Uterine Fibroids

Treatment Advances with Focused Ultrasound

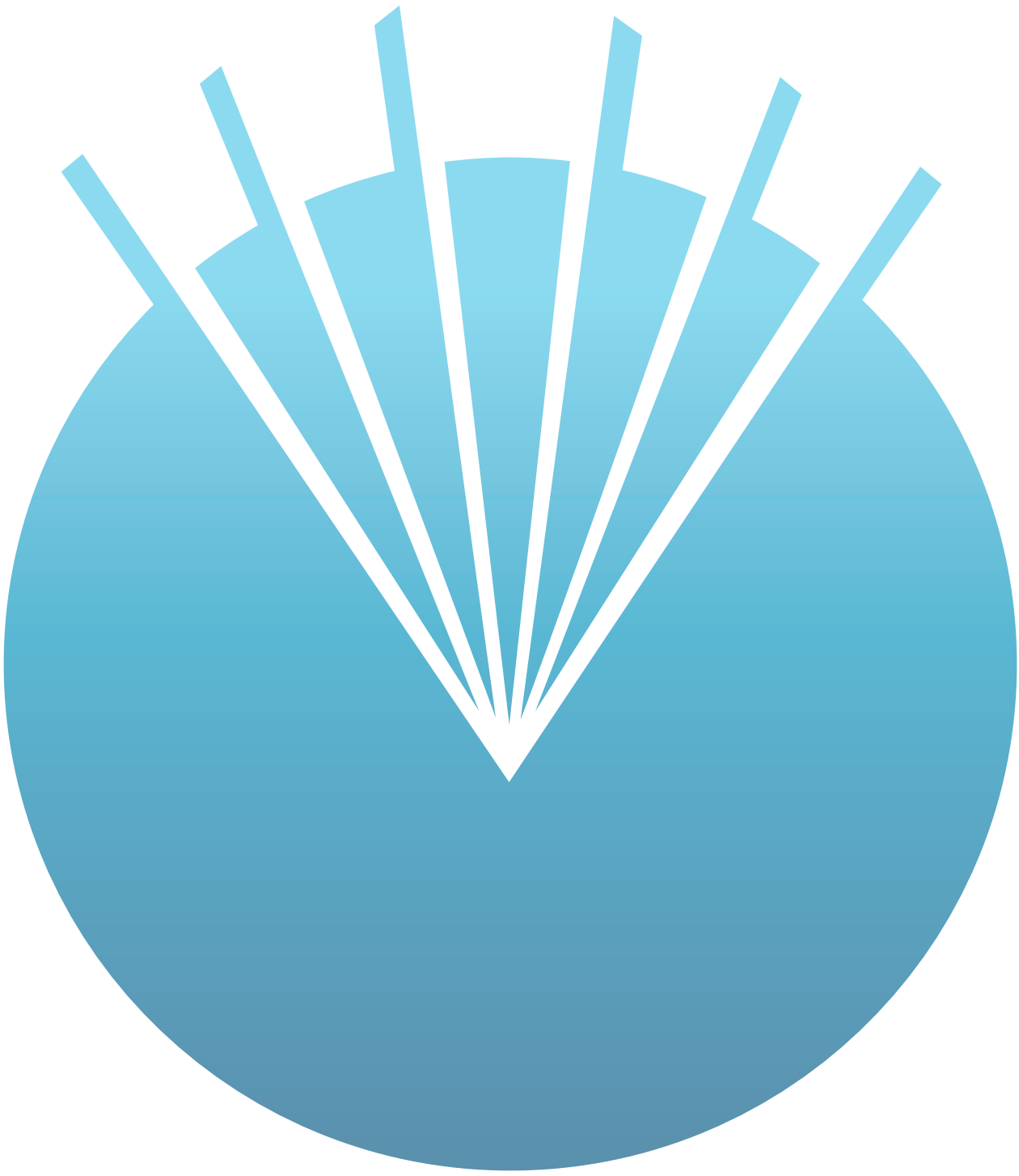
Virtual Workshop White Paper

16 April 2025 | 8 am – 12 pm ET

Sponsored by

Focused Ultrasound Foundation

Haifu



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Executive Summary

The Focused Ultrasound Foundation (FUSF), along with the meeting sponsor, Chongqing Haifu Medical Technology Co., Ltd., hosted a virtual workshop on Advances in the Focused Ultrasound Treatment of Uterine Fibroids on April 16, 2025. This invitational workshop brought together critical stakeholders, including researchers, clinicians, industry leaders, government representatives, and others, to share and combine knowledge to advance the field.

The primary goal was to discuss how to improve patient outcomes and reduce barriers to FUS access for fibroid treatments. This workshop focused on identifying gaps in knowledge and evidence to establish a roadmap for technological advancements, clinical trials, and commercialization strategies needed to bridge these gaps.

Despite 25 years of development and having fibroids as the first approved application for this technology, FUS has not achieved widespread adoption due to barriers including cost, MRI availability, and a healthcare landscape that undervalues women's health. Participants highlighted the exceptional safety profile of FUS compared with surgical alternatives, and comparable efficacy to established treatments including myomectomy and uterine artery embolization, while avoiding common surgical complications such as infection and bleeding.

Experts discussed technological optimization needs, including improved treatment planning, real-time monitoring, and workflow enhancements through artificial intelligence (AI) integration. A significant focus was placed on the the role of FUS versus other treatment modalities, in particular myomectomy, for fertility. Research priorities were identified, including developing unified prediction models for patient selection, standardized imaging protocols, and investigating different FUS mechanisms of action, including histotripsy.

Regarding fertility preservation and optimization, the panel acknowledged the need for more data comparing FUS with surgical alternatives, though existing evidence suggests promising pregnancy outcomes. The commercialization discussion highlighted significant barriers to FUS adoption in the US, including a lack of insurance coverage (despite FDA approval in 2004). Potential strategies to enhance adoption include making FUS technology available in OB-GYN offices, focusing on adenomyosis as an additional treatment indication, and increasing patient education and advocacy.

We extend our sincere gratitude to the steering committee members below for generously contributing their time and expertise to create the agenda for the fibroid workshop. We would also like to extend our deep appreciation to **Elizabeth A. Stewart**, MD for her steadfast support and leadership in advancing the clinical adoption of focused ultrasound.

Martijn Boomsma, MD, PhD, *Isala Hospital Zwolle*
Peji Ghanouni, MD, PhD, *Stanford University*
Loes Knorren, MD, *Isala Hospital Zwolle*
Selva Supermaniam, MD, *Mahkota Medical Centre*
Rosie Xing, PhD, *Chongqing Haifu Medical Technology Co. Ltd.*

Sincerely,

Suzanne LeBlang, MD

Introduction

Suzanne LeBlang, MD, welcomed participants and thanked the meeting sponsor, Chongqing Haifu Medical Technology Co., Ltd. (Haifu Medical).

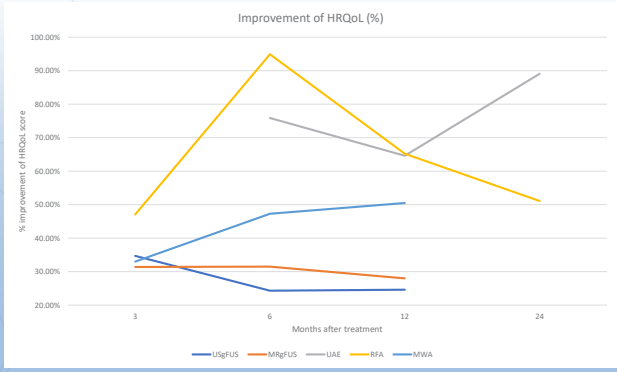
Throughout the workshop, attendees were encouraged to consider the four burning questions:

1. What is the safety and efficacy of high intensity FUS compared to other standard-of-care procedures?
2. How can we optimize the FUS treatment and what innovations are necessary to enhance the adoption into clinical practice?
3. In what patient population would FUS for fibroids be most beneficial, especially as it relates to preserving fertility?
4. How can we enhance commercialization of a FUS machine for fibroids and what regulatory and reimbursement issues need to be addressed?

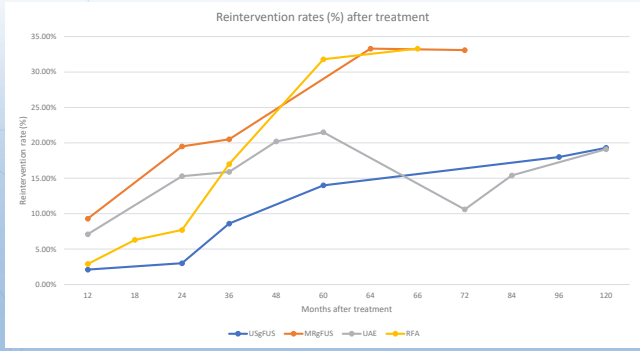
Suzanne LeBlang, MD, emphasized the exciting growth and innovation in using FUS to treat uterine fibroids. There are approximately eight companies in this space; three are MRI-guided and five are ultrasound-guided. From the 2024 FUS Foundation State of the Field report, nearly 50% of the now almost 1 million patients treated to date with FUS were for women's health issues, and most of these were for fibroid treatments.[1] These numbers support the importance of moving this clinical application for fibroids forward to treat millions of other women with uterine fibroids.

Elizabeth A. Stewart, MD, described the 25-year journey that began in 1999 with initial discussions about clinical trials for FUS to treat uterine fibroids. The first feasibility studies were published in 2003, demonstrating safe targeting of the uterus through the abdominal wall.[2] After significant publication challenges, their pivotal trial results were published, leading to FDA approval for the first device in 2004.[3] Despite years of development, this technology has not achieved wider adoption because of barriers, including MRI availability and a political landscape that undervalues women's health and quality of life compared to diseases that cause mortality.

HRQoL improvement



Reintervention rates



Safety profile

USgFUS
Minor: 78,0%
Major: 0,4%
N=27.053

MRgFUS
Minor: 35,7%
Major: 0,4%
N=2919

UAE
Minor: 87,8%
Major: 7,1%
N=434

RFA
Minor: 27,8%
Major: 0,5%
N=2945

MWA
Minor: 25,0%
Major: 0,3%
N=732

Discuss Safety and Efficacy of FUS Treatment Compared to Other Standard-of-Care Procedures

Moderators
Suzanne LeBlang, MD (Radiologist) and **Elizabeth A. Stewart**, MD (OB-GYN)

Dr. Stewart compared FUS (both USgFUS and MRgFUS) with other treatment modalities like uterine artery embolization (UAE), radiofrequency ablation (RFA), and microwave ablation (MWA). The data presented on the slides on pages 3-4 was compiled by Dr. **Loes Knorren**. These comparisons show that FUS treatments provide near equivalent symptom reduction and improvements in quality of life compared with more widely used procedures. Fibroid-specific treatments (including FUS) target individual fibroids, unlike UAE, which affects most fibroids simultaneously. Despite this, long-term data suggest that three-quarters of women receiving treatment of any kind do not need additional intervention and patients that received USgFUS had a lower reintervention rate compared with those treated with MRgFUS. Factors affecting retreatment include inadequate initial treatment, poor fibroid selection, mismatched expectations, and concurrent conditions like endometriosis or adenomyosis. Importantly, the safety profile of MRgFUS and USgFUS are equivalent at <1% major adverse events, similar to RFA and MWA, and are significantly better than UAE at 7%. FUS provides significant advantages over surgical procedures as it can be performed in an ambulatory environment without general anesthesia, decreased risk of infection, and has a lower risk of bleeding in patients who are often anemic at baseline.

Panelists
Jay Berman, MD (OB-GYN), **Gina Hesley**, MD (Radiologist), **Jae Seong Lee**, MD (OB-GYN), and **Miranda Veer-ten Kate**, PhD, MD (Radiologist)

Questions

Q: What is the safety and efficacy of FUS treatment compared to other standard-of-care procedures?

- The primary safety concern during procedures is preventing bowel injury by ensuring a safe beam path, while patient selection should also consider abdominal wall thickness, scars, and fibroid intensity on T2-weighted MRI to minimize complications such as abdominal wall edema.
- Another safety concern is managing skin heating through improved cooling systems, though scars remain problematic due to heat accumulation. To mitigate this risk, patients receive only moderate sedation to ensure they can still communicate pain or discomfort during treatment.
- From a gynecologist's perspective, FUS is considered a reasonably safe procedure with acceptable side effects, offering a broad therapeutic window like myomectomy, successfully treating various sizes, numbers, and types of fibroids as well as cases with adenomyosis, sometimes providing better outcomes than myomectomy itself. Dr. Lee shared case examples demonstrating the ability to treat many types and numbers of fibroids.

- FUS enables the successful treatment of many complex fibroid cases because it can deliver ultrasound energy at exact locations with precise dosage, unlike standard procedures with limited direct access to treatment sites, and may help patients avoid hysterectomy.
- FUS offers the ability to deliver energy without invasive access, avoiding the surgical and anesthetic risks of RFA procedures, while still providing comparable efficacy to myomectomy for treating various types and sizes of fibroids as well as adenomyosis cases. With RF ablation, the main complications to consider are risks of anesthesia, Foley catheter placement, and laparoscopic abscesses. Bowel injury and infection to the uterus are very rare.

Q: How can the issue of necrotic fibroid expulsion following FUS treatment be addressed, including patient preparation, potential hysteroscopic resection scheduling, and education of referring providers to prevent emergencies, particularly for intracavitary fibroids?

- The FIGO classification system is used to describe the location of fibroids. Submucosal fibroids include Type 0 pedunculated intracavitary, Type 1: <50% intramural, and Type 2 ≥50% intramural. Other fibroids are Type 3 intramural contacting endometrium, Type 4 intramural, Type 5 subserosal and ≥50% intramural, Type 6 subserosal and <50% intramural, Type 7 subserosal pedunculated, and Type 8 others, including cervical. FUS treatment is typically appropriate for treating submucosal or intramural fibroids but not for huge submucosal fibroids, diffuse uterine fibroids (myomatosis), or those exceeding certain size thresholds, as proper selection enables safe treatment with controlled power and precise focus away from intestinal or other sensitive tissues. Patients should be informed that they may experience vaginal bleeding as submucosal and intracavitary fibroids resolve and are instructed to seek medical attention if they have a fever or discharge, and then follow up every 3 months. Dilation and curettage is needed in some cases. RFA can treat type FIGO 0 or 1 fibroids beforehand with the administration of prophylactic antibiotics.
- Intracavitary fibroids can be treated with FUS based on size and location.
- It is essential to counsel patients about fibroid treatment expectations based on location, maintain communication to avoid surgery when possible, and make treatment decisions for intracavitary and submucosal fibroids (types 0 or 1) collaboratively with gynecologists, determining whether resection or RFA is appropriate, depending on fibroid size.

Q: Is MRI thermometry still considered an essential safety feature for FUS procedures, as was debated in the early 2000s, or has the evolution of instrumentation reduced its importance for monitoring tissue temperature during treatments?

- MRI thermometry has been a valuable safety feature for FUS procedures, allowing providers to precisely monitor energy delivery location and temperature increases, enhancing both treatment effectiveness and patient safety while reassuring patients about the procedure. Effective treatment and low recurrence rates depend on complete ablation of the entire lesion, as incomplete treatment leaves tissue that can regrow, causing symptom recurrence and potentially creating misunderstandings about the procedure's effectiveness.
- USgFUS may allow for more complete treatment. Instead of thermometry, gray

scale changes can guide treatment with all types of fibroids. Advances in software with USgFUS can help monitor the gray scale changes during the treatment.

- Type 1 fibroids require 400 watts for less than 24 seconds, type 2 fibroids need less than 32 seconds, and type 3 fibroids need more than 45 seconds per sonication but don't show increased effectiveness. No off-target heating is noted with USgFUS machines so MR thermometry is not not essential for safety.

Q: How has the high vascularity of uterine fibroids, which initially posed challenges for other treatments, become an advantage for FUS therapy compared with treating less vascular conditions like breast fibroadenomas?

- Advancements in FUS technology now allow practitioners to deliver precisely controlled energy and combine imaging techniques like MRI angiography with medical therapies to effectively treat even highly vascular fibroids and adenomyosis, representing significant progress in both equipment capabilities and provider techniques.
- Consider pretreatment of Type 3 fibroids with GnRH agonist for 2-3 months then treat with FUS
- Targeting vessels during FUS treatment of fibroids doesn't appear to produce the same post-procedural pain and fever profiles as UAE, with practitioners preferring to target the fibroid cells while monitoring patient pain responses under sedation.

In conclusion, the safety profile of FUS for fibroid treatment stands out as exceptional, avoiding bleeding risks, bowel injuries, and complications associated with myomectomy or hysterectomy. While efficacy wasn't fully discussed, technological advancements now enable the treatment of larger uteri and more complex cases than was possible when the technology was first introduced in clinical trials.

Summary

1. FUS has improved safety compared to surgical procedures, although care must be taken to avoid bowel injury and skin damage.
2. For submucosal and intracavitary fibroids, proper counseling of patients and referring physicians about the possibility of expulsion and infection is needed to ensure proper follow up which can be managed with antibiotics or at times, may necessitate a D&C.
3. Although MR thermometry is helpful to guide treatment safety and success, USgFUS systems can visualize the gray scale bubble cloud and software updates can help guide treatments.
4. Targeting the vessels with FUS is not relied on to treat fibroids and in practice does not seem to elicit the same pain as UAE.

Optimize FUS Treatment to Enhance the Adoption into Clinical Practice

Moderators
Martijn Boomsma, MD, PhD (Radiologist) and **Loes Knorren**, MD

Martijn Boomsma, MD, PhD, stated that the purpose of this session was to address expectation management for referring physicians, patients, and treatment teams alike. Too often, there are unexpected outcomes, both positive and negative. The goal is to improve the ability to predict treatment results, enabling physicians to inform patients about the expected non-perfused volume reduction, symptom improvement percentage, and whether these outcomes will be satisfactory for their specific case.

Loes Knorren, MD, explained that there is data with more patients available for USgFUS, however, there are higher quality randomized controlled trials with MRgFUS. In the Netherlands, FUS is still not a reimbursed therapy for treating uterine fibroids, mainly because there is not enough high-level evidence available. Consider performing comparative trials with USgFUS and MRgFUS treatments, to determine any significant differences in safety and efficacy. Optimizing treatment ultimately concerns cost-effectiveness: reducing treatment times allows for more efficient use of MRI resources and treating more patients, while increasing treatment effectiveness (higher non-perfused volume rates) can reduce reintervention rates, further improve cost-effectiveness and potentially expanding implementation of these techniques.

FUS treatment eligibility depends on multiple patient factors (BMI, subcutaneous fat thickness, age, and abdominal wall scarring) and fibroid characteristics (size, T2 signal intensity, T1 contrast enhancement, uterine position and vascularization). Current research combines multiple factors into predictive screening models for fibroid treatment, including machine learning approaches, nomograms using oxytocin experimentation and ultrasonographic features, MRI characteristics with diffusion-weighted imaging, fibroid-specific outcome prediction, and radiomics models based on MRI sequences. Despite promising approaches, most studies remain limited by small sample sizes and a lack of external validation across different centers. Collaboration among FUS clinics to pool data and validate models could ultimately create a universally applicable screening tool for FUS treatments.

Ultrasound offers practical advantages as a first-line screening tool as it is readily available in gynecological consultation rooms, more affordable, and faster than MRI. However, collaborative research is needed to determine whether ultrasound screening can be as effective as MRI in identifying eligible patients for treatment.

Developing an ideal device for treatments aims to combine various sonication capabilities, shortened procedure times, improved visualization and monitoring, possibly with advanced thermometry for MR-guided systems (or other portable alternatives), ultimately achieving maximum non-perfused volumes with minimal complication risks. Researchers are investigating real-time non-perfused volume visualization technologies, which could significantly improve treatment efficiency by helping clinicians target precisely and know when to stop treatment. Some of these techniques for MRgFUS systems include diffusion weighted imaging, susceptibility weighted imaging, intravoxel coherent motion, and synthetic contrast enhanced T1 imaging. USgFUS practitioners are able to inject intravenous contrast agents during the treatment to detect any residual areas of perfusion that merit further ablation.

Panelists:
Hao Chen, PhD, **Min He**, MD (OB-GYN), **James O-Reilly**, **Jorik Slotman**, PhD, and **Sin Yuin Yeo**, PhD

Questions

Q: How can we optimize the FUS treatment, and what innovations are necessary to enhance the adoption into clinical practice?

- To successfully implement FUS technology in clinical practice, researchers must prioritize improving treatment effectiveness through a research agenda based on urgency and developed in collaboration with FUS centers worldwide.
- The adoption of FUS technology is hindered by gynecologists' limited exposure to ultrasound physics, suggesting the need for expert systems that can distill specialized knowledge into accessible formats for clinicians without extensive experience in the field.
- Multiple factors impede the adoption of FUS technology, including knowledge gaps among gynecologists, high reintervention rates, and lengthy treatment durations that contribute to insurance hesitancy, suggesting that accelerating procedures through technical innovations could significantly enhance clinical implementation.
- Improving FUS treatment efficiency involves enhancing the beam-on fraction of time rather than just reducing total procedure duration, which could be achieved through reducing physician cognitive load via pre-planning, MRI-fusion techniques, or AI models that better understand tissue absorption rates.
- Treatment optimization requires determining which approach, targeting blood vessels, enhancing ablation with microbubbles, or using multi-point rasterization, works best for specific fibroid types, requiring close collaboration between technical and clinical experts.
- A comprehensive workflow optimization for FUS treatments should be optimized for the specific user (radiologists vs. gynecologists) through:
  - AI-assisted patient screening
  - Pre-treatment parameter planning
  - Better acoustic contact techniques
  - Position optimization tools showing treatment coverage percentages
  - Temperature monitoring
  - Outcome evaluation
- **Min He**, MD, a gynecologist who transitioned from MRgFUS to USgFUS, noted that while MRI provides superior temperature mapping, ultrasound offers faster treatment times and fewer limitations on fibroid number, location, and size.
- USgFUS effectively treats multiple fibroids with shorter treatment times (1-2 hours average) while preserving fertility, as demonstrated by patients who successfully underwent IVF after treatment.
- There was also a suggestion to optimize both patient selection protocols and machine capabilities through AI integration and MRI/ultrasound fusion for 3D guidance, especially for complex cases requiring combination approaches.

Q: How does the Arrayus device differ from prior devices on the market?

- **James O'Reilly** explained that Arrayus developed a dense phased array ultrasound technology with full electronic steering, which differs significantly from traditional transducers that use geometric focusing and mechanical steering with limited electronic capabilities. Key differences include:
  - Able to shape the whole pressure field rather than being limited to considering a single focal point
  - Ability to change the size and shape of energy deposition 250 times per second, anywhere in the aperture of the array
  - Fast enough to rasterize a treatments volume for parallel treatment of a region that is substantially larger than a single acoustic focus
  - Full power control across the entire array, allowing local amplitude adjustments to protect critical structures in the acoustic field or improve focal quality
  - Multi-focal capability
  - Potential to create "null" areas using AI to protect critical structures through local destructive interference
  - Transudcer size 17 cm in diameter with similar penetration depth
  - Reduced patient positioning challenges

Q: How is AI incorporated into FUS treatment?

- **Hao Chen**, PhD, mentioned optimizing USgFUS treatments through a patient-centered approach, developing AI solutions across the entire treatment cycle from preoperative screening and planning to real-time navigation and post-treatment monitoring.
  - They're building large variant foundation models using thousands of patient records and integrating extended reality technologies to provide real-time feedback during procedures, to maximize patient benefits through collaboration between AI engineers and medical practitioners.
- Participants advocated for collaboration within the FUS community to develop unified, open-source segmentation tools by combining datasets from multiple research groups who have created their own volume measurement and segmentation models.
- A collaborative effort to pool high-quality data across the community is essential for properly training AI models and significantly advancing the field of FUS treatment, as a lack of high-quality data slows the development of AI models.
- Focusing on AI safety and proactively addressing regulatory challenges during development will significantly reduce time-to-market for treatment planning tools and closed-loop feedback systems.
- Combine advanced AI, extended reality, and generative AI by leveraging large-scale data.

Q: What are the ways to monitor treatment in real time?

- Diffusion-weighted imaging analysis shows promise for providing real-time information during MRgFUS treatments, potentially allowing clinicians to

better target treatment, determine treatment completion, and reduce overall treatment time.

- Identifying and ablating 'feeding' vessels could achieve vascular occlusion for numerous fibroids.
- USgFUS systems provide for real time intraprocedural monitoring by noting hyperechoic foci at the sonication target and also by using Color Doppler. There is also the ability to inject IV contrast during the treatment to note residual areas of fibroid viability that can then be targeted and ablated during the same session.

Q: How can side effects be minimized if a large volume is ablated simultaneously?

- The Arrayus device features a large treatment area with electronic steering capabilities and can target a small or more diffuse focal spot.
- Dense arrays enable aberration correction that requires accurate image segmentation, which is a process in development for the Arrayus device through work with larger datasets and AI models to achieve tighter focus and correct for inhomogeneous tissue.

Q: What clinical trials are needed to address the lack of evidence for ultrasound FUS, and are we ready to conduct comparative studies in this field?

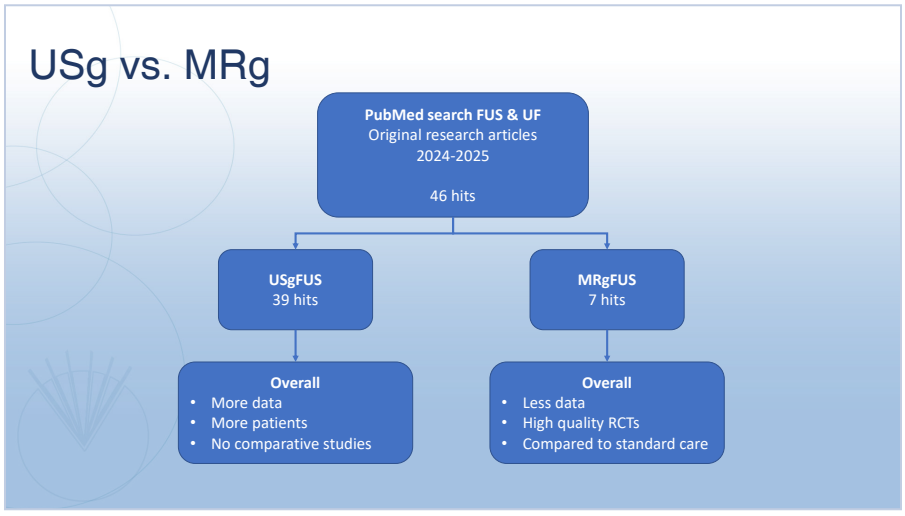
- **Min He**, MD, said that after 20 years of USgFUS experience in uterine applications and reporting some randomized controlled trials, a multi-center clinical study comparing fertility outcomes post FUS ablation for fibroids is currently underway across more than 20 hospitals, with results expected to be published later in 2025.

Martijn Boomsma, MD, PhD, summarized that collaboration and infrastructure are needed to promote productive cooperation. Well-developed AI models should be created. Hardware improvements are still required, but progress has been made as skin heating and bypassing scars is not much of an issue. Additionally, better collaboration between industry and clinicians is needed. Participants agreed that creating a collaborative research agenda focusing on key topics across different institutions, with specific lead institutes potentially guiding various agenda items, could move the field forward. A topic of particular interest was addressing the discrepancy between thermometry-based necrotic volume predictions and contrast-enhanced non-perfused volume observations. Another observation notes that the dynamic nature of AI in imaging presents challenges, as changes in image acquisition and processing methods can affect screening outcomes and disrupt prediction models that rely on MRI parameters. This highlights the need for basic uniformity in imaging protocols and clinical data parameters across all sites to ensure consistent AI application and performance.

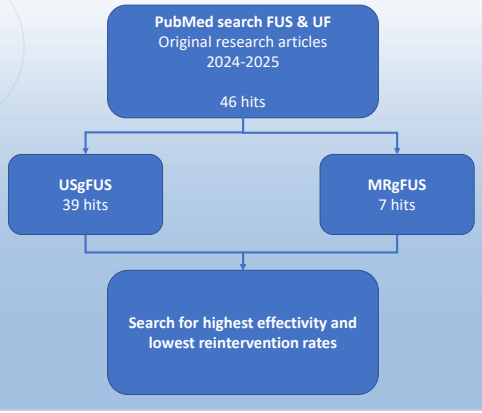
Panelists also suggested a few additional considerations, such as investigating different types of FUS. When considering fibroid treatments, it's important to identify which mechanism of action, whether direct ablation, histotripsy, cavitation models, or enhancement with microbubbles, is most appropriate for specific fibroid types, potentially requiring combinations of these approaches to achieve successful treatment outcomes based on how different fibroids absorb ultrasound energy. Treatment effectiveness evaluation should expand beyond the non-perfused volume ratio to consider other metrics like total fibroid load, recognizing that optimal outcome parameters vary depending on fibroid type, for accurately predicting long-term results and symptom reduction.

Summary

1. Collaboration is needed to develop a universal screening tool and algorithm, which may utilize US rather than MRI imaging.
2. Need to optimize workflow across all types of FUS procedures to decrease procedure time and increase ease of use as there is a barrier of clinicians "understanding" the physics of FUS.
3. AI will be critical in optimizing treatments and a working group to accumulate and use high quality data is essential.
4. Explore various mechanisms of action of FUS for different fibroid types.



USg vs. MRg



Optimizing treatment

Why?

↓ Treatment time → ↑ Cost-effectiveness
↑ Effectivity of treatment → ↑ NPVr
↑ NPVr → ↓ Reintervention rates
↓ Reintervention rates → ↑ Cost-effectiveness → ↑ Implementation

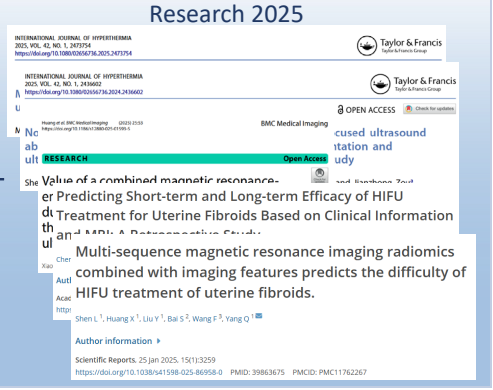
View

1. Optimizing screening
2. Optimizing treatment

Optimizing screening

- Eligibility multifactorial
  - Patient
    - BMI
    - Subcutaneous fat tissue
    - Age
    - (Caesarean) scar
  - Fibroid
    - Size
    - T2 signal intensity
    - T1 contrastenhancement
    - Distance of dorsal side to skin
    - Vascularization
    - …

Research 2025



Optimizing screening

- AI models to predict NPVr/clinical outcomes
  - Small groups
  - Often not externally validated
  - Not directly applicable in clinical practice or in other clinics

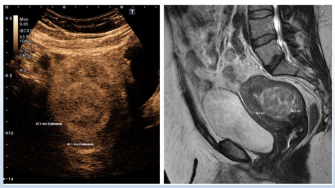
→ Collaboration of FUS clinics
→ Combining data & externally validation
→ 'Perfect' screening model applicable in every FUS centre

Optimizing screening

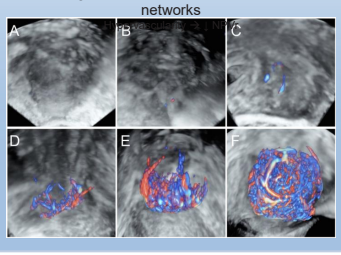
- Reducing screening MRI's = reducing costs

- Place for US screening?
  - Contrastenhanced ultrasound (CEUS)
  - Adler-grade
  - E.g. pre-screening whether MRI is needed
    - Cheaper
    - Faster
    - As effective?

CEUS vs. T1w contrastenhanced MRI



Adler-grade classification of UF vascular networks



Optimizing treatment

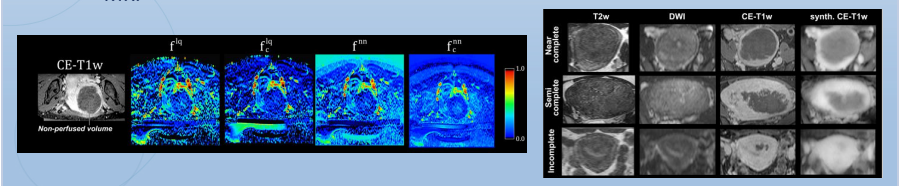
- 'Dream machine'
  - Efficient sonications
  - Short treatment time
  - Good visualization
  - Adequate thermometry
  - Small/portable system?

  → Highest possible NPVr in every treatment, with low risk of complications

Optimizing treatment

- Real-time NPVr visualization
  - Targeted treatment
  - Efficient treatment (knowing when to stop)

  → Alternatives to CET1w MRI: diffusion weighted imaging (DWI), susceptibility weighted imaging (SWI), intravoxel incohorent motion (IVIM), synthetic CET1w MRI



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Determine candidacy for FUS Treatment with Particular Emphasis on Preserving Fertility

Moderators
Pejman Ghanouni, MD PhD (Radiologist) and **Selva Supermaniam**, MD (OB-GYN)

Pejman Ghanouni, MD, PhD, gave a brief overview of relevant data on reproductive outcomes following various interventions for uterine fibroids. There were similar rates of pregnancy following USgFUS, MRgFUS, and UAE treatments. There is currently no evidence on fertility outcomes after FUS from randomized controlled trials. FUS appears to be a safe treatment that doesn't damage the surrounding myometrium, endometrium, or ovarian function, though evidence is limited.

Panelists
Kirsi Joronen, MD, PhD (OB-GYN), **John Petrozza**, MD (OB-GYN), and **Jordi Rodríguez**, MD (OB-GYN)

Questions

Q: In what patient population would FUS for fibroids be most beneficial, especially concerning preserving fertility?

- FUS can be recommended for all patients with symptomatic uterine fibroids or who desire future fertility and are suitable candidates (Funaki type 1 or 2 fibroids with medium/low vascularization).
- Good FUS candidates can include patients with Federation of Gynecology and Obstetrics (FIGO) type 0, 1, or 2 fibroids larger than 3 cm that are difficult to remove via hysteroscopic resection, and those with type 3 or 4 intramural fibroids (1-3 cm).
- FUS-treated patients can achieve full-term pregnancies with few complications and successful vaginal deliveries, though more comparative studies with larger samples are needed. Dr. Rodriguez published a retrospective series of 43 patients treated with FUS who went on to have successful pregnancies and now they have up to 100 pregnancies with 61 successful deliveries.
- Fertility preservation and treating infertility are considered two different clinical scenarios by some groups.
  - In Finland, surgery is typically the preferred treatment when fibroids are identified as the cause of infertility.

Q: How long should a patient wait to become pregnant following FUS?

- The patient should wait until complete restoration of the uterine cavity for a FIGO 0, which can range from a minimum of 3 months and up to around 6 months depending on fibroid size.
- For 3cm FIGO type 1-3 fibroids, 3 months can be sufficient. For 4-5 cm fibroids, likely need to wait 3-6 months.

- If no cavity distortion, and in young patients, may get pregnant right away.
- Following myomectomy, patients should also wait a minimum of 3 months (up to 6 months), depending on the extent of surgery.

Q: What is your perspective on FUS versus myomectomy for addressing fertility concerns in women?

- There is limited data on fertility; some studies on myomectomy show benefits for certain types of fibroids (FIGO 0, 1, 2, and 3).
- Basic science studies have demonstrated improvements in implantation factors after myomectomy, which is promising evidence supporting surgical intervention.
- There is limited data on fertility after FUS, and there have been no comprehensive studies of infertile patients where fibroids were the only factor, and FUS was the treatment.
- There is a limited availability of surgeons skilled in performing laparoscopic myomectomies, which are technically challenging procedures.
- Alternative approaches like FUS could become the gold standard of treatment, but more data on implantation and reproductive outcomes are needed before this happens.
  - Because randomized controlled trials take a long time, just measuring implantation markers following FUS could give an early indication of fertility.
- **John Petrozza**, MD, stated that despite unclear guidelines on when to perform C-section after myomectomy, FUS could be beneficial by potentially reducing the need for C-sections after fibroid treatment and affect a women's decision to choose FUS over myomectomy. The potential to decrease the need for C-section by even as little as 10% is important.
- Look at implantation markers in patients who are trying to conceive and compare myomectomy vs FUS. Control for age, BMI, and other clinical factors.
- **Selva Supermaniam**, MD, said that patients should be offered two options (FUS and laparoscopic myomectomy) with their respective benefits: FUS avoids uterine incisions while myomectomy completely removes fibroids.
  - Treatment recommendations could also be age-based, with FUS recommended for younger patients under 35 (with surgery remaining a future option) and myomectomy for patients 36 to 38 years, where time is more critical.
- **Jordi Rodriguez**, MD, mentioned that for patients with large (7-9 cm), highly vascularized fibroids seeking fertility treatment, FUS is not recommended due to low success rates (approximately 20%), as this could delay more effective surgical interventions and extend the time to pregnancy. Also avoid treating large fibroids >8 cm.
- Experiences differ between European and Asian practices, where Korean clinicians achieve better results with large, vascularized fibroids using powerful sonication enhancers like microbubbles.
- **Kirsi Joronen**, MD, PhD, and **Selva Supramaniam**, MD, exclude Funaki Type 3 if patient desires fertility as they are too vascular despite using oxytocin.

- FUS appears to provide pregnancy outcomes equivalent to surgery for fibroids, with highly informed patients often selecting this option despite facing barriers, though randomized controlled trials remain challenging as patients frequently attempt to circumvent randomization to obtain their preferred treatment.

Q: Could physicians treat asymptomatic uterine fibroids with non-invasive procedures when cost is not a barrier, reimbursable, or wait until symptoms develop?

- **Kirsi Joronen**, MD, PhD, Recommended against treating asymptomatic fibroids preventively even in places with reimbursed procedures, such as Finland, because most fibroids remain asymptomatic, all procedures carry some risk, and medical science cannot yet reliably predict which fibroids will become problematic.
- **Jordi Rodriguez**, MD, noted that this is a difficult situation but they have treated some young patients with asymptomatic Type 1 and 2 fibroids, potentially avoiding future surgeries.
- **John Petrozza**, MD, observed that many patients experience what appears to be fibroid recurrence, but it is the growth of small fibroids left behind during myomectomy (especially in African American populations).
- For these cases, there is the potential for combined approaches where FUS could complement surgical treatments by addressing small fibroids that cannot be surgically removed, potentially reducing further growth.
- Some colleagues perform RFA and then hysteroscopic resection but likely more damage to normal myometrium with RFA compared with FUS.
- FUS could be valuable for shrinking fibroids before hysteroscopic procedures, allowing for less invasive surgical techniques and better outcomes, ultimately keeping patients from requiring repeated operations.

Q: What do you recommend for your patients to consider?

- For FUS in the USA, there is limited regional availability and a lack of insurance reimbursement; patients have very few opportunities to consider FUS as a treatment option.
- With multiple treatment options available (medical therapy, UAE, FUS, and surgery), the challenge is finding the best individualized approach for each patient rather than declaring one universal "best treatment" for fibroids.
- For vascular fibroids, surgery is recommended over FUS for fertility patients.
  - However, there are several techniques to improve FUS for vascular fibroids such as prior injection of ethanol, sclerosing agents, and microbubbles (Sonozoid). These also allow the use of lower powers during the HIFU procedure.
- FUS is strongly recommended for patients with previous myomectomies who now have multiple fibroids, as repeat surgeries are complicated and risk hysterectomy.
- From the gynecological surgeon's perspective, all interventions cause inflammation, with surgery potentially creating adhesions and complications, making minimally invasive options with faster recovery and fewer scars preferable when allowing patients to make informed decisions between treatments.
- Is there value in early treatment for patients with hereditary leiomyomatosi and renal cell cancer (HLRCC) syndrome?

- HLRCCH leiomyomas can be identified through immunohistochemisty of excised f tissue from myomectomies; a diagnostic benefit lost with non-invasive techniques.
- Patients with these hereditary syndromes could still benefit from FUS procedures, though they would require closer monitoring since their fibroids tend to grow more rapidly and generally recur (as new fibroids) rather than persist.

In summary, the panel would like to have more data on fertility and the ability to conceive following FUS to confidently recommend it to patients considering pregnancy or patients with infertility. The group would also like data on various treatment options for comparison, not just FUS. Dr. Stewart agrees and educates patients on both myomectomy and FUS. She tried to perform the RCT addressing this issue, but it was difficult to recruit (NCT00730886, clinicaltrials.gov). Sophisticated patients seek out FUS option. More data is needed.

Summary

1. Recommend hysteroscopic resection for small fibroids FIGO 0-2 but also consider HIFU especially for fibroids >3cm and then consider adding hysteroscopy to remove any smaller remnant.
2. If there was distortion of the uterine cavity from fibroids, recommend waiting 3-6 months after FUS to conceive
3. Need well-designed study of myomectomy vs FUS for fertility – consider studying implantation markers instead of just pregnancy rates. HIFU is very promising in these patients but needs more data.
4. Treating with FUS instead of myomectomy could potentially decrease C- section rates.
5. Treatment of asymptomatic fibroids is controversial as we do not know the natural growth patterns of fibroids.
6. FUS after myomectomy for residual or recurrent fibroids is a good target population.
7. Consider studying HIFU enhancers such as ethanol or microbubbles to increase treatment efficacy and safety, especially vascular fibroids.

Reproductive outcomes

	Number of patients	Number of pregnancies	Live birth rate	Miscarriage rate	Pooled estimate of pregnancy
USgFUS	1866	635	73,5%	10,9%	18,7-78,5%
MRgFUS	747	55	70,0%	15,5%	18,7-78,5%
UAE	848	250	70,8%	19,2%	17,3-44,5%
RFA	470	40	60,0%	20,0%	2,1-7,6%
MWA	169	10	33,3%	0,0%	5,3%

Enhance Commercialization of a FUS Machine for Fibroids and Address Regulatory and Reimbursement Issues

Moderators
Pejman Ghanouni, MD PhD (Radiologist) and **Rose Xing**, PhD

Dr. Ghanouni provided background on coding and reimbursement challenges for MRI-guided FUS treatment. In the United States , uterine fibroid treatments remain stuck with temporary tracking codes after nearly 20 years, forcing many patients to pay out of pocket. Different codes exist for non-fibroid applications, particularly highlighting recent progress in neurosurgery and prostate treatments, which have achieved permanent Current Procedural Terminology codes. Dr. Ghanouni contrasted insurance coverage for uterine fibroid treatments, noting that RFA received ACOG's Level B recommendation and insurance approval despite limited non-randomized data, while FUS therapy is broadly deemed "investigational" by United States insurers despite higher levels of evidence and effectiveness. This disparity might be influenced by Relative Value Units, as hysterectomy, laparoscopic myomectomy, and RFA procedures offer generous physician compensation, potentially affecting treatment recommendations.

Professor Xing emphasized that commercialization is essential for FUS technology to extend beyond academic centers and reach patients broadly. Despite 171 potential FUS applications in development, the first FDA-approved indication (fibroids) still struggles with commercialization. Sharing experience from Haifu Medical's 340 centers worldwide (mostly commercialized), she argued that successful implementation requires simultaneously addressing market adoption, regulatory hurdles, and reimbursement challenges while incorporating patient perspectives and preferences into research and development efforts.

Panelists
Jessica Foley, PhD, **Subha Muravada**, PhD, and **Elizabeth A. Stewart,** MD (OB-GYN)

Questions

Q: Is patient education important in improving market adoption for FUS?

- Patient demand is crucial for treatment acceptance, as demonstrated by FUS patients who typically are self-directed.
- UAE succeeded partly because overwhelming patient interest eventually reduced insurance barriers and benefited from more flexible procedural coding that facilitated reimbursement.
- United States FDA approval serves as a global benchmark for medical technologies, with many countries following the FDA's lead.
    - Developing nations often lack the clinical research infrastructure to conduct their own studies, making it difficult for local policymakers to include new technologies like FUS in national reimbursement plans and recognize the high regulatory standards set by the FDA.

Q: How could we encourage organizations such as the American College of Obstetricians and Gynecologists (ACOG) to support FUS for fibroids with the same enthusiasm they have shown for RFA?

- ACOG is less likely to advocate for FUS because it's typically performed outside their specialty's control, medical innovation consistently arrives later for women's health conditions for complex reasons that might include both safety concerns and gender bias.
- FUS adoption for fibroids faces challenges in a crowded treatment landscape, unlike essential tremor, where limited alternatives exist.
- Specialty control matters: neurosurgeons perform brain-FUS themselves, while OB-GYNs typically only serve as referring physicians for fibroid treatments. Making FUS technology available in OB-GYN offices could dramatically change adoption rates by giving gynecologists direct control of the procedure.
- Low utilization of FUS for fibroids persisted even after FDA approval, suggesting deeper issues like potential specialty "turf battles" between gynecologists and radiologists.
- Current coding challenges may hamper progress, with questions about whether existing fibroid codes might be "poisoning the well" for new procedures.
- USgFUS was explicitly introduced to OB-GYNs as a non-invasive option for women's health conditions like fibroids and adenomyosis, and was also designed for integration into existing OB-GYN practices based on physician skill sets and patient selection criteria.
- Haifu Medical's market entry strategy involves working with three key societies in each country: an OB-GYN society, a minimally invasive surgery society, and a fertility society.
    - USgFUS can be used in the physician's office setting as it only requires sedation and allows specialist access.

Q: Would gynecologists who previously adopted similar medical technologies be open to implementing a new portable FUS device that requires minimal sedation and can be used outside hospital settings?

- After FDA approval of MRgFUS, some outpatient gynecologist-led centers emerged but ultimately failed to survive.
    - While incorporating FUS into OB-GYN practice could improve adoption, it presents a steep learning curve compared to current OB-GYN skillsets.
- Widespread implementation would require successfully aligning three key factors: patient demand, provider acceptance, and accessibility; these elements weren't effectively coordinated after the initial FDA approval.
- Addressing the learning curve through robust international training programs is essential for commercializing ultrasound-guided technology.
    - Haifu Medical collaboration with professional OB-GYN societies has established that gynecologists typically require 20 to 40 cases to achieve proficiency, with 21 international training bases now established in China to support a certification process.

Q: How significant was MRI guidance as a barrier to adoption?

- MRI guidance was a significant adoption barrier for gynecologists, with both knowledge requirements and financial considerations being major factors, as ultrasound technology is now much more affordable than MRI equipment.
- Technological advancements (including AI, improved treatment planning, monitoring algorithms, and hardware) could revitalize the fibroid treatment field by addressing previous limitations that created negative physician bias, such as lengthy procedure times and partial treatment capabilities, potentially reintroducing optimized devices to gynecologists with improved workflows and multiple treatment options for patients.
- The COEQUaL study aims to address these issues by understanding women's barriers to accessing comprehensive treatment options, investigating whether patients are not hearing about all alternatives, do not see the full array as available, or face delayed care pathways affecting treatment decisions.

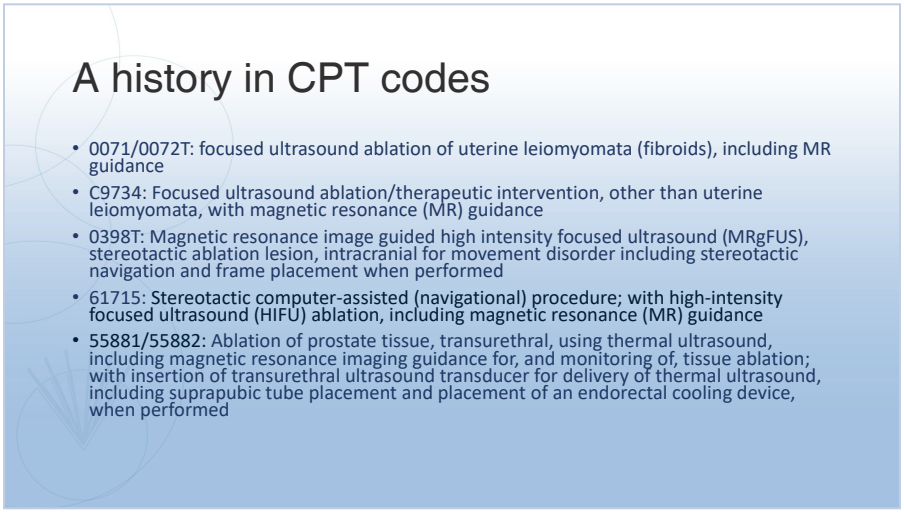
Q: Would treating adenomyosis with FUS potentially see higher adoption rates among gynecologists, since their current options are limited to either hysterectomy or hormonal medications, making them more willing to refer patients to this uterine-sparing technology despite not being MRI or ultrasound specialists themselves?

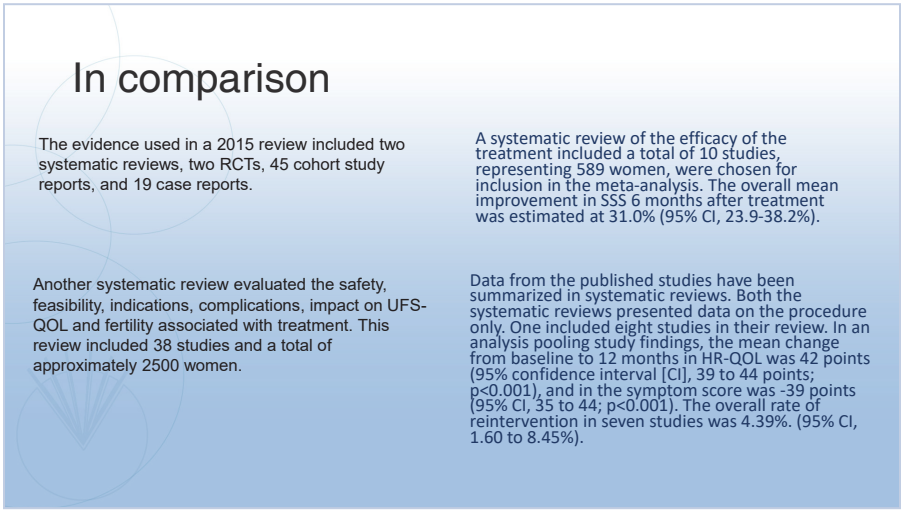
- Focusing on adenomyosis treatment with FUS has potential advantages, but gynecologists would still need education to overcome the misconception that adenomyosis only affects women in their late 40s rather than younger fertility patients, though it could provide an innovative alternative for patients who decline hysterectomy, particularly given early successful treatments of adenomyomas initially misidentified as fibroids.
- Real-world experience shows that minimally invasive OB-GYN surgeons who become familiar with FUS technology recognize that it offers greater advantages for treating adenomyosis compared to laparoscopic surgery and other approaches.
- Adenomyosis significantly impacts fertility and quality of life, making OB-GYNs more receptive to FUS technology, with adoption typically starting with adenomyosis cases before expanding to fibroid treatments, and the European Society of Endoscopy endorsed it as the preferred non-invasive approach for adenomyosis patients.
- It is also important to engage with the International FIGO on women's health broadly, noting that an expert consensus on fibroids (including both MRgFUS and USgFUS treatments) will be released at the October FIGO meeting, which should significantly increase global physician awareness, with adenomyosis potentially being the next indication for developing similar guidelines.

In conclusion, **Pejman Ghanouni**, MD, PhD, highlighted the contrast between data-focused discussions and the multifactorial challenges facing FUS adoption for women's health conditions, including education gaps, limited treatment locations, and insurance barriers. This field faces unique obstacles, unlike other medical innovations that have advanced without randomized controlled trials. The discussion emphasized the unacceptable inequity in women's healthcare access, where effective, minimally invasive tools exist but remain unavailable to many patients.

Summary:

1. Making FUS technology available in OB-GYN offices could dramatically change adoption rates by giving gynecologists direct control of the procedure and increase participation by ACOG. Recognize they need strategic and comprehensive training as FUS requires a different skillset.
2. Need to reeducate patients and physicians as the procedure time and outcomes are very different than 20 years ago for both MRgFUS and USgFUS.
3. New medications introduced during COVID are also underutilized so studying women's preferences and choices for fibroid treatments is being addressed in the COEQUaL study
4. Consider applying FUS for adenomyosis as the next indication to promote to patients and physicians as it occurs in young patients and definitive treatment is only hysterectomy.





In comparison: MRgFUS

- **Investigational and Not Medically Necessary:**
  - Other uses of focused ultrasound ablation are considered **investigational and not medically necessary** for all other non-oncologic indications, including but not limited to:…Uterine fibroids.
- "Well-designed clinical studies evaluating the safety and efficacy of MRgFUS using relevant outcome measures are lacking. Studies have generally lacked comparison to the current accepted treatments of uterine fibroids. Additionally, based on the prevalence of uterine fibroids, a relatively small number of women have been studied in clinical trials. The published evidence regarding MRgFUS does not adequately address the potential for regrowth of treated uterine fibroids over time, particularly beyond 3 to 5 years. In order to demonstrate MRgFUS as a safe and effective treatment option for uterine fibroids, well-designed RCTs with sufficient follow-up periods and appropriate clinical outcome measures are needed to compare therapy with alternative treatments."
- The American College of Obstetricians and Gynecologists (ACOG) stated in their practice bulletin, Management of Symptomatic Uterine Leiomyomas (2021):
  - Limited, low-quality data suggest that magnetic resonance-guided focused ultrasound and high-intensity focused ultrasound are associated with a reduction in leiomyoma and uterine size. However, small randomized comparative trial data suggest that compared with UAE, magnetic resonance-guided focused ultrasound is associated with less improvement in symptoms and quality-of-life measures and a higher risk of reintervention.

In comparison: RFVTA

- **Medically Necessary**

  The use of laparoscopic or transcervical radiofrequency ablation as a treatment for symptomatic uterine fibroids (e.g. excessive uterine bleeding or pelvic discomfort caused by uterine fibroids) is considered **medically necessary** when *all* of the following criteria are met:

  1. Uterine preservation is desired; **and**
  2. Fibroids are less than 10 cm in any diameter; **and**
  3. Uterine size does not exceed 16 weeks' gestation.
- "The American College of Obstetricians and Gynecologists (ACOG) guideline on management of symptomatic uterine leiomyomas (June 2021) included the following "Level B" recommendation (recommendation based on limited or inconsistent scientific evidence), "Laparoscopic radiofrequency ablation can be considered as a minimally invasive treatment option for the management of symptomatic leiomyomas in patients who desire uterine preservation and are counseled about the limited available data on reproductive outcomes". The bulletin noted that "laparoscopic RFA with a leiomyoma specific FDA-approved device has been studied primarily in nonrandomized trials" and the recommendation was based in part on recent meta-analyses, Bradley (2019) and Lin (2019), discussed above.

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Roadmap

1. Create a working group to develop a universal screening study and algorithm, which may utilize US rather than MRI imaging.
2. Create a working group to incorporate AI: Accumulate and use high quality data to improve treatment workflow across MRgFUS and USgFUS.
3. Need well designed study of myomectomy vs FUS for fertility – consider studying implantation markers instead of just pregnancy rates.
4. Increase adoption of FUS by OB-GYN's by dedicating educational resources and ensuring FUS technology is available in offices and increase participation by ACOG.
5. Consider applying FUS for adenomyosis as the next indication to promote to patients and physicians as it occurs in young patients and definitive treatment is only hysterectomy.
6. Explore various MOA of FUS for different fibroid types including potential HIFU enhancers such as ethanol or microbubbles, to increase treatment efficacy and safety.

Conclusion

Suzanne Leblang, MD, thanked the moderators and panelists for identifying barriers and strategic priorities moving forward. She noted that this conversation will catalyze meaningful progress in expanding access to these crucial technologies.

Appendix: Tables 1-9

Table 1. Overview of safety profile of minimally invasive treatment options for symptomatic uterine fibroid according to the Society of Interventional Radiology (SIR) criteria. (SIR A/B = minor complications, SIR C/D/E/F = major complications)

	USgHIFU	MRgHIFU	UAE
Safety	N=27.053 ☐ Minor: 78,0% (21.114/27.053) ☐ Major: 0,4% (71/17.402) *all complications see Table 5	N=2919 ☐ Minor: 35,7% (1043/2919) ☐ Major: 0,4% (12/2919) *all complications see Table 6	N=434 ☐ Minor: 87,8% (381/434) ☐ Major: 7,1% (31/434) *all complications see Table 7
Remarks	Data from one retrospective study, including patients from 19 centres in China. The study included uterine fibroids (n=17.402), uterine adenomyosis (n=8434), cesarean scar pregnancies (n=876) and placenta accreta (n=341). Only major complications were specified for UF patients.	Data from a systematic review, including 43 studies. Possible underreporting of minor complications. Pooled results	Seven studies included comparing UAE with surgery, one study included comparing UAE with HIFU. Pooled results.
References	(1)	(2)	(3)

(Continuation of table)	RFA*	MWA	
Safety	N=2945 ☐ Minor: 27,8% (820/2945) ☐ Major: 0,5% (14/2945) *all complications see Table 8	N=732 ☐ Minor: 25,0% (183/732) ☐ Major: 0,3% (2/732) *all complications see Table 9	MRgHIFU = magnetic resonance guided high intensity focused ultrasound MWA = microwave ablation RFA = radiofrequency ablation UAE = uterine artery embolization USgHIFU = ultrasound guided high intensity focused ultrasound * Including laparoscopic, percutaneous and vaginal RFA
Remarks	One systematic review including twenty-eight studies included. Complications were inconsistently collected and reported across studies, often with unclear documentation of severity. Method of RFA is combined in this presentation of complications. Complications per method are specified in Table 8. Pooled results.	One systematic review included and seven additional studies. Pooled results.	
Reference	(4)	(5–12)	

Table 2. Overview of symptom reduction of minimally invasive treatment options for symptomatic uterine fibroids

	USgHIFU	MRgHIFU	UAE
Symptom reduction	tSSS reduction ☐ 3m: 40,3% (n=1224) ☐ 6m: 46,1% (n=2967) ☐ 12m: 47,7% (n=2752) ☐ 24m: 40,2% (n=68) ☐ 36m: 51,5% (n=44) HRQoL improvement ☐ 3m: 34,7% (n=994) ☐ 6m: 24,3% (n=2613) ☐ 12m: 24,6% (n=2425)	tSSS reduction ☐ 3m: 38,1% (n=538) ☐ 6m: 48,6% (n=874) ☐ 12m: 58,2% (n=534) ☐ 24m: 58,0% (n=103) ☐ 36m: 58,0% (n=49) HRQoL improvement ☐ 3m: 31,4% (n=115) ☐ 6m: 31,5% (n=140) ☐ 12m: 28,0% (n=37)	tSSS reduction ☐ 6m: 56,9% (n=251) ☐ 12m: 61,5% (n=458) ☐ 24m: 61,8% (n=398) ☐ 36m: 56,0% (n=176) ☐ 48m: 67,9% (n=70) HRQoL improvement ☐ 6m: 75,9% (n=249) ☐ 12m: 64,6% (n=373) ☐ 24m: 89,1% (n=222) ☐ 48m: 105,7% (n=67) ☐ 60m: 21,4% (n=94)
Remarks	Results based on pooled means from 15 included studies.	Results based on pooled means from a systematic review including 16 studies and two additional studies. Only studies with unrestrictive treatment protocols were included.	Results based on pooled means from included studies, all RCT's.
References	(13–27)	(28–30)	(8,31–35)

(Continuation of table)	RFA	MWA	
Symptom reduction	tSSS reduction ☐ 3m: 52,6% (n=833) ☐ 6m: 63,0% (n=801) ☐ 12m: 67,8% (n=948) ☐ 24m: 58,5% (n=402) ☐ 36m: 61,7% (n=306) ☐ 64m: 55,3% (n=17) HRQoL improvement ☐ 3m: 47,1% (n=1935) ☐ 6m: 94,9% (n=695) ☐ 12m: 65,2% (n=1968) ☐ 24m: 51,1% (n=276) ☐ 36m: 105,5% (n=238) ☐ 64m: 121,6% (n=17)	tSSS reduction ☐ 3m: 52,5% (n=550) ☐ 6m: 57,3% (n=610) ☐ 12m: 71,2% (n=423) ☐ 24m: 93,6% (n=50) HRQoL improvement ☐ 3m: 33,0% (n=566) ☐ 6m: 47,3% (n=594) ☐ 12m: 50,5% (n=506)	MRgHIFU = magnetic resonance guided high intensity focused ultrasound MWA = microwave ablation RFA = radiofrequency ablation UAE = uterine artery embolization tSSS = transformed symptom severity scale, USgHIFU = ultrasound guided high intensity focused ultrasound
Remarks	Data from systematic review and one additional study. Results based on pooled means from included articles.	Results based on pooled means from included articles.	
References	(4,36)	(6–8,10–12,37–42)	

Table 3. Overview of reproductive outcomes of minimally invasive treatment options for symptomatic uterine fibroids

	USgHIFU	MRgHIFU	UAE
Reproductive outcomes	N=1866 Number of pregnancies = 635 Average age: 33,5 years ☐ Live birth rate: 73,5% (467/635) ☐ Ongoing pregnancies: 4,7% (30/635) ☐ Miscarriage rates: 10,9% (69/635) ☐ Pooled estimate of pregnancy: 18,7-78,5%	N=747 Number of pregnancies = 55 Average age: 40 years ☐ Live birth rate: 70% (40/55) ☐ Ongoing pregnancies: 15,5% (9/55) ☐ Miscarriage rates: 15,5% (9/55) ☐ Pooled estimate of pregnancy: 18,7-78,5%	N=848 Number of pregnancies = 250 Average age: 37,1 years ☐ Live birth rate: 70,8% (177/250) ☐ Ongoing pregnancies: 1,6% (4/250) ☐ Miscarriage rates: 19,2% (48/250) ☐ Pooled estimate of pregnancy: 17,3-44,5%
Remarks	Data from a systematic review and meta-analysis. Inclusion of 6 studies.	Data from a systematic review and meta-analysis. Inclusion of 6 studies.	Data from a systematic review and meta-analysis. Inclusion of 7 studies.
References	(43)	(43)	(43)

(Continuation of table)	RFA	MWA	
Reproductive outcomes	N=470 Number of pregnancies = 40 Average age: 38,4 years ☐ Live birth rate: 60% (24/40) ☐ Ongoing pregnancies: 0% (0/40) ☐ Miscarriage rates: 20% (8/40) ☐ Pooled estimate of pregnancy: 2,1-7,6%	N=169 Number of pregnancies = 10 (in 9 women) Average age: 34,2 years ☐ Induced abortions: 66,7% (6/9) ☐ Live births: 33,3% (3/9) ☐ Miscarriage rates: 0% (0/9) ☐ Pregnancy rate: 5,3% (9/169)	MRgHIFU = magnetic resonance guided high intensity focused ultrasound MWA = microwave ablation RFA = radiofrequency ablation UAE = uterine artery embolization USgHIFU = ultrasound guided high intensity focused ultrasound
Remarks	Data from a systematic review and meta-analysis. Inclusion of 6 studies.	All unplanned pregnancies.	
References	(43)	(44)	

Table 4. Overview of reintervention rates of minimally invasive treatment options for symptomatic uterine fibroids

	USgHIFU	MRgHIFU	UAE
Reintervention rates	Reintervention rates ☐ 12m: 2,1% (n=4371, 6 studies) ☐ 24m: 3,0% (n=862, 2 studies) ☐ 36m: 8,6% (n=1987, 3 studies) ☐ 60m: 14,0% (n=1448, 3 studies) ☐ 96m: 18,0% (n=2052, 3 studies) ☐ 120m: 19,3% (n=1987, 2 studies)	Reintervention rates ☐ 12m: 9,3% (n=248, 4 studies) ☐ 24m: 19,5% (n=133, 2 studies) ☐ 36m: 20,5% (n=249, 3 studies) ☐ 63,5m: 33,3% (n=87, 1 study) ☐ 72m: 33,1% (n=99, 1 study)	Reintervention rates ☐ 12m: 7,1% (n=7112, 13 studies) ☐ 24m: 15,3% (n=404, 7 studies) ☐ 36m: 15,9% (n=7309, 8 studies) ☐ 48m: 20,2% (n=198, 3 studies) ☐ 60m: 21,5% (n=2321, 10 studies) ☐ 72m: 10,6% (n=284, 2 studies) ☐ 84m: 15,4% (n=8139, 5 studies) ☐ 120m: 19,1% (n=444, 3 studies)
Remarks	Data from systematic review and two additional studies. Pooled reintervention rates.	Inclusion of studies with unrestrictive treatment protocols only. Data from a systematic review and five additional studies. Pooled reintervention rates.	Data from 31 studies. Pooled reintervention rates.
References	(15,45,46)	(28,30,32,47–49)	(32,33,35,50–77)

(Continuation of table)	RFA	MWA	
Reintervention rates	Reintervention rates ☐ 12m: 2,9% (n=787, 12 studies) ☐ 18m: 6,3% (n=205, 2 studies) ☐ 24m: 7,7% (n=404, 5 studies) ☐ 36m: 17,0% (n=447, 5 studies) ☐ 60m: 31,8% (n=66, 1 study) ☐ 66m: 33,3% (n=66, 1 study)	No studies report on reintervention rates. Two studies on recurrence rates <12 months: ☐ Jin et al. (2023): 4,5% (3/66 patients) ☐ He et al. (2024): 16,2% (11/68 fibroids)	MRgHIFU = magnetic resonance guided high intensity focused ultrasound MWA = microwave ablation RFA = radiofrequency ablation UAE = uterine artery embolization USgHIFU = ultrasound guided high intensity focused ultrasound
Remarks	Data from systematic review and one additional study. Pooled reintervention rates.	No studies report on reintervention rates. Therefore, recurrence rates were reported.	
References	(4,36)	(37,78)	

Table 5. Complications after USgHIFU			
Minor (SIR A/B) (n=27.053)		**Major (SIR C/D/E/F) (n=17.402 (UF patients only))**	
Mild lower abdominal pain	8376 (31,0%)	Skin burns	26 (0,15%)
Sacrococcygeal pain	2866 (10,6%)	Leg pain	10 (0,06%)
Abnormal vaginal discharge	1297 (4,8%)	Urinary retention	7 (0,04%)
Lower limb paresthesia	207 (0,8%)	Vaginal bleeding	6 (0,03%)
Nausea and vomiting	108 (0,4%)	Hyperpyrexia	5 (0,02%)
Erythema on skin	86 (0,3%)	Renal failure	4 (0,02%)
Fever	82 (0,3%)	Acute cystitis	3 (0,02%)
Hematuria	24 (0,1%)	Bowel injury	3 (0,02%)
Skin blisters	20 (0,1%)	Intrauterine infection	2 (0,01%)
		Deep vein thrombosis	2 (0,01%)
		Hydronephrosis	1 (0,00%)
		Pubic symphysis injury	1 (0,00%)
		Thrombocytopenia	1 (0,00%)
		Sciatic nerve injury	1 (0,00%)

Table 6. Complications after MRgHIFU			
Minor (SIR A/B) (total n=2919)		**Major (SIR C/D/E/F) (total n=2919)**	
Pain/discomfort	500 (17,1%)	Fibroid expulsion	6 (0,2%)
Nausea/dizziness/malaise/fatigue	192 (6,6%)	Skin burn surgical treatment	2 (0,1%)
Vaginal bleeding or discharge	101 (3,5%)	Deep venous thrombosis	1 (0,0%)
UTI or urine retention	66 (2,3%)	Sciatic nerve palsy	1 (0,0%)
Abdominal edema	64 (2,2%)	UTI requiring admission	1 (0,0%)
Skin redness/rash	45 (1,5%)	Infection necrotic fibroid tissue	1 (0,0%)
Skin burns	42 (1,4%)		
Neuropraxia	27 (0,9%)		
Subcutaenous fat tissue burning	3 (0,1%)		
Hematuria	2 (0,1%)		
Allergic reaction (urticaria) to iv meperidine	1 (0,0%)		

Table 7. Complications after UAE			
Minor (SIR A/B) (total n=434)		**Major (SIR C/D/E/F) (total n=434)**	
Pain	76 (17,5%)	Readmission, cause unspecified	6 (1,4%)
Others	64 (14,7%)	Severe pain and fibroid expulsion (unspecified whether treatment for fibroid expulsion was needed)	4 (0,9%)
Nausea	52 (12,0%)	Fibroid expulsion requiring intervention	2 (0,5%)
Postembolization syndrome	44 (10,1%)	Pain and pelvic infection requiring readmission	2 (0,5%)
Vaginal discharge	35 (8,1%)	Pain requiring readmission	2 (0,5%)
Urinary tract infection	18 (4,1%)	Pain and fever requiring readmission	2 (0,5%)
Hot flashes	16 (3,7%)	Temporary amenorrhea	2 (0,5%)
Fibroid tissue expulsion	15 (3,5%)	Persistent severe pain requiring hysterectomy	2 (0,5%)
Hematoma	13 (3,0%)	Deep venous thrombosis	1 (0,2%)
Postpuncture hematoma	8 (1,8%)	Hematometria	1 (0,2%)
Sepsis	6 (1,4%)	Hypertension requiring medium care admission	1 (0,2%)
Hypertension	6 (1,4%)	Pelvic sepsis requiring IV antibiotics	1 (0,2%)
Urinary incontinence	6 (1,4%)	Pneumonia	1 (0,2%)
Fever	4 (0,9%)	Sepsis	1 (0,2%)
Allergic reaction/rash	3 (0,7%)	Severe vasovagal event requiring atropine	1 (0,2%)
Groin hematoma	3 (0,7%)	Pelvic abcesses requiring hysterectomy	1 (0,2%)
Thigh parestesia	2 (0,5%)	Postembolization syndrome	1 (0,2%)
Urinary retention	2 (0,5%)		
Endometritis	2 (0,5%)		
Renoureteral colic	2 (0,5%)		
Spontaneous blood clot in gluteal artery during procedure	1 (0,2%)		
Anal fissure	1 (0,2%)		
Vulvovaginitis	1 (0,2%)		
Wound bleeding	1 (0,2%)		

Table 8. Complications after RFA, specified per method				
Laparoscopic RFA				
	Minor (SIR A/B) (total n=73)		**Major (SIR C/D/E/F) (total n=73)**	
	Abdominal pain	6 (8,2%)		
	Epigastric arterial damage during surgery	1 (1,4%)		
Laparoscopic ultarsonographic RFA				
	Minor (SIR A/B) (total n=439)		**Major (SIR C/D/E/F) (total n=439)**	
	Abdominal pain	11 (2,5%)	Severe bleeding abdominal wall, hematoma	1 (0,2%)
	GI symptoms	7 (1,6%)	Pelvic abcesses in posterior cul-de-sac	1 (0,2%)
	Cutaneous erythema	5 (1,1%)	Superficial laceration of sigmoïd colon caused by ultrasound probe	1 (0,2%)
	UTI	5 (1,1%)	Uterine perforation with D&C leading to hysterectomy	1 (0,2%)
	Upper respiratory tract infection	4 (0,9%)		
	Superfecial uterine serosal burn/laceration	2 (0,5%)		
	Intraoperative bleeding	1 (0,2%)		
	Migraine	1 (0,2%)		
	Possible hematoma by RF probe	1 (0,2%)		
	Postprocedural vaginal bleeding	1 (0,2%)		
	Vaginal discharge	1 (0,2%)		
	Vertigo requiring admission	1 (0,2%)		
Percutaneous Ultrasonographic RFA				
	Minor (SIR A/B) (total n=304)		**Major (SIR C/D/E/F) (total n=304)**	
	Abdominal pain	46 (15,1%)	Abdominal pain resulting in hysterectomy	1 (0,3%)
	Cutaneous erythema	20 (6,6%)	Lapsc. Hysterectomy due to prolapsed fibroid	1 (0,3%)
	Vaginal discharge	11 (3,6%)	Serious infection	1 (0,3%)
	Lowgrade fever	9 (3,0%)		
	Fibroid tissue loss	5 (1,6%)		
	Fluid in pelvic pouch in Usg	5 (1,6%)		
	First degree burn of thigh	1 (0,3%)		
	UTI	1 (0,3%)		
	Delayed drainage via transabdominal RFA access tract	1 (0,3%)		
	Laceration of uterine serosa	1 (0,3%)		
	Laceration of adhesions requiring sutures	1 (0,3%)		
Transvaginal ultrasonographic RFA				
	Minor (SIR A/B) (total n=1882)		**Major (SIR C/D/E/F) (total n=1882)**	
	Abdominal pain	433 (23,0%)	Intestinal perforation	3 (0,2%)
	Vaginal discharge	72 (3,8%)	Hysterectomy due to intracavitary expulsion of fibroid	2 (0,1%)
	Infection	59 (3,1%)	Intestinal heat requiring surgery	1 (0,1%)
	Low fever	15 (0,8%)		
	Mild dural puncture	3 (0,2%)		
	Fluid in pelvic pouch	1 (0,1%)		
Transcervical RFA				
	Minor (SIR A/B) (total n=247)		**Major (SIR C/D/E/F) (total n=247)**	
	Fibroid tissue loss	45 (18,2%)	Deep venous thrombosis	1 (0,4%)
	Abdominal pain	16 (6,5%)		
	Vaginal discharge	10 (4,0%)		
	Infection	7 (2,8%)		
	Dysmenorrhea	7 (2,8%)		
	UTI	2 (0,8%)		
	Fever	1 (0,4%)		
	Fibroid expulsion	1 (0,4%)		

Table 9. Complications after MWA

Minor (SIR A/B) (total n=732)		Major (SIR C/D/E/F) (total n=732)	
Vaginal discharge	73 (10,0%)	Infection requiring admission and antibiotic treatment	1 (0,1%)
Lower abdominal pain	66 (9,0%)	Perforation of small intestine	1 (0,1%)
Unspecified	17 (2,3%)		
Bloody vaginal discharge	9 (1,2%)		
Heat sensation	9 (1,2%)		
Low grade fever	4 (0,5%)		
Admission due to postoperative pain	2 (0,3%)		
Nausea	1 (0,1%)		
Pyelonephritis	1 (0,1%)		
UTI	1 (0,1%)		
Low grade fever	Missing		
Lower abdominal pain	Missing		
Vaginal discharge	Missing		

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Abbreviations

ACOG	American College of Obstetricians and Gynecologists
FIGO	Federation of Gynecology and Obstetrics
FUS	Focused Ultrasound
FUSF	Focused Ultrasound Foundation
HIFU	High-intensity focused ultrasound
RVU	Relative value units
UAE	Uterine artery embolization

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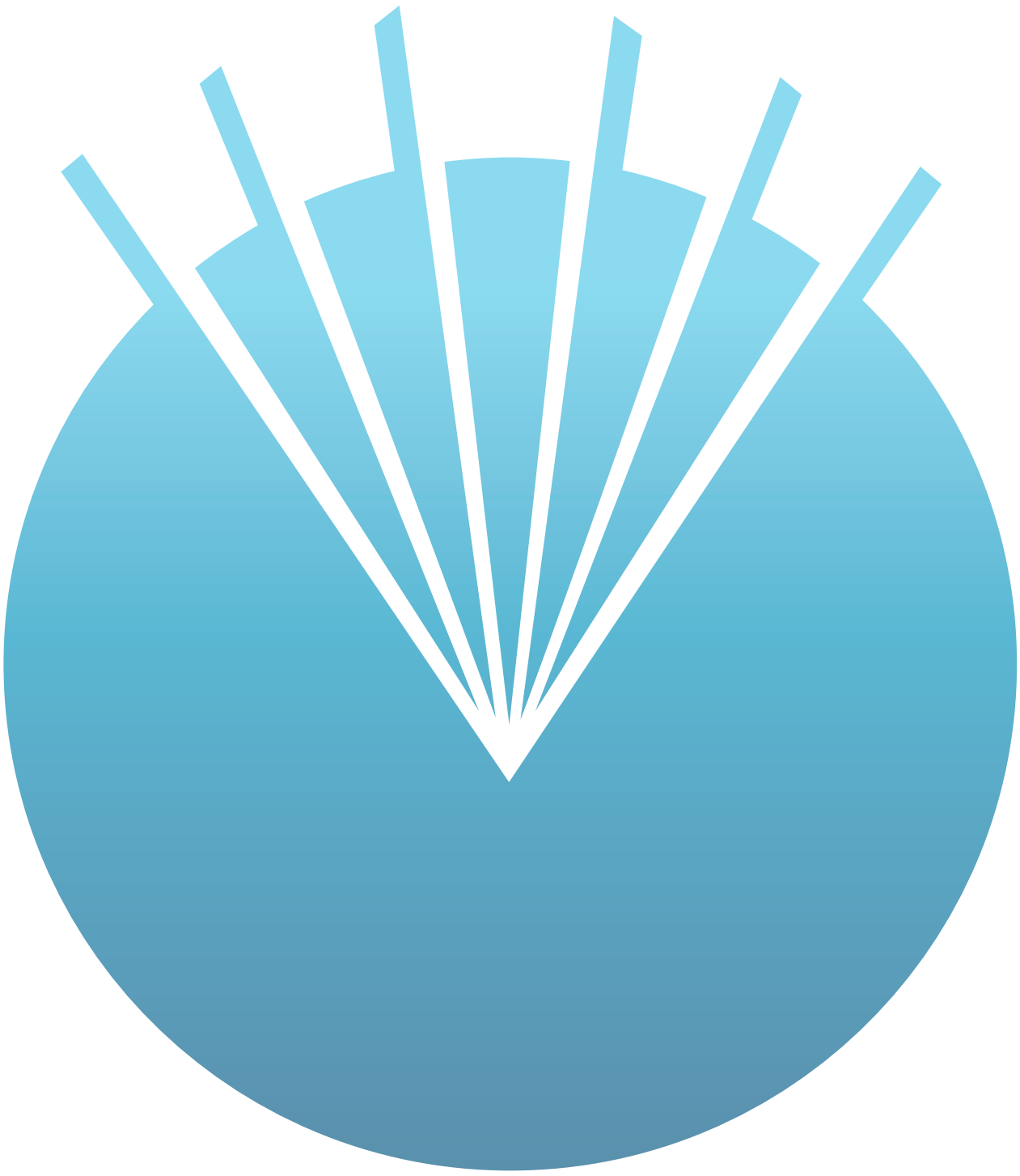

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