the procedure. Symptoms were assessed using the UFS-QoL. The EQ-5D was used to obtain a descriptive profile of patient health status. This includes a visual analogue scale from 0 to 100, in which higher scores represent better health states and 5 questions about mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. These are scored from 1 to 5 (ranging from 'no problem' to 'extreme problems' and then converted to create a summary index that is representative of overall health. Patients were also queried about surgical reinterventions for abnormal uterine bleeding and any pregnancies.

Study population issues: The mean baseline symptom severity score was 64.9. The mean number of ablated fibroids per patient was 2.1 and the mean diameter of ablated fibroids was 2.5 cm. There is some patient overlap with Brölmann H (2016).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **17** **Mean symptom severity score** • Baseline=64.9±16.9 • Follow up=27.6±36.1; p=0.002 **Mean health-related quality of life score** • Baseline=27.2±22.4 • Follow up=76.0±32.6; p=0.0001 There were improvements in all 6 dimensions (concern, activities, energy and mood, control, self-consciousness, and sexual function). **Mean EQ-5D visual analogue scale scores** • Baseline=70.3±22.2 • Follow up=79.8±25.5; p=0.042 **Mean EQ-5D summary index** • Baseline=0.79±0.23 • Follow up=0.83±0.26; p=0.599 **Surgical reinterventions=11.8% (2/17)** There were no surgical reinterventions during the first 3.5 years of follow up. Two patients had a hysterectomy: 1 at 3.5 years after the ablation procedure and the other about 4 years after ablation. Both hysterectomies were done for abnormal uterine bleeding. No patients had medical treatment with selective progesterone-receptor modulators, gonadotropin-releasing hormone agonists, or any other drugs used to treat abnormal uterine bleeding. **Pregnancies** There was a single pregnancy during the first year after ablation, which resulted in a term delivery by elective repeat caesarean section.	No safety data were reported.
Abbreviations used: EQ-5D, EuroQoL 5-dimension questionnaire.	

Study 6 Bongers M (2019)

Details

Study type	**Case series (the OPEN clinical trial)**
Country	UK, the Netherlands, Switzerland, Germany
Recruitment period	2017 to 2018
Study population and number	**n=37** **Patients with symptomatic uterine fibroids**
Age	Mean 42 years
Patient selection criteria	Inclusion criteria: age 18 years or over, at least 1 submucous myoma (type 1 or 2) or transmural fibroid (type 2-5). Exclusion criteria: pre-existing adhesions within the endometrial cavity or the existence of type 0 fibroids or endometrial polyps of any size.
Technique	The Sonata system (Gynesonics Inc., US) was used. No adjunctive measures that would prevent adhesiogenesis or concomitant procedures that would promote adhesions (such as dilation and curettage) were permitted. There were no set limits on fibroid size or number.
Follow up	**6 weeks**
Conflict of interest/source of funding	The institutions of participating investigators received research support from Gynesonics Inc. Two authors are consultants for Gynesonics. One author is an advisory board member for Hologic, Olympus, Ethicon and Gedeon Richter.

Analysis

Follow-up issues: Two patients withdrew from the study after treatment because they did not return for a second-look hysteroscopy. One patient was excluded from the analysis because of an unevaluable hysteroscopy video.

Study design issues: Prospective multicentre case series. The primary endpoint was the incidence of newly formed adhesions after treatment as ascertained by second-look hysteroscopy at 6 weeks. Additional analyses included adverse events, treatment recovery duration and any surgical reinterventions. Videos of baseline and follow-up hysteroscopy were scored by a committee of 3 independent readers, using the European Society of Hysteroscopy intrauterine adhesion classification system.

Study population issues: The mean number of ablated fibroids per patient was 1.4 and the mean ablated fibroid diameter was 3.4 cm (range 1 to 8). Of the 34 patients with evaluable hysteroscopies, 6 had apposing endometrial cavity-indenting fibroids that were treated.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 37

Mean length of stay=22 hours (range 2.2 to 69.9)

There were no reinterventions reported in the trial.

Return to normal functions (days)
<table>
<tr><th>Parameter</th><th>n</th><th>mean±sd</th><th>median</th><th>Min, max</th></tr>
<tr><td>Activities</td><td>31</td><td>3.8±3.13</td><td>3.0</td><td>0, 13</td></tr>
<tr><td>Diet</td><td>33</td><td>0.6±0.66</td><td>1.0</td><td>0, 2</td></tr>
<tr><td>Sleep</td><td>33</td><td>0.8±1.39</td><td>0.0</td><td>0, 6</td></tr>
<tr><td>Urinary function</td><td>32</td><td>0.4±0.80</td><td>0.0</td><td>0, 4</td></tr>
<tr><td>Occurrence of bowel movement</td><td>33</td><td>1.2±1.82</td><td>1.0</td><td>0, 7</td></tr>
</table></td><td>One patient had a serious adverse event that was deemed to be unrelated to the device or procedure. The patient was admitted 18 days after ablation with nonspecific abdominal pain. CT and ultrasound were both normal and the event was assessed as not gynaecological in origin. No other adverse events were reported.

Of the 34 patients with evaluable hysteroscopies, none had signs of de novo adhesiogenesis at 6 weeks.</td></tr>
<tr><td colspan="2">Abbreviations used: SD, standard deviation.</td></tr>
</table>

Study 7 Bends R (2018)

Details

Study type	**Case report**
Country	Germany
Recruitment period	Not reported
Study population and number	**n=1** **Pregnancy and delivery after transcervical radiofrequency ablation**
Age	33-year old woman
Patient selection criteria	Not applicable
Technique	The Sonata system (Gynesonics Inc., US), which integrates intrauterine ultrasound imaging with a radiofrequency treatment device, was used. The procedure was done under general anaesthesia.
Follow up	**33 months**
Conflict of interest/source of funding	Two authors are consultants for Gynesonics Inc. and 1 author is the medical director at Gynesonics.

Key efficacy and safety findings

Efficacy	Safety
The patient presented with heavy menstrual bleeding attributable to uterine fibroids. Transvaginal sonography revealed a 28-mm submucous fibroid (FIGO type 2). The fibroid was ablated using transcervical radiofrequency ablation and intrauterine sonography. 2 weeks after the ablation procedure, contrast-enhanced MRI indicated that 60% of the fibroid was no longer perfused. At 24 months, imaging revealed no residual fibroid and the patient noted eumenorrhoea. 33 months after ablation, the patient noted secondary amenorrhoea and was confirmed to be pregnant. She went into labour at 39 weeks of gestation and had a normal spontaneous vaginal delivery of a liveborn female infant. There were no complications.	There were no intraoperative complications. There were no postoperative adverse events other than transient symptoms such as mild uterine cramping and minimal bleeding.

Study 8 Bradley LD (2019)

Details

Study type	**Systematic review and meta-analysis**
Country	Location of study sites: 'intercontinental', Mexico, US, Canada, Germany, Italy, Korea, Latin America, Norway, Denmark, China, Spain
Recruitment period	Search date: May 2019. Treatment periods ranged from 2003 to 2018
Study population and number	**n=1,283 (32 articles)**: 19 articles on laparoscopic RFA, 8 on transvaginal RFA, 5 on transcervical RFA **Patients with symptomatic uterine fibroids**
Age	Median 42 years
Patient selection criteria	Prospective studies of RFA for symptomatic uterine fibroid treatment were eligible for inclusion. Case reports and studies with fewer than 10 patients were excluded, as were studies in which patients had concomitant surgery and studies that reported no main outcomes. No date or language restrictions were applied to the searches.
Technique	Laparoscopic, transvaginal or transcervical RFA.
Follow up	**Median 12 months (range from in-hospital to 5.3 years)**
Conflict of interest/source of funding	Gynesonics Inc. provided funding for the study. One author reports principal investigator support from Bayer, scientific advisory boards for AbbVie, Bayer, Allergan and PCORI, and royalties from Elsevier and Wolter Kluwer, all unrelated to the submitted work. One author reports consultancy with Ethicon Endo, Medtronic, Cooper Surgical, and Olympus, all unrelated to the submitted work. One author reports consultancy with Gynesonics, related to the submitted work.

Analysis

Study design issues: The conduct, analysis and reporting of the review adhered to the Preferred reporting Items for Systematic Reviews and Meta-analyses (PRISMA). Only prospective studies were included. 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 and health-related quality of life on the UFS-QoL and surgical reinterventions. The National Institute of Health assessment tool was used to evaluate the methodological quality of eligible studies. Among the 20 prospective primary studies (reported in 32 articles), study quality was rated as good or fair for 19 of the 20 studies.

Study population issues: The number of treated fibroids ranged from 1 to 5 (median 1.7) per patient, and fibroid volume ranged from 10 cm^3 to 305 cm^3 (median 74 cm^3). Baseline UFS-QoL scores ranged from 22 to 77 for health-related quality of life (median 49) and 32 to 76 for symptom severity score (median 55).

Other issues: All the included studies on transcervical RFA are also described separately in table 2.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 1,283

Random effects meta-analysis procedure and recovery results, weighted means (95% CI)
<table>
<tr><th></th><th>Pooled result</th><th>Transcervical RFA</th><th>Laparoscopic RFA</th><th>Transvaginal RFA</th></tr>
<tr><td>Procedure time (minutes)</td><td>49 (41 to 56)</td><td>44 (36 to 51)</td><td>73 (56 to 91)</td><td>24 (20 to 28)</td></tr>
<tr><td>Time to discharge (hours)</td><td>8.2 (6.3 to 10.0)</td><td>2.5 (2.3 to 2.7)</td><td>10.7 (5.9 to 15.5)</td><td>2.5 (2.4 to 2.6)</td></tr>
<tr><td>Time to return to normal activities (days)</td><td>5.2 (3.3 to 7.1)</td><td>3.3 (1.1 to 5.4)</td><td>9.0 (3.8 to 14.1)</td><td>-</td></tr>
<tr><td>Time to return to work (days)</td><td>5.1 (3.7 to 6.5)</td><td>3.6 (3.1 to 4.1)</td><td>6.5 (3.8 to 9.2)</td><td>-</td></tr>
</table>
There was substantial heterogeneity among studies for each of these outcomes (I^2 ranged from 85% to more than 99%; all p<0.001).

Mean decrease in fibroid volume by follow-up period
• 3 months=47%, I^2=54% (p=0.02)
• 6 months=55%, I^2=0% (p=0.44)
• 12 months=66%, I^2=43% (p=0.07)
• >12 months=71%, I^2=0% (p=0.42)

In metaregression that adjusted for differences in baseline fibroid volume, using laparoscopic RFA as the reference comparator, fibroid volume reduction was 4% greater with transcervical RFA (p=0.81) and 10% greater with transvaginal RFA (p=0.47) at 12 months.

Increase in health-related quality of life scores by follow-up period
• 3 months=30 points
• 6 months=37 points
• 12 months=39 points
• >12 months=31 points
p<0.001 compared with baseline for all periods (I^2 ranged from 86% to 99%; all p<0.001)

Decrease in symptom severity scores by follow-up period
• 3 months=29 points
• 6 months=36 points
• 12 months=42 points
• >12 months=40 points
p<0.001 compared with baseline for all periods (I^2 ranged from 46% to 99%; all p≤0.06)

Cumulative rate of reintervention at 1, 2 and 3 years=4.2%, 8.2% and 11.5%

Reintervention rate at 12 months=2.7% for transcervical RFA, 3.8% for laparoscopic RFA and 5.3% for transvaginal RFA.</td><td>No safety data were reported.</td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval; RFA, radiofrequency ablation</td></tr>
</table>

Study 9 Lukes A (2020)

Details

Study type	**Cohort study (longer term follow up of SONATA trial)**
Country	US and Mexico
Recruitment period	2015 to 2016
Study population and number	**n=147** Women with symptomatic uterine fibroids
Age	Mean 43 years (range 31 to 50)
Patient selection criteria	Premenopausal women aged 25 years to 50 years with regular and predictable menstrual cycles, objective evidence of heavy menstrual bleeding, and with up to 10 fibroids of International Federation of Gynecology and Obstetrics (FIGO) types 1, 2, 3, 4 or 2-5 (transmural), each of 1 to 5 cm in diameter. At least 1 fibroid was required to have either indented or abutted the endometrial cavity (FIGO type 1, 2, 3 or 2-5). Women were excluded if they expressed a desire for future pregnancy, had any type 0 fibroids 1.0 cm or larger or endometrial polyps 1.5 cm or larger or multiple polyps of any size, bulk symptoms attributable to subserous fibroids, prior confounding procedures (endometrial ablation, uterine artery embolisation, uterine artery occlusion, or hyperthermic ablation of fibroids), uterine volume 1,000 cm^3 or above, presence of tubal implants for sterilisation or clinically significant adenomyosis.
Technique	The Sonata system (Gynesonics Inc., US), which integrates intrauterine ultrasound imaging with a radiofrequency treatment device, was used. 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.
Follow up	**3 years**
Conflict of interest/source of funding	Gynesonics Inc. provided funding for the study. The institutions of the authors received research support from Gynesonics. for participation in the SONATA trial. The authors have received travel and lodging expenses for attendance at investigator meetings.

Analysis

Follow-up issues: Follow-up data at 3 years were available for 90% (130/147) of patients.

Study design issues: Prospective, multicentre cohort study. Outcomes included surgical reintervention rates for heavy menstrual bleeding, symptom severity score (SSS) and health-related quality of life (HRQoL) subscales of the Uterine Fibroid Symptom and Quality-of-Life Questionnaire. Scores were reported on a scale from 0 to 100 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. The minimal clinically important difference was considered to be a 10-point decrease for SSS, a 20-point increase for HrQoL, and a 0.074-point increase for EQ-5D.

Study population issues: The mean number of fibroids ablated per patient was 3. At baseline, all patients had a general health status below the 25th percentile compared with sex- and age-matched norms, as measured by the EQ-5D.

Other issues: Patient overlap with Chudnoff S (2019) and Miller C (2019).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **130** **Mean symptom severity score** • Baseline=55±19 • 3-year follow up=22±21; p<0.001 **Mean health-related quality of life scores** • Baseline=40±21 • 3-year follow up=83±23; p<0.001 **Mean EQ-5D scores** • Baseline=0.72±0.21 • 3-year follow up=0.88±0.16; p<0.001 **Patient satisfaction with treatment at 3 years=94% (99/105)** (71% of patients reported that they were very satisfied, 14% were moderately satisfied, 9% were somewhat satisfied) **88% (92/105) of patients reported reduced fibroid symptoms at 3 years.** **Mean percentage of missed work time** • Baseline=2.9% • 3-year follow up=1.4%; p<0.001 **Mean overall percentage of work impairment** • Baseline=51% • 3-year follow up=12%; p<0.001 **Mean percentage of activity impairment because of fibroid symptoms** • Baseline=58% • 3-year follow up=14%; p<0.001 **3-year rate of surgical intervention for heavy menstrual bleeding calculated by the binomial and Kaplan-Meier methods were 9.2% and 8.2% respectively.** **Pregnancy** Two pregnancies were reported. One woman delivered at 38 weeks gestation by elective repeat caesarean section 31 months after the procedure. One miscarriage was reported in a 40-year old patient 29 months after the procedure.	There were no serious complications or adverse events related to the device or procedure during the second or third year of patient follow up.
Abbreviations used: EQ-5D, EuroQoL 5-dimension questionnaire; UFS-QoL, Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire	

Validity and generalisability of the studies

- No comparative studies were identified.
- There are published data from the UK.
- One small study reported outcomes from long-term follow up (mean 64 months) [5] and 1 case series had 3-year follow-up[9].
- All the studies used the Sonata system (previously called VizAblate).
- Most studies excluded women who desired future pregnancy.
- The studies included a range of fibroid types (International Federation of Gynecology and Obstetrics type 1, 2, 3, 4, and 2 to 5 [transmural]).
- Inclusion criteria of the studies required at least 1 fibroid to have either indented or abutted the endometrial cavity.
- Women with type 0 fibroids were excluded from the studies.

Existing assessments of this procedure

A Health Technology Assessment on 'Intrauterine Ultrasound-Guided Transcervical Radiofrequency Ablation' was published by the Ludwig Boltzmann Institute in 2020.[10] The report included 3 single-arm case series studies (FAST-EU, IDE and OPEN Trial) published in 7 publications (234 patients). It concluded that 'the current evidence is not sufficient to prove that TFA is more effective and equally safe or equally effective, but safer than alternative uterine preserving interventions for symptomatic fibroids. Consequently, inclusion in the hospital benefit catalogue is currently not recommended.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Ultrasound-guided high-intensity transcutaneous focused ultrasound for symptomatic uterine fibroids. NICE interventional procedures guidance 657 (2019). Available from http://www.nice.org.uk/guidance/IPG657

- Hysteroscopic morcellation of uterine leiomyomas (fibroids). NICE interventional procedures guidance 522 (2015). Available from http://www.nice.org.uk/guidance/IPG522
- Magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids. NICE interventional procedures guidance 413 (2011). Available from http://www.nice.org.uk/guidance/IPG413
- Uterine artery embolisation for fibroids. NICE interventional procedures guidance 367 (2010). Available from http://www.nice.org.uk/guidance/IPG367
- Magnetic resonance (MR) image-guided percutaneous laser ablation of uterine fibroids. NICE interventional procedures guidance 30 (2003). Available from http://www.nice.org.uk/guidance/IPG30
- Laparoscopic laser myomectomy. NICE interventional procedures guidance 23 (2003). Available from http://www.nice.org.uk/guidance/IPG23

NICE guidelines

- Heavy menstrual bleeding: assessment and management. NICE guideline 88 (2018). Available from http://www.nice.org.uk/guidance/NG88

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One professional expert questionnaire for transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids was submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- Ongoing trials
  - Transcervical Radiofrequency Ablation of Uterine Fibroids Global Registry (SAGE) (NCT03118037); Cohort study; Germany; n=100; Estimated Study Completion Date: December 2023

References

1. Chudnoff S, Guido R, Roy K et al. (2019) Ultrasound-guided transcervical ablation of uterine leiomyomas. Obstetrics and Gynecology 133: 13–22
2. Miller C, Osman K (2019) Transcervical radiofrequency ablation of symptomatic uterine fibroids: 2-year results of the SONATA pivotal trial. Journal of Gynecologic Surgery 35: 345–9
3. Brölmann H, Bongers M, Garza-Leal J et al. (2016) The FAST-EU trial: 12-month clinical outcomes of women after intrauterine sonography-guided transcervical radiofrequency ablation of uterine fibroids. Gynecological Surgery 13: 27–35
4. Huirne J, Brooks E (2018) Improvement in health utility after transcervical radiofrequency ablation of uterine fibroids with the sonata system: health utility after radiofrequency ablation. European Journal of Obstetrics & Gynecology and Reproductive Biology 224: 175–80
5. Garza-Leal J (2019) Long-term clinical outcomes of transcervical radiofrequency ablation of uterine fibroids: the VITALITY study. Journal of Gynecologic Surgery 35: 19–23
6. Bongers M, Quinn SD, Mueller MD et al. (2019) Evaluation of uterine patency following transcervical uterine fibroid ablation with the Sonata system (the OPEN clinical trial). European Journal of Obstetrics & Gynecology and Reproductive Biology 242: 122–5
7. Bends R, Toub DB, Römer T (2018) Normal spontaneous vaginal delivery after transcervical radiofrequency ablation of uterine fibroids: a case report. International Journal of Women's Health 10: 367–9
8. Bradley LD, Pasic RP, Miller LE (2019) Clinical performance of radiofrequency ablation for treatment of uterine fibroids: systematic review and meta-analysis of prospective studies. Journal of Laparoendoscopic & Advanced Surgical Techniques 29: 1–11
9. Lukes A, Green MA (2020) Three-year results of the SONATA pivotal trial of transcervical fibroid ablation for symptomatic uterine myomata. Journal of Gynecologic Surgery
10. Lambert R and Strohmaier C (2020) Intrauterine Guided Transcervical Radiofrequency Ablation – Systematic Review. Decision Support Document No. 120; 2020. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	09/11/2020	Issue 11 of 12, November 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	09/11/2020	Issue 11 of 12, November 2020
MEDLINE (Ovid)	09/11/2020	1946 to November 06, 2020
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	09/11/2020	1946 to November 06, 2020
EMBASE (Ovid)	09/11/2020	1974 to 2020 Week 45
International HTA database (INAHTA)	09/11/2020	-

Trial sources searched 08/08/2019

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched 08/08/2019

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Uterine Neoplasms/
2	Leiomyoma/
3	Myofibroma/
4	Myoma/
5	(uter* adj4 (neoplasm* or tumour* or tumor* or growth*)).tw.

6 (fibroma* or myofibroma* or leiomyoma* or leimyoma* or angioleiomyoma* or angiomyoma* or myoma*).tw.
7 (fibromyoma* or fibroleiomyoma*).tw.
8 ((fibroid* or myoma*) adj4 (tumour* or tumor* or uter* or submucos* or subseros* or intramural* or pedunculated or cervical or cervix or womb)).tw.
9 or/1-8
10 exp Radiofrequency Ablation/
11 (radiofrequen* adj4 ablat*).tw.
12 (radio frequen* adj4 ablat*).tw.
13 (radio-frequen* adj4 ablat*).tw.
14 (rf adj4 ablat*).tw.
15 rfa.tw.
16 exp Ultrasonic Therapy/
17 Ablation Techniques/
18 (Transcervic* or intrauter*).tw.
19 (ultrasound* or ultrason* or sonograph* or ablat*).tw.
20 18 and 19
21 sonata.tw.
22 9 and 21
23 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 20 (55019)
24 9 and 23
27 22 or 24
28 animals/ not humans/
29 27 not 28

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in table 2
Bongers M, Gupta J, Gara-Leal JG et al. (2019) The INTEGRITY trial: preservation of uterine-wall integrity 12 months after transcervical fibroid ablation with the Sonata system. Journal of Gynecologic Surgery 35: 299–303	Case series n=50 FU=12 months	No areas on MRI indicated any loss of uterine wall integrity, compared with baseline imaging. Transcervical fibroid ablation with the Sonata system was associated with preservation of uterine wall integrity in this patient cohort.	Secondary analysis of FAST-EU trial, which is described in table 2.
Bongers M, Brölmann H, Gupta J et al. (2015) Transcervical, intrauterine ultrasound-guided radiofrequency ablation of uterine fibroids with the VizAblate® System: three- and six-month endpoint results from the FAST-EU study. Gynecological Surgery 12: 61–70	Case series n=50 FU=6 months	Perfused fibroid volumes were reduced at 3 months by an average of 68.8±27.8 % ($p<0.0001$). At 6 months, mean menstrual pictogram and symptom severity scores decreased by 60.8±38.2 and 59.7±30.4%, respectively; the mean HRQOL score increased by 263±468%. There were 2 serious adverse events (overnight admissions for abdominal pain and bradycardia, respectively) and no surgical reinterventions. These 6-month results suggest that the VizAblate System is safe and effective in providing relief of abnormal uterine bleeding associated with fibroids, with appropriate safety and a low reintervention rate.	A more recent report with longer follow up of the same study is included (Brölmann H, 2016).
Brooks EA, Singer AM, Delvadia DR et al. (2020) The choices study: Facility level comparative cost, resource utilization, and outcomes analysis of myomectomy compared to transcervical fibroid ablation. ClinicoEconomics and Outcomes Research 12: 299-306	Non-randomised comparative study n=88	Transcervical fibroid ablation (TFA) has a significantly shorter operating room time and length of stay than myomectomy for the treatment of symptomatic uterine fibroids. All procedure, anaesthesia, 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	The primary outcomes relate to cost and use of resources.

		compared to myomectomy, including inpatient, abdominal, or laparoscopic myomectomy.	
Garza-Leal JG, Leon IH, Toub D (2014) Pregnancy after transcervical radiofrequency ablation guided by intrauterine sonography: Case report. Gynecological Surgery 11: 145–9	Case report n=1	This reports the outcome of the first viable pregnancy after intrauterine sonography-guided radiofrequency ablation of a uterine fibroid.	A case report of pregnancy, which is already described in table 2.
Garza-Leal JG, Toub D, Leon IH et al. (2011) Transcervical, intrauterine ultrasound-guided radiofrequency ablation of uterine fibroids with the VizAblate system: safety, tolerability, and ablation results in a closed abdomen setting. Gynecological Surgery 8: 327–34	Case series n=19	There were no complications or thermal serosal injury. For fibroids 5 cm or smaller, 67% of the fibroid volume was ablated (range 15 to 100%); median 75%).	More recent and larger studies are included.
Hudgens J, Johns DA, Lukes AS et al. (2019) 12-month outcomes of the US patient cohort in the SONATA pivotal IDE trial of transcervical ablation of uterine fibroids. International Journal of Women's Health 11: 387–94	Case series n=125 FU=12 months	This analysis of US patients in the SONATA pivotal IDE trial demonstrates results consistent with those in the full cohort. TFA with Sonata significantly reduced fibroid symptoms with a low surgical reintervention rate through 12 months. These results support the efficacy and safety of the Sonata system as a first-line treatment for women affected by symptomatic uterine fibroids.	Results from the full cohort are included in table 2 (Chudnoff S, 2019).
Pschadka G, Engelhardt M, Niehoff C et al. (2019) Term delivery in an infertile patient after transcervical radiofrequency fibroid ablation and assisted reproductive technology. Journal of Gynecologic Surgery 35: 253–5	Case report n=1	This is the first report of a pregnancy and delivery in an infertile couple who underwent transcervical radiofrequency ablation of a uterine fibroid followed by assisted reproduction.	A case report of pregnancy, which is already described in table 2.
Sandberg EM, Tummers FHMP, Cohen SL et al. (2018) Reintervention risk and quality of life outcomes after uterine-sparing interventions for fibroids: a systematic review and meta-analysis. Fertility and Sterility 109: 698-707e1	Systematic review n=17,789 (85 articles)	Stratified by treatment options, reintervention risk after 60 months was 12.2% (95% confidence interval [CI] 5.2% to 21.2%) for myomectomy, 14.4% (95% CI 9.8% to 19.6%) for UAE, 53.9% (95% CI 47.2% to 60.4%) for HIFU, and 7% (95%CI 4.8% to 9.5%) for hysteroscopy. For the other treatment options, no studies were available at 60months. For quality of life outcomes, symptoms improved after	Review only includes 1 study on transcervical ultrasound-guided radiofrequency ablation.

		treatment for all options. The HIFU procedure had the least favourable outcomes.	
Taheri M, Galo L, Potts C et al. (2019) Nonresective treatments for uterine fibroids: a systematic review of uterine and fibroid volume reductions. International Journal of Hyperthermia 36: 295-301	Systematic review 81 articles	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 randomised or comparative, would enable definitive conclusions.	Review does not present separate results for transcervical radiofrequency ablation.
Toub DB (2017) A new paradigm for uterine fibroid treatment: transcervical, intrauterine sonography-guided radiofrequency ablation of uterine fibroids with the Sonata system. Current Obstetrics and Gynecology Reports 6: 67-73	review	The Sonata System is a promising treatment modality for uterine fibroids. As an incisionless, minimally invasive treatment that does not require general anaesthesia or hospitalisation, it has the potential for redefining the current paradigm for management of symptomatic fibroids.	The relevant studies cited in the review are already included in table 2 or the appendix.