



Contents lists available at ScienceDirect

# European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: [www.elsevier.com/locate/ejogrb](http://www.elsevier.com/locate/ejogrb)

Full length article

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



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

<sup>a</sup> Máxima Medisch Centrum, Veldhoven, the Netherlands<sup>b</sup> Grow-School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands<sup>c</sup> Imperial College, London, United Kingdom<sup>d</sup> St. Mary's Hospital, London, United Kingdom<sup>e</sup> Universitätsspital Bern, Bern, Switzerland<sup>f</sup> University of Tübingen, Tübingen, Germany<sup>g</sup> University Medical Centre Mannheim, Heidelberg University, Mannheim, Germany<sup>h</sup> Department of Gynecology, Federal Fluminense University–UFF, Niterói, Brazil<sup>i</sup> Obstetrics and Gynecology, Stamford Hospital, Stamford, Connecticut, United States<sup>j</sup> Amsterdam University Medical Centre, Amsterdam, the Netherlands<sup>k</sup> University Hospital for Gynecology, Pius-Hospital, University Medicine Oldenburg, Germany<sup>l</sup> Carl von Ossietzky University Oldenburg, Germany

### ARTICLE INFO

#### Article history:

Received 3 March 2019

Received in revised form 4 September 2019

Accepted 18 September 2019

#### Keywords:

Fibroids

Intrauterine adhesions

Radiofrequency ablation

Sonata

Intrauterine sonography

### 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  $3.4 \pm 1.8$  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.

© 2019 Elsevier B.V. All rights reserved.

### 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].

\* Corresponding author at: Máxima Medisch Centrum, Postbus 7777, 5500 MB Veldhoven, the Netherlands.

E-mail address: [m.bongers@mmc.nl](mailto:m.bongers@mmc.nl) (M. Bongers).

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  $22.1 \text{ h} \pm 17.99 \text{ h}$  (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 assessable 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 ≤ 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

SC and MB are consultants for Gynesonics. Inc. AT is an advisory board member for Hologic, Olympus, Ethicon and Gedeon Richter. The institutions of participating investigators (MB, SQ, MM, BK, BT, MS, RDW) received research support from Gynesonics.

## Acknowledgements

The authors thank David B. Toub, MD, MBA, Medical Director of Gynesonics, and Taraneh G. Farazi, PhD, VP of Clinical Affairs at Gynesonics for contributing to the review of this manuscript.

## 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>.

## References

- [1] Zimmermann A, Bernuit D, Gerlinger C, Schaeffers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. *BMC Womens Health* 2012;12:6.
- [2] Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol* 2003;188:100–7.
- [3] Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. *Am J Obstet Gynecol* 2012;206(211):e1–9.
- [4] Lefebvre G, Vilos G, Allaire C, et al. The management of uterine leiomyomas. *J Obstet Gynaecol Can* 2003;25:396–418.
- [5] Yang JH, Chen MJ, Wu MY, Chao KH, Ho HN, Yang YS. Office hysteroscopic early lysis of intrauterine adhesion after transcervical resection of multiple apposing submucous myomas. *Fertil Steril* 2008;89:1254–9.
- [6] Berman JM. Intrauterine adhesions. *Semin Reprod Med* 2008;26:349–55.
- [7] Li C, Wei ML, Lin XN, Huang QX, Huang D, Zhang SY. Effects of early intervention of second-look office hysteroscopy in the prevention of adhesion reformation for moderate-severe Asherman's syndrome. *Zhonghua Yi Xue Za Zhi* 2013;93:3617–9.
- [8] Lin B, Akiba Y, Iwata Y. One-step hysteroscopic removal of sinking submucous myoma in two infertile patients. *Fertil Steril* 2000;74:1035–8.
- [9] Roy KK, Singla S, Baruah J, Sharma JB, Kumar S, Singh N. Reproductive outcome following hysteroscopic myomectomy in patients with infertility and recurrent abortions. *Arch Gynecol Obstet* 2010;282:553–60.
- [10] Yang JH, Chen MJ, Chen CD, Chen SU, Ho HN, Yang YS. Optimal waiting period for subsequent fertility treatment after various hysteroscopic surgeries. *Fertil Steril* 2013;99:2092–6 e2093.
- [11] Fischer K, McDannold NJ, Tempany CM, Jolesz FA, Fennessy FM. Potential of minimally invasive procedures in the treatment of uterine fibroids: a focus on magnetic resonance-guided focused ultrasound therapy. *Int J Womens Health* 2015;7:901–12.
- [12] Garza-Leal JG, Toub D, León IH, et al. Transcervical, intrauterine ultrasound-guided radiofrequency ablation of uterine fibroids with the VizAblate System: safety, tolerability, and ablation results in a closed abdomen setting. *Gynecol Surg* 2011;8:327–34.
- [13] Ghezzi F, Cromi A, Bergamini V, Scarperi S, Bolis P, Franchi M. Midterm outcome of radiofrequency thermal ablation for symptomatic uterine myomas. *Surg Endosc* 2007;21:2081–5.
- [14] Hahn M, Brucker S, Kraemer D, et al. Radiofrequency volumetric thermal ablation of fibroids and laparoscopic myomectomy: long-term follow-up from a randomized trial. *Geburtshilfe Frauenheilkd* 2015;75:442–9.
- [15] Iversen H, Dueholm M. Radiofrequency thermal ablation for uterine fibroids: long-term clinical outcomes and reinterventions. *J Minim Invasive Gynecol* 2017;24:1020–8.
- [16] Jones S, O'Donovan P, Toub D. Radiofrequency ablation for treatment of symptomatic uterine fibroids. *Obstet Gynecol Int* 2012;2012:194839.
- [17] Kim CW, Shim HS, Jang H, Song YG. The effects of uterine artery embolization on ovarian reserve. *Eur J Obstet Gynecol Reprod Biol* 2016;206:172–6.
- [18] Kong CY, Meng L, Omer ZB, et al. MRI-guided focused ultrasound surgery for uterine fibroid treatment: a cost-effectiveness analysis. *AJR Am J Roentgenol* 2014;203:361–71.
- [19] Lee BB, Yu SP. Radiofrequency ablation of uterine fibroids: a review. *Curr Obstet Gynecol Rep* 2016;5:318–24.
- [20] Recaldini C, Carrafiello G, Lagana D, et al. Percutaneous sonographically guided radiofrequency ablation of medium-sized fibroids: feasibility study. *AJR Am J Roentgenol* 2007;189:1303–6.
- [21] Stewart EA, Rabinovici J, Tempany CM, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. *Fertil Steril* 2006;85:22–9.
- [22] Stewart EA, Gostout B, Rabinovici J, Kim HS, Regan L, Tempany CM. Sustained relief of leiomyoma symptoms by using focused ultrasound surgery. *Obstet Gynecol* 2007;110:279–87.
- [23] AAGL practice report: practice guidelines for management of intrauterine synechiae. *J Minim Invasive Gynecol* 2010;17:1–7.
- [24] Bongers M, Brolmann H, Gupta J, Garza-Leal JG, Toub D. Transcervical, intrauterine ultrasound-guided radiofrequency ablation of uterine fibroids with the VizAblate(R) System: three- and six-month endpoint results from the FAST-EU study. *Gynecol Surg* 2015;12:61–70.
- [25] Brolmann H, Bongers M, Garza-Leal JG, 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.
- [26] Garza Leal JG, Hernandez Leon I, Castillo Saenz L, Lee BB. Laparoscopic ultrasound-guided radiofrequency volumetric thermal ablation of symptomatic uterine leiomyomas: feasibility study using the halt 2000 ablation system. *J Minim Invasive Gynecol* 2011;18:364–71.
- [27] Toub DB. A new paradigm for uterine fibroid treatment: transcervical, intrauterine sonography-guided radiofrequency ablation of uterine fibroids with the sonata system. *Curr Obstet Gynecol Rep* 2017;6:67–73.
- [28] 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.