GLOBAL CONGRESS ON MIGS

SYLLABUS

609-FIBR:
Fibroids: Non-Extirpative Surgical Medical and Radiologic

Scientific Program Chair
Mauricio S. Abrão, MD

Honorary Chair
Thomas Lyons, MD, MS

President
Ted. T.M. Lee, MD
Professional Education Information

Target Audience
This educational activity is developed to meet the needs of surgical gynecologists in practice and in training, as well as other healthcare professionals in the field of gynecology.

Accreditation
AAGL is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The AAGL designates this live activity for a maximum of 2.50 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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</table>
609-FIBR: Fibroids: Non-Extirpative Surgical Medical and Radiologic

Co-Chairs: Sarah L. Cohen-Rassier and David J. Levine
Faculty: Ayman Al-Hendy, Marisa L. Cañete, Scott G. Chudnoff, Jessica Shepherd

Course Description
This course provides a comprehensive update of the options for non-extirpative treatment of uterine fibroids, including medical management, radiologic techniques (Focused Ultrasound Surgery and Uterine Artery Embolization) and surgical procedures using Radiofrequency Ablation. A balanced discussion will take place to review optimal patient candidates for each treatment option, as well as tips and tricks for success. Video examples and interactive discussions will help illustrate the topics and techniques.

Learning Objectives
At the conclusion of this course, the participants will be able to: 1) Optimize uterine fibroid treatment selection based on patient goals, symptoms and pathology; 2) describe tips for success with radiofrequency surgical techniques; 3) discuss how to safely prescribe medical treatment options for uterine fibroids.

Course Outline
9:45 am Welcome, Introduction and Course Overview
9:50 am Medical Treatment of Uterine Fibroids A. Al-Hendy
The Advantages and Disadvantages of Extirpative versus S. Chudnoff
Ablative Techniques
10:10 am Vaginal Radiofrequency of Fibroids: Scientific Evidence and M.L. Cañete
Application of the Technique
10:30 am Transcervical and Transabdominal Treatment of Fibroids D. Levine
Utilizing Ultrasonic Directed RF Energy
10:50 am Fibroids- How Does Health Care Disparities Impact our J. Shepherd
Patients
11:10 am Slide Show of Tough Cases- Discuss the Best Option from S. Cohen-Rassier
Multidisciplinary Approach
11:30 am Questions & Answers All Faculty
12:15 pm Adjourn
PLANNER DISCLOSURE
The following members of AAGL have been involved in the educational planning of this workshop (listed in alphabetical order by last name).
Linda J. Bell, Admin Support, AAGL*
Linda D. Bradley, MD, Medical Director, AAGL*
Erin T. Carey, MD, MSCR
Honorarium: Teleflex Medical, MedIQ
Mark W. Dassel, MD
Contracted Research: Myovant Sciences
Linda Michels, Executive Director, AAGL*
Vadim Morozov, MD
Speaker: AbbVie
Consultant: Medtronic, Lumenis
Erinn M. Myers, MD
Contracted Research: Laborie Medical Technologies, Teleflex Medical
Other: Unrestricted educational grant to support NC FPMRS Fellow Cadaver Lab: Boston Scientific Corp. Inc.
Amy Park, MD
Speaker: Allergan
Nancy Williams, COO, CME Consultants*
Harold Y. Wu, MD*
Sarah L. Cohen-Rassier, MD, MPH*
David J. Levine, MD
Consultant: Gynecare
Speakers Bureau: Gynecare
Jim Tsaltas, MBBS, FRANZCOG
Education Partner and Fellowship Funding: Covidien
Speakers Bureau: Covidien
Audrey T. Tsunoda, MD, MPH
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Linda Michels, Executive Director, AAGL*

FACULTY DISCLOSURE
The following have agreed to provide verbal disclosure of their relationships prior to their presentations. They have also agreed to support their presentations and clinical recommendations with the “best available evidence” from medical literature (in alphabetical order by last name).
Ayman Al-Hendy, MD, PhD
Consultant: Abb-Vie, AstraZeneca, Bayer, Crila, MDStemCells Inc., Myovant, NIH, OBS-EVA, Rosalind Inc.
Marisa L. Cañete, MD
Speaker Bureau: RF Medical
Scott G. Chudnoff, MD, MS
Consultant: CooperSurgical, MicroCube, Myovant Sciences
Sarah L. Cohen-Rassier, MD, MPH*
David J. Levine, MD
Consultant: Gynecare
Speakers Bureau: Gynecare
Jessica A. Shepherd, MD, MBA
Consultant and Speakers Bureau: AbbVie
Speakers Bureau: Acessa Health
Consultant: Hologic
Consultant: Cynosure
Content Reviewers have nothing to disclose.

Asterisk (*) denotes no financial relationships to disclose.

All relevant financial relationships noted have been mitigated.

SCIENTIFIC PROGRAM COMMITTEE
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Contracted Research: Allergan Pharmaceutical, Blue Seas Medical Spa – Investor, Eximis Surgical, Inc.
Speakers Bureau: Allergan Pharmaceutical
Uterine Fibroid Treatment: The Role of GnRH Receptor Antagonists on Long-Term Medical Management

Ayman Al-Hendy MD, PhD, FRCSC, FACOG
Professor
University of Chicago, Chicago, Illinois, USA

Disclosures

• Receiving research/consultation fund from the following entities
  • Abb-Vie
  • AstraZeneca
  • Bayer
  • Cilia
  • MDStemCells Inc.
  • Myovant
  • NIH
  • OBS-EVA
  • Rosalind Inc.
  • USDA

Objectives

• Pathophysiology
• Risk factors
• Symptoms
• Knowledge gaps/Unmet needs

Uterine Fibroids

- Most common pelvic tumor, occur in 80% of women
- Significant source of morbidity: leading indication for hysterectomy
- Major cause of gynecologic dysfunction:
  - Menometrorrhagia and anemia
  - Pelvic pressure/bulk symptoms
  - Infertility, recurrent miscarriage, preterm labor
- Range of clinical disease is extraordinary: lesions can routinely range from 5 mm to >25 cm in size
- It is well accepted that each fibroid lesion originates independently from single altered myometrial stem cells

Classification

- Most fibroids start as intramural then towards serosa (subserosal), or towards mucosa (submucosal).
- Submucosal most symptomatic → intramural → subserosal

Manifestations of Uterine Fibroids

Uterine fibroids can lead to:

- HMB
- Abdominal distention or distortion
- Anemia and fatigue
- Pressure symptoms and pelvic pain
- Dysmenorrhea
- Infertility/recurrent miscarriage

Uterine fibroids have a significant impact on QoL and are the leading indication for hysterectomy in the United States.
Majority of Women With Uterine Fibroids Experience Heavy Menstrual Bleeding


Of the women affected by UF, up to 50% are symptomatic.

73% of women with symptomatic UF report HMB as a primary symptom. 1

Uterine Fibroids Exosomes

Immunohistochemistry Demonstrates Reduced Expression of BMPR-1A, BMPR-1B, and BMPR-2 in Leiomyoma-Associated Endometrium

Where do Uterine Fibroids come from?

UEFA Champions
May 2018

Normal Myometrial Stem Cell

Moravek et al., Hum Reprod Update, 2015
Mas et al., Hum Reprod, 2015
Bulun. NEJM, 2013

Where do Uterine Fibroids come from?

- Myometrial Stem Cell
  - Tumorigenic Driver Mutation
  - Leiomyoma Tumor Forming Stem Cell
  - Self-Renewal
  - Differentiation
  - Fibroid Tumor cells

Abundant E2/P4
Limited Vitamin D
Retinoic acid
COMT Over-expression
Others

Mas et al., J Am Assoc Gynecol Laparosc, 2015
Bulan. NEM, 2013
Moravek et al., Hum Reprod Update, 2015

Risk Factors for Uterine Fibroid

- Chronic inflammation
- DNA damage and impaired DNA repair
- E2 and P4 responsiveness
- EDCs exposure
- Obesity
- Racial discrimination
- Chronic stress
- Altered microbiota
- Vitamin D deficiency
- Genome instability
- AECI1 Mutations

Bariani et al., Endocrine Reviews, 2021

Where do Uterine Fibroids Come from?

- Normal Uterine Tissue
- Fibroid Tissue

EARLY HIT
LATE HIT
OUTCOME

Mas et al., J Am Assoc Gynecol Laparosc, 2015
Bulan. NEM, 2013
Moravek et al., Hum Reprod Update, 2015

Where do Uterine Fibroids Come from?

Mas et al., J Am Assoc Gynecol Laparosc, 2015
Bulan. NEM, 2013
Moravek et al., Hum Reprod Update, 2015

Where do Uterine Fibroids Come from?

Mas et al., J Am Assoc Gynecol Laparosc, 2015
Bulan. NEM, 2013
Moravek et al., Hum Reprod Update, 2015
Managing Fibroids

Treatment Based on Patient Goals

- What is the patient goal?
  - Preserve fertility
  - Preserve uterus

There Are Many Treatment Options

- The UF treatment landscape
  - Medical
  - Interventional
  - Surgery
  - Symptom management
  - Targeted therapy
  - Myomectomy
  - Hysterectomy

Medical Management of HMB Associated with Uterine Fibroids

- GnRH=gonadotropin-releasing hormone; IUD=intrauterine device.

Long-Standing Options for Treating Uterine Fibroids Have Limited Efficacy or Tolerability Issues

- TRANEXAMIC ACID (TA)
  -TA significantly reduced the mean menstrual blood loss in women with fibroids, but data was pooled with that of women without fibroids.

- LEVONORGESTREL (LNG) - IUD
  - Significant reduction in visual bleeding score shown in a small study comparing LNG-IUD and pregnancy in women with fibroids.

- COMBINED ORAL CONTRACEPTIVES (COC)
  - Duration limited due to side effects: Significant bone mineral density loss, hot flushes, vaginal dryness.

- GnRH AGENTS
  - Suppression tailored to side effects: Significant bone mineral density loss, hot flushes, vaginal dryness.

Newer Options Are Needed
Medical Treatment of Uterine Fibroids

Non-Hormonal/Natural Treatment of Uterine Fibroids

- COMT inhibitors
- EGCG (green tea extract)
- Vitamin D
- Vitamin D receptor agonists
- Localized gene therapy/nanoparticles
- Localized bacterial collagenase

Vitamin D Deficiency is More Common in African Americans

- Vit D deficiency (< 20ng/ml) and insufficiency (<30ng/ml)
  - is up to 10 more common in African American (42%) compared to Caucasians (4%).
- Causes:
  - High melanin contents
  - Lactose intolerance
  - Dietary habits
  - Others

Vitamin D deficiency & Uterine Fibroids: A Global Phenomenon

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Data</th>
</tr>
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<tbody>
<tr>
<td>Srivastava et al. JGOG 2019</td>
<td>2019</td>
<td>VD deficiency + UF occurrence +, size +</td>
</tr>
<tr>
<td>Beig et al. JGOG</td>
<td>2019</td>
<td>VD deficiency + UF occurrence +, size +</td>
</tr>
<tr>
<td>Chyli Szaflarska et al. TDOS</td>
<td>2018</td>
<td>VD deficiency + UF occurrence +</td>
</tr>
<tr>
<td>Cabrera et al. JWR</td>
<td>2016</td>
<td>VD deficiency + UF occurrence +</td>
</tr>
<tr>
<td>Mitro et al. Reprod Toxicol</td>
<td>2015</td>
<td>VD deficiency + UF occurrence, size +</td>
</tr>
<tr>
<td>Atmos et al. ECM</td>
<td>2015</td>
<td>VD deficiency + UF occurrence +</td>
</tr>
<tr>
<td>Reid et al. Epidemiol</td>
<td>2015</td>
<td>VD deficiency + UF occurrence, size +</td>
</tr>
<tr>
<td>Salley and Al-Hendy, Reprod Sci</td>
<td>2010</td>
<td>VD deficiency + UF occurrence, size +</td>
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</table>
Human Uterine Fibroids Expressed Lower Levels of VDR than Adjacent Normal Myometrium (n=40).

Vitamin D3 Treatment showed concentration dependent growth inhibition of Cultured HuLM Cells.

Vitamin D3 Reduced ECM associated Protein Expression in Cultured HuLM Cells as Collagen type 1, Fibronectin, plasminogen activator inhibitor-1 (PAI-1) and α-actin.

• Vitamin D3 Treatment reduced β-catenin Expression in Cultured HuLM Cells

Vitamin D3 and Uterine fibroids at the molecular level:

Knockdown VDR induces Wnt4/β-catenin, mTOR signaling and induces proliferation of UTSM cells as well as ECM related protein expression.

Vitamin D3 blocked Estrogen induced HuLM cell proliferation via reduction of ER and PR expression.

VDR is inversely related with ERα and PR-A/B in human uterine fibroids explants

Eker rats carry a germline genetic defect in Tsc2 (Tsc22Δ)

Females develop multiple, proliferative smooth muscle lesions (leiomyoma) in the uterus when Other Tsc2 allele is mutated or deleted (LOH)

60% of female Tsc22Δ rats by 16 mo

Tumors are hormone dependent with molecular/biochemical correlates to human UL

Everitt et al., AJP, (1995)
Howe et. al., AJP, (1995)

14-16 months old with visible leiomyoma tumors

Control group (n=6) Treated group (n=6)
Vitamin D3 delivered by micro-osmotic pumps (0.5μg/kg) per day for 3 week
Ethylene glycol (vehicle) for 3 week

Vitamin D3 Treatment Shrinks Uterine Leiomyoma Tumors in the Eker Rat Model


Vitamin D Analogues

Paricalcitol (Zemplar)
FDA 1998: Secondary Hyperparathyroidism
C27H44O3 416.64
19-Nor-1α,25-dihydroxyvitamin D
Dramatic Shrinkage of Fibroid Lesions in Nude Mice after 4 weeks of Paricalcitol Treatment

Weekly change in tumor volume

Start
Week
1st week
2nd week
3rd week
4th week

0 50 100 150 200 250 300 350

No visible Deleterious Effects of Paricalcitol Treatment on Reproductive Organs

Vitamin D Anti-Uterine Fibroids in Pilot Clinical Trials

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<td>Hajhashemi et al. CIBM</td>
<td>2019</td>
<td>Human - 50,000 IU every 2 weeks for 10 weeks. Leiomyomas size in vitamin D group significantly decreased as compared to placebo group (52.08 vs 61.11 mm, respectively, P=0.05)</td>
</tr>
<tr>
<td>Casavolti et al. Medicine</td>
<td>2016</td>
<td>Human (53 women). A significant increase in the 25-OH-D3 serum level was observed after 12 months of supplementation, and a lower rate of surgical or medical treatment due to the &quot;progression to extensive disease&quot; was reported (13.2% vs 30.9%)</td>
</tr>
</tbody>
</table>

Real Madrid UEFA Champions May 2017

Green Tea Extract (EGCG, Epigallocatechin Gallate)

Zhang et. al, AJOG, 2012

Pro-apoptotic effects of epigallocatechin gallate on human leiomyoma cells

Zhang et. al, F & S, 2011
Epigallocatechingallate (EGCG) treatment increases health-related quality-of-life (HRQL) in patients with uterine fibroids. SS score dramatically decreased with 4 months' (visit 5) treatment for patients in the EGCG group, compared to the placebo group. Comorbid conditions that require a long-term treatment, such as infertility and uterine fibroids, were assessed in women who received EGCG or placebo. Compliance throughout the 4-month treatment period (visit 1 to visit 5) was high among the remaining participants, but six patients dropped out of the placebo group. Compliance was better in the EGCG group, with only two patients dropping out. The mean fibroid volume decreased by 24.25 (±38.09) in the EGCG group, compared to an increase of 0.24 (±5.3) in the placebo group, indicating a significant decrease (t= 5.25; P < 0.0001). A P-value of <0.05 was considered statistically significant.

**Medical Treatment of Uterine Fibroids**

**NON-Hormonal**
- COMT inhibitors
- EGCG (Green Tea Extract)
- Vitamin D
- VDR Agonists
- Localized Gene Therapy/Nanoparticles
- Localized Bacterial Collagenase

**Hormonal**
- GnRHa
- Elagolix
- Relugolix
- Linzagolix
- RU486
- Ulipristal
- Proellex
- Vilaprisan
- Asoprisnil
- Aromatase Inhibitors
Hormonal Treatment of Uterine Fibroids

Estradiol Levels Within the Therapeutic Window May Improve Symptoms and Maintain Bone Health

Oral GnRH Antagonists

GnRH Receptor Antagonists: Mechanism of Action
Amenorrhea data were a non-ranked endpoint that was not controlled for multiplicity.  


CI=confidence interval.

*ELARIS UF-3 EXTEND is a Phase 3 extension study that evaluated up to an additional 6 months of elagolix + E2/NETA in women who completed the initial 6 months of treatment with elagolix + E2/NETA.

**Final month was defined as the last 28 days before and including the last treatment period visit date.


BID=twice daily.

*300 mg only dosing was used as reference arm

alt=“Amenorrhea Rates in Women on Elagolix + E2/NETA”}

**Baseline Characteristics**

<table>
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<tr>
<th>Characteristics 1</th>
<th>ELARIS UF-1</th>
<th>ELARIS UF-2</th>
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| Race (%)  
White            | 29.4        | 28.6        | 32.0        | 31.4        |
| Other             | 2.0         | 3.0         | 1.0         | 2.7         |
| Age, years        | 33.8 (7.7)  | 33.3 (6.8)  | 33.8 (7.2)  | 33.2 (6.9)  |
| BMI†              | 34.8 (5.7)  | 34.6 (5.3)  | 34.5 (5.4)  | 34.5 (5.3)  |
| Weight, kg        | 119.0 (17.4)| 119.0 (15.0)| 118.0 (17.8)| 119.0 (14.8)|
| Height, m         | 1.63 (0.08) | 1.61 (0.07) | 1.63 (0.08) | 1.62 (0.07) |

*Race was reported by the women.
†The BMI is the weight in kilograms divided by the square of the height in meters.

Other Efficacy Analysis

**Pivotal Trial Groups Included Women With a Variety of Fibroid and Uterine Characteristics**

<table>
<thead>
<tr>
<th>Fibroid Location</th>
<th>Primary Fibroid Volume</th>
<th>Uterine Volume</th>
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<td>Subserosal</td>
<td>Median 16.2 cm³</td>
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| Intramural         | Range 1.3 cm³ to 1081.5 cm³ | Range 716.6 cm³ to 2802.7 cm³
| Subserosal         |                         |                 |

**Other Efficacy Analysis**

**Study Design**

Elagolix 300 mg + E2/NETA was studied in 2 replicate, double-blind, randomized (1:1:2), placebo-controlled, Phase 3 studies.

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<tr>
<th>Category 1</th>
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<td>ELARIS UF-2</td>
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Phase 3 Studies

Study Design

Screening period (2.5–3.5 months)

Washout period (randomized 1:1:2)

Additional 6-month extension treatment

Post-treatment period (up to 12 months)

Final month

*Final month was defined as the last 28 days before and including the last treatment period visit date.


Error bars=95% CI.

†p<0.001; statistical significance vs placebo from a logistic regression model, including treatment as the main effect and baseline MBL volume as a covariate.

‡Data shown are for 205 patients.

Other Efficacy Analysis

**Pivotal Trial Groups Included Women With a Variety of Fibroid and Uterine Characteristics**

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Primary Endpoint: Subgroup Analysis Based on FIGO Classification

**Responder Rates for MBL (Pooled ELARIS UF-1 and ELARIS UF-2 Data)**

<table>
<thead>
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<th>FIGO Classification</th>
<th>Placebo</th>
<th>Elagolix + E2/NETA</th>
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</thead>
<tbody>
<tr>
<td>Hybrid</td>
<td>17.1%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Submucosal</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Intramural</td>
<td>1.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Cervical</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

These data were not controlled for multiplicity.

Primary endpoint: MBL below the heavy bleeding threshold (<80 mL) during the final month.

Error bars = 95% confidence interval. AE = Adverse Event

ELARIS UF-Extend: Safety Results

<table>
<thead>
<tr>
<th>Abnormalities Reported in UF-EXTEND in Women Who Received up to 12 Months of Elagolix with and Back Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elagolix + E2/NETA</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Mean percent change (95% CI)</td>
</tr>
<tr>
<td>Month 0</td>
</tr>
<tr>
<td>Reference:</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Month 12</td>
</tr>
<tr>
<td>Reference:</td>
</tr>
<tr>
<td>Negative</td>
</tr>
</tbody>
</table>

Change in Lumbar Spine Bone Mineral Density

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo</th>
<th>Elagolix + E2/NETA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUMBAR SPINE MINERAL DENSITY BMD (g/cm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute change from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study Design: LIBERTY Program

Study Population for RWS
- Women who completed the 24-week LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and met the responder criteria at 1 year
- Women who completed the LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and did not meet the responder criteria at 1 year
- Women who completed the LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and met the responder criteria at 1 year and did not meet the responder criteria at 12 months

LEBILITY 1 and 2 (Phase 3)
- Women who completed the 24-week LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and met the responder criteria at 1 year
- Women who completed the 24-week LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and did not meet the responder criteria at 1 year
- Women who completed the 24-week LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and met the responder criteria at 1 year and did not meet the responder criteria at 12 months

LIBERTY LTE
- Women who completed the 24-week LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and met the responder criteria at 1 year
- Women who completed the 24-week LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and did not meet the responder criteria at 1 year
- Women who completed the 24-week LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and met the responder criteria at 1 year and did not meet the responder criteria at 12 months

RANDOMIZED WITHDRAWAL
- Women who completed the 24-week LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and met the responder criteria at 1 year
- Women who completed the 24-week LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and did not meet the responder criteria at 1 year
- Women who completed the 24-week LIBERTY 1 or 2 trials and the 28-week LIBERTY LTE study and met the responder criteria at 1 year and did not meet the responder criteria at 12 months

Relugolix

Relugolix CT = relugolix 60 mg × 1 tablet 1 time and placebo × 1 tablet 1 time.
Relugolix Combination Therapy: LIBERTY Trials Study Design

Population
• Premenopausal women 18-50 with a diagnosis of uterine fibroids and heavy menstrual bleeding; menstrual blood loss of >80 mL per cycle (alkaline hematin method)

Primary endpoint
• Proportion of responders with < 80 mL uterine blood loss/cycle and at least a 50% reduction in menstrual blood loss by alkaline hematin method

Uterine Fibroids and Heavy Menstrual Bleeding
N ~ 390, each LIBERTY 1 & 2, 1:1:1

Double-Blind Treatment: 24 weeks
Relugolix QD 12 weeks
Relugolix CT QD 12 weeks
Relugolix Combination Therapy QD

WEEK 24
Primary Endpoint

WEEK 52
Extension Study (N=477)
Relugolix CT QD
Placebo

Relugolix Combination Therapy Demonstrated Significant Improvement in Heavy Menstrual Bleeding After 24 Weeks

Primary endpoint:
Proportion of women responding with:
• Menstrual blood loss (MBL) volume* of < 80 mL
• ≥ 50% reduction from baseline to Week 24 (last 35 days of treatment) in MBL volume

Proportion of Women (%)

Relugolix Combination Therapy

Placebo


Liberty 1 (N=387)
Liberty 2 (N=381)

Relugolix Combination Therapy Demonstrated Significant Improvement in Heavy Menstrual Bleeding After 24 Weeks

Percent Change From Baseline in Menstrual Blood Loss Volume: at Week 24 (pooled data)

LS Mean Percent Change in MBL Volume from Baseline (%)

Relugolix Combination Therapy

Placebo

P < 0.0001

Percent Change in MBL Volume From Baseline to Week 52

Reduction in Menstrual Blood Loss Volume Was Maintained Over 52 weeks

Hemoglobin Levels with Relugolix Combination Therapy in Women with Anaemia at Baseline

Percent Change in Hemoglobin From Baseline to Week 52 in Anemia-evaluable Population

Randomized treatment
Extension period: all patients received Relugolix Combination Therapy

Proportion of Patients with Minimal-to-No Pain (Maximum NRS Score ≤ 1) During the Last 35 Days of Treatment

Mean Maximum NRS Score Over Time (24 Weeks)
### Amenorrhea with Relugolix Combination Therapy

#### Secondary Endpoint

Proportion of women with amenorrhea during the last 35 days of the study.

- **LIBERTY 1**
  - 84 (51.6%)
  - p<0.0001

- **LIBERTY 2**
  - 85.5 (52.0%)
  - p<0.0001

#### Menstrual Blood Loss in second year of the Liberty program

- Absolute Mean MBL Volume (mL)
  - Placebo: 113
  - Relugolix CT: 106

#### Summary of Adverse Events Over 52 Weeks of Treatment

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (n = 163)</th>
<th>Relugolix Combination Therapy (n = 162)</th>
<th>Delayed Relugolix Combination Therapy (n = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>118 (71.8%)</td>
<td>127 (77.8%)</td>
<td>126 (76.9%)</td>
</tr>
<tr>
<td>Leading To Discontinuation</td>
<td>2 (1.2%)</td>
<td>5 (3.1%)</td>
<td>0 (0.6%)</td>
</tr>
<tr>
<td>Grade 3 or greater</td>
<td>27 (16.5%)</td>
<td>12 (7.5%)</td>
<td>21 (13.0%)</td>
</tr>
<tr>
<td>Serious</td>
<td>18 (11.0%)</td>
<td>8 (5.0%)</td>
<td>12 (7.4%)</td>
</tr>
<tr>
<td>Serious Leading To Discontinuation</td>
<td>1 (0.6%)</td>
<td>5 (3.1%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Fatal Event</td>
<td>0 (0.0%)</td>
<td>2 (1.2%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

#### BMD Changes with Relugolix Combination Therapy at Week 24

- Percent change from baseline
- **LIBERTY 1**
  - L1: Relugolix CT
  - L2: Placebo
- **LIBERTY 2**
  - L1: Relugolix CT
  - L2: Placebo
Linzagolix

Phase 3 registration studies
PRIMROSE 1 (US) and PRIMROSE 2 (EU/US)

PRIMROSE 1 and 2 achieved primary endpoint for both doses
Responder* analysis at week 24

PRIMROSE 1 and 2 achieved sustained reduction in MBL
Responder* analysis at week 52

---

Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Relugolix Combination Therapy</td>
</tr>
<tr>
<td>Placebo</td>
<td>Relugolix Combination Therapy</td>
</tr>
<tr>
<td>Placebo</td>
<td>Relugolix Combination Therapy</td>
</tr>
</tbody>
</table>

---

Randomized treatment Extension period: all patients received Relugolix Combination Therapy

Percent Change in Lumbar Spine BMD to Week 52

Relugolix Combination Therapy Maintained Lumbar Spine Bone Mineral Density Over 52 Weeks

LS Mean Percent Change from Baseline (%)

Baseline W12 W24 W36 W52

Placebo

Relugolix Combination Therapy (n = 163)

Delayed Relugolix Combination Therapy (n = 149)

---

Error bars are 95% CI

P=0.003

P<0.001

P<0.001

P<0.001

n=103 n=94 n=102 n=102 n=97 n=98 n=205 n=191 n=200

---

Responder* analysis at week 24

PRIMROSE 1 and 2 achieved sustained reduction in MBL

---

*Proportion of women with menstrual bleeding ≤ 80 mL (by alkaline hematin method) and ≥ 50% reduction from baseline

---

Phase 3 registration studies
PRIMROSE 1 (US) and PRIMROSE 2 (EU/US)

Placebo (P1 only)

200 mg + ABT

100 mg + ABT

24-Week Post-Treatment Follow-up

---

Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo</th>
<th>Relugolix</th>
<th>Placebo</th>
<th>Relugolix</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>56 (44%)</td>
<td>64 (50%)</td>
<td>51 (40%)</td>
<td>49 (38%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (5%)</td>
<td>6 (5%)</td>
<td>12 (9%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>32.3 (7.5)</td>
<td>31.4 (7.6)</td>
<td>31.4 (7.3)</td>
<td>32.1 (7.6)</td>
</tr>
<tr>
<td>Mean TUV, cc</td>
<td>398 (325)</td>
<td>380 (317)</td>
<td>470 (428)</td>
<td>408 (402)</td>
</tr>
</tbody>
</table>

---

Results of Linzagolix studies have been published in various journals and presented at relevant conferences. For more information, please refer to the original studies and publications cited in the text.
Significant pain reduction maintained at weeks 52 and 64

Pain assessed on Numerical Rating Scale: 0-10

LGX 200 mg without ABT significantly reduces uterine volume

Substantial reduction compared to placebo & LGX 200 mg with ABT at Week 24

Minimal BMD change with both doses, plateauing after week 24

Expected age-related BMD decline observed in placebo arm at Week 52

Favorable tolerability profile

Summary of adverse events—week 24 to 52

Pregnancy and UF

- UF less than 4 cm pre-pregnancy
  - Disappeared on US postpartum

Menopause and UF

- Reduces bleeding and pain, and decreases fibroid growth before menopause
  - Improves quality of life following surgery or in those who declined surgery

Completed family/mid-reproductive age

- goal: Bridge to pregnancy
  - Pregnancy can ameliorate UF disease course

Goal: Bridge to menopause

- 24 months course then re-evaluate
  - Early menopause

Let’s Make Uterine Fibroids a Medical Disease Again!

Elagolix, relugolix, linzagolix

- Stops uterine bleeding
- Improves quality of life
- Limited data on return of symptoms after treatment
- Long-term improvement

Symptomatic UF patient journey can benefit from medical treatment

Pregnancy and UF

- UF less than 4 cm pre-pregnancy
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Ali & Al-Hendy, BOR, 2017

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- 24 months course then re-evaluate
  - Early menopause

Ali & Al-Hendy, BOR, 2017
There Are Many Treatment Options

- Medical
- Interventional
- Surgery

- Symptom management
- Targeted therapy
- Myomectomy
- Hysterectomy

Goal of Therapy: Eliminate symptoms while preserving the uterus whenever possible

Guidelines from the American College of Obstetricians & Gynecologists support women pursuing alternatives to hysterectomy irrespective of their gestational intention.

The Future Treatment Paradigm?

- Symptomatic
- Unresponsive
- Does not tolerate
- Wants definitive therapy
- Others (uterine artery embolization, endometrial ablation, high frequency ultrasound, etc.)

Medical Therapy

Physician patient to achieve shared decision-making to find best option for her

Shifting Paradigm in the Treatment of Peptic Ulcer Disease

Strategies used during the 20th century for counteracting action of gastric acid

Inflexion occurs during the 1980s with introduction of drugs inhibiting gastric acid secretion

UEFA Champions
May 2017

Thank you
FIBR-609: The Advantages and Disadvantages of Extirpative versus Ablative Techniques

Scott G. Chudnoff, MS, MSc
Chair of Obstetrics & Gynecology and Women’s Health – Maimonides Medical Center

AAGL 50th Global Congress, Austin, Texas
PG Session: Fibroids: Non-Extirpative Surgical Medical and Radiologic
November 14th, 2021

Disclosures
I have served as an investigator for Acessa, Gynesonics, Bayer and Philips

I serve / have served as a consultant for Cooper Surgical, Myovant, and Microcube

Objectives
To describe the difference between extirpative vs. non-extirpative treatments
Review the advantages and disadvantages of each modality

Different Treatment Options

Extirpative
- Myomectomy
- Hysteroscopic
- Laparoscopic / Robotic
- Hysterectomy
- Vaginal
- Abdominal
- Laparoscopic

Non-Extirpative
- Medical Modalities
  - Selective Progesterone Receptor Modulators
  - Selective Estrogen Receptor Modulators
  - Danazol
  - GnRH Agonists
  - GnRH Antagonists
- Surgical / Ablative Modalities
  - UAE
  - High intensity focused US
  - RFA (laparoscopic/transcervical)
  - Cryosurgery
  - Myolysis

What is extirpative?

verb (used with object), ex·tir·pat·ed, ex·tir·pat·ing. to remove, destroy totally; to exterminate; to pull up by or as if by the roots, or up to a distance of the length of hair.

https://www.dictionary.com/browse/extirpate

Call to Action

Addressing heterogeneous outcomes in uterine fibroid research: a call to action
Amine P. Tarek, MPH; Jennifer Al Nabab, MS, MPH; Ellen S. Tabone, MA; Franco R. Myers, MD, MPH

The problem: There is a notable lack of high-quality evidence to inform uterine fibroid treatment decisions. In part, because of the use of heterogeneous outcomes and instruments in clinical studies to date and the inconsistent measurement of outcomes that are most important to patients.

A solution: Development of a core outcome set and uterine fibroid tumors that would use a multidimensional approach will ensure that a consistent, stakeholder-based set of outcomes is accessible across different studies and would complete transparency for investigators who seek to elucidate the evidence needs of patients, providers, payers, regulators, and other stakeholders.
Extirpative Methods

- Hysterectomy
- Myomectomy

The Misunderstood Organ

Hippocrates

“the womb wasn’t a fixed item but wandered about the body looking for trouble”

“women’s complaint characterized by nervousness, fluid retention, insomnia and lack of appetite”

“hysteria is a blockage in the womb”

Galen

“Arising from the touch of the genital organs required by the treatment, there follows twitchings accompanied at the same time by pain and pleasure...from that time she is free of all the evil she felt”

HYSTERECTOMY

HYSTER = Uterus
ECTOMY = Remove
**History of Hysterectomy**

- 120
- 1843
- 1853
- 1920's
- 1930's
- 1988

**Hysterectomy**

- Definitive management
  - "Gold Standard"
- Most invasive procedure
- Prolonged hospital stay and recovery

**History of Myomectomy**

- 1809
- 1840
- 1845
- 1840
- 1920
- 1976
- 1976

**Myomectomy**

- Uterine sparing
- Considered standard of care for infertility
- Performed hysteroscopically, laparoscopically, and abdominally

**Non-extirpative modalities**

- Medical
  - Hormonal manipulation
- Energy-based ablation

- Ischemic
  - Uterine Artery Embolization
  - Suture Ligature

**Aspects for Evaluation of Treatment Options**

- Future Fertility
- Risk of complications
- Rate of failure (acutely)
- Rate of failure (long-term)
- Amount of symptom alleviation
- Time to return to daily activities
- Procedural resources
- Costs
- Learning curve
Treatments by Invasiveness

- Most Invasive
  - Abdominal Hysterectomy
  - Abdominal Myomectomy
- Least Invasive
  - Laparoscopic / Robotic Hysterectomy
  - Laparoscopic / Robotic Myomectomy
  - Transvaginal Hysterectomy
  - Transvaginal Myomectomy
  - Medical Management
    - Medical Management
      - Laparoscopic / Robotic Myomectomy
      - Laparoscopic Radiofrequency Ablation
      - Uterine Artery Embolization
      - Transvaginal Radiofrequency Ablation
      - MRI Guided High Frequency Focused Ultrasound Ablation

EMMY Trial (2005)
- Multicenter, RCT, N=177
- Compared patient outcomes between UAE and hysterectomy

FIRSTT Study (2019)
- RCT, N=91
- Compared patient outcomes between MRgUS and UAE

Outcomes
- Reintervention: Reintervention was higher in MRgUS group (30%) compared to UAE group (13%)
- Quality of Life: Symptoms improved in both groups; however, HRQL and SSS subscale significantly improved in UAE group
- Pain Scores: VAS scores lower in UAE group, however not statistically significant
- Sexual Function: Similar improvement in sexual function in both treatment groups
- AMH: AMH absolute change greater in UAE group at 24 months (-0.6 vs -0.2)

FEMME Trial (2020)
- Multicenter, RCT, N=254
- Measured QOL in groups undergoing UAE and myomectomy


Risk of Cancer - Explicative

Prevalence of undiagnosed uterine leiomyosarcoma in women undergoing hysterectomy or myomectomy for benign indications

Séverine Lenge 1, Nicola Pluchino 2, Aurore Fehlmann 1, Roberto Masi 2, Meriem Boukrid 2, Ines Ben Jemaa 2, Patrick Petignat 2, Jean Dubuisson 2

Can Non-Exirpative Treatments Change the Algorithm?

- Desires future fertility
  - Severe symptoms
  - Mild / no symptoms
- Attempts pregnancy
  - Treat fibroids
  - Attempt pregnancy
- Wait until symptoms worsen
10:30 Vaginal Radiofrequency of Fibroids: Scientific Evidence and Application of the Technique

Presenting Author Name: Maria Luisa Cañete Palomo MD PhD
Director of Fibroid Clinic of Santa Elena Clinic (Madrid, Spain)

Disclosure

- Speakers Bureau: RF Medical

Objectives

- show how to diagnose with doppler ultrasound and elastography and to explain how to treat fibroids with vaginal radiofrequency

Types of radiofrequency

1. Acessa™ SYSTEM is RF via LPS guided by ultrasound
2. RF by vaginal ultrasound with Sonata® system
3. RF by Vaginally ultrasound with electrode
The myomas were intramural in 36 cases (78.3%), submucosal in 8 cases (17.4%) and non-pedunculated subserosal in 6 cases (13.0%).

Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (cm)</th>
<th>3-month follow-up</th>
<th>6-month follow-up</th>
<th>12-month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (baseline)</td>
<td>30.0 ± 10.2</td>
<td>28.0 ± 6.0</td>
<td>18.0 ± 5.0</td>
<td>10.0 ± 3.0</td>
</tr>
<tr>
<td>Myoma volume (cm³)</td>
<td>30.0 ± 10.2</td>
<td>28.0 ± 6.0</td>
<td>18.0 ± 5.0</td>
<td>10.0 ± 3.0</td>
</tr>
<tr>
<td>Pregnancy reduction (mg/dL)</td>
<td>8.0 ± 2.0</td>
<td>6.0 ± 1.0</td>
<td>4.0 ± 0.5</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>Myoma volume (cm³)</td>
<td>30.0 ± 10.2</td>
<td>28.0 ± 6.0</td>
<td>18.0 ± 5.0</td>
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<td>6.0 ± 1.0</td>
<td>4.0 ± 0.5</td>
<td>2.0 ± 0.5</td>
</tr>
</tbody>
</table>

* Mean difference is significant at the 0.05 level.
What is my contribution to vaginal radiofrequency?

- 1. Diagnosis of fibroid with DU (Doppler ultrasound): for the diagnosis, vascularization, and the end point in the vaginal radiofrequency
- 2. 3D ultrasound: help me exact location
- 3. And I use Elastography: I have information about the hardness, the consistency of the fibroids
3. Elastography and Ro curve before RF (you can know the hardness of the fibroid)

3.- Elastography and Ro curve after RF (you can know the hardness of the fibroid)

**types of radiofrequency**

1. **Acessa™ SYSTEM** is RF via LPS guided by ultrasound

2. RF by vaginal ultrasound with **Sonata® system**

3. RF by Vaginally ultrasound with electrode

**Radiofrequency Indications**

- **Size**: < 180 cm³, are the best results. Ideal patient < 75 cm³
- **Age**: less reintervention risk in > 45 old
- **Young people** with delayed gestational wishes and a growing fibroid: the evidence is explained. The goal of stopping growth
- **Number of fibroids**: < 3 (total volume < 180 cm³)
- **Pedunculates and fibroids with difficult access are contraindicated.**

**Define the goal of treatment**

1. Stop the growth of the fibroid
2. Decrease bleeding, resolve anemia
3. Reduce pain
4. Decrease the feeling of pressure in the bladder
5. Solve dyspareunia

**Vaginal radiofrequency with Doppler ultrasound**
Vaginal radiofrequency with Doppler ultrasound

- 46 OLD
- Intramural fibroid 30x32x28 mm
- Vascularization type 3
- ELASTOGRAPHY Ro curve +2.3
- Anormal Menstrual Bleeding

RF 1 minute

Advantages of RF of vaginal Fibroids

1. Preserves the uterus with minimal damage
2. It’s performed with sedation, the procedure lasts 20 minutes
3. The patient goes home as soon as she recovers from sedation: 30-60 minutes
4. Symptoms such as excessive bleeding or pain improve quickly
5. Post-procedure pain is very mild, there is little bleeding, and no injuries occur
6. Reoperation is possible

End point with RF
Vaginal RADIOFREQUENCY
Dra ML Cañete

60 total patients

<table>
<thead>
<tr>
<th>Media</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (25-54 years)</td>
</tr>
<tr>
<td>Reoperation rate</td>
</tr>
<tr>
<td>Follow-up: 0-2 years</td>
</tr>
<tr>
<td>Follow-up: 2-4 years</td>
</tr>
</tbody>
</table>

Complications

- Thermal injury requiring laparoscopy, 30 minutes
- Very mild Pain
- Normal activity in 48 h

Size of fibroids

- 37 patients: 75-280 cm³
- 23 patients: <75 cm³
- Best results: <75 cm³

References


Transcervical and Transabdominal Treatment of Fibroids Utilizing Ultrasonic Directed RF Energy

David J. Levine M.D.
Director of Minimally Invasive Gynecologic Surgery
Mercy Hospital St. Louis

Disclosures
Consultant to Gynesonics

Why do we need new technology?
Find a better mouse trap
Cheaper
Faster
Safer
Procedure looking for an indication
Generally motivated by poor long term results or limited options post procedure

Radiofrequency Ablation of Uterine Fibroids
Volumetric, image-guided ablation:
• Optimizes ablated volume of targeted fibroid
• Avoids multiple passes of energized needles through the serosa
• Treats the fibroids that are likely to be symptomatic
• Incites thermal fixation and coagulative necrosis
• Avoids infarction-related postembolization syndrome seen with UAE

Coagulative Necrosis
• Cell Death
  Function of temperature and time
  Human Cells
  42-46 °C for 45 minutes
  55 °C for 2-6 minutes
  60 °C nearly instantaneous
  100 °C H2O vaporization, tissue desiccation/charring
• Ablation Volume
  Temperature and duration of time at given temperature
  Needle probe characteristics (size, shape, number)
  Target tissue characteristics (heat sinks, scarring, heterogeneity)
• No "Post-UAE Syndrome"

Heavy menstrual bleeding
Pressure symptoms
Uterine preservation

indications

Page 30
RF Ablation vs Myolysis

- **Myolysis**
  - Bipolar cauterization of fibroid capsule and myometrium/serosa
  - Multiple punctures around the periphery of the tumors
  - No needle guidance with ultrasound
- **RF Ablation**
  - Limited to the fibroid
  - Ultrasound guided

**Contraindications for the laparoscopic and transcervical approach**

- Patients who are not candidates for laparoscopic surgery due to intrabdominal adhesions or lack of uterine mobility due to scarring or adjacent pathology
- Uterine size greater than 14 weeks (this may vary with experience)
- Suspected or undiagnosed uterine malignancy
- Active genital infection
- Metal implants near the ablation site or along the RF return path (hip and back implants knee is not in the path)
- Future pregnancy

**Preop evaluation**

- Ultrasound or MRI with proper fibroid measurements and mapping
- Endometrial sampling
- Blood work and LDH 3 isoenzyme panel (if over 40)

**Number of IM vs SM Fibroids**

<table>
<thead>
<tr>
<th>Type</th>
<th>Ultrasound (US)</th>
<th>cMRI</th>
<th>TVUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>200</td>
<td>110</td>
<td>80</td>
</tr>
<tr>
<td>SM</td>
<td>120</td>
<td>50</td>
<td>15</td>
</tr>
</tbody>
</table>

**FIGO Fibroid Classification**

<table>
<thead>
<tr>
<th>Leiomysoma Subclassification System</th>
<th>0</th>
<th>1</th>
<th>2-5</th>
<th>6-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Submucosal</td>
<td>0</td>
<td>Submucosal Intraventricular</td>
<td>Submucosal Intramural</td>
<td>Submucosal Transmural</td>
</tr>
<tr>
<td>O-Other</td>
<td>3</td>
<td>Contact Endometrium, Intra-Submucosal Intra-Submucosal</td>
<td>Submucosal Submucosal</td>
<td>Submucosal Submucosal</td>
</tr>
</tbody>
</table>

**Accessa**

- 2 transabdominal midline ports one for laparoscopic visualization and one for ultrasound wand and ProVu guidance system

**Sonata**

- Transcervical insertion of ultrasound probe with SMART Guide handpiece
The Intrauterine Ultrasound Probe and the RFA Handpiece combine to form a single integrated Treatment Device

Main Procedure Steps:
- Access the endometrial cavity through a transcervical approach
- Locate and target a fibroid
- Graphically select the ablation size and location
- Deploy Introducer and then Needle Electrode into the fibroid
- Ablate (time at temperature is automatically selected based on the ablation zone)
- Repeat if needed

Depending on size, one ablation will require 2-7 minutes (time at temperature)

SMART Targeting Guide: Setting Margins of Ablation in Real Time

Graphic courtesy of live sonographic image set by operator using the control knob on the RFA Handpiece, determining:
- Ultrasound axis of ablation
- Mechanical safety stops limit depth for Introducer and Needle Electrode advancement
- Duration of radiofrequency energy delivery

In this example, the ablation is appropriately sized to ablate 100% of the fibroid while the green ellipsoid (Thermal Safety Border) is safely located within the uterine serosa

- complications
  - Laparoscopic approach
  - Abdominal wall hematoma
  - Pelvic abscess
  - Superficial colonic laceration
  - Transcervical
  - Endometritis

Comparative data at 12 months

Acessa:
- 82% reduction in menstrual bleeding of which 40% experienced a 50% reduction
- 45% mean fibroid volume reduction and 24% decrease in uterine volume
- 94% patient satisfaction
- 1 serious adverse event
- Return to normal activity in 4-9 days

Sonata:
- 95% reduction in menstrual bleeding of which 65% reported at least 50% reduction
- 96% reported symptom relief
- No adverse events
- 50% returned to normal activity the next day

Laparoscopic approach
- Abdominal wall hematoma
- Pelvic abscess
- Superficial colonic laceration
- Transcervical
- Endometritis
- Pelvic abscess
**Significant Reduction in Menstrual Blood Loss**

- Mean MP score declined through 12 months, with mean and median reductions of 54% and 72% at 12 months, respectively.
- 90% of patients (44/49) experienced a reduction in menstrual blood loss by 3 months post-ablation.

**Significant Improvements in Patient-Reported Outcomes**

- Mean 55.1% reduction in symptom severity at 12 months.
- 277% increase in health-related quality of life.
- Mean reduction in SSS of 35.3 points from baseline.
- 10-point reduction in SSS is clinically significant.
- The majority of patients experienced ≥ 10-point reduction in SSS: 82% of patients at 3 months, 86% at 6 months, 78% at 12 months.

36 month followup data:

- Both techniques showed continued significant reduction and health improvements sustained.
- Transabdominal reported 11% cumulative reintervention rate (1% from undiagnosed adenomyosis).
- Transcervical reported 8% surgical reintervention for heavy menstrual bleeding.

**Conclusion**

Management of symptomatic fibroids with both transabdominal and transcervical modalities has demonstrated long term benefit with minimal surgical reintervention.

The Transcervical approach is incisionless, 24-48 hr. return to normal activity and is best utilized for severe menorrhagia due to submucosal and intramural fibroids.

The Transabdominal approach can treat all fibroids requires general anesthesia is technically more challenging, return to normal activity in 4-9 days.

**References**

- Chudnoff et al. Outpatient Procedure for the Treatment and Relief of Symptomatic Uterine Fibroids OBGYN 2013 121(5)1075-82
- Berman et al. Three year outcome from the Halt trial A prospective analysis The Journal of Minimally Invasive Gynecology 2014 21 (5) 767
- LukesA, Green MA Three year Results of the Sonata Pivotal Trial of Transcervical Fibroid Ablation for Symptomatic Uterine Myomata J. Gynecol Surg 2020 36:5 228-233
DISPARITY IN WOMENS HEALTH CARE:
A FIBROID PROBLEM WITH A SOLUTION

JESSICA SHEPHERD MD, MBA, FACOG
CHIEF MEDICAL OFFICER- VERYWELL HEALTH
SANCTUM MED + WELLNESS

DATA ON EXISTENCE OF DISPARITIES

• In 2002, the IOM released Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care.
• It reported evidence of healthcare inequality—irrespective of income, insurance status, or education.

REASONS FOR INEQUALITIES

• Subtle differences in the way individuals respond to treatment.
• Variations in individual help-seeking behavior.
• Barriers in language proficiency, literacy level and cultural beliefs.

REASONS FOR INEQUALITIES

• A healthcare professional’s beliefs may influence patient interaction.
• The healthcare professional may be limited in the amount of time available to gather information.
• An unconscious prejudice or bias may exist.

WHY IS IT IMPORTANT?

• The US Census Bureau estimates that by 2050, one in every two Americans will be an African/American, Hispanic/Latino, American Indian/Alaskan Native, or Native Hawaiian/Pacific Islander.

• Black women are at least twice as likely as white women to remove their uterus through a hysterectomy.
• A third of hysterectomies are done during peak childbearing years between ages 18 and 44.
• Despite minimally invasive options, Black women continue to dominate the percentages of women having hysterectomies for benign disease.
LACK OF RESEARCH

• In addition to the racial health disparity of the disease, uterine fibroids represent a health disparity on another level: there is a disparity between the immense burden of disease and the resources that have historically been devoted to study of the condition.

WHERE TO FILL THE GAP

• Effective preventative and non-surgical treatment options are urgently needed for young women.
• More research is needed to fill in these gaps and tackle the immense problem of uterine fibroids.
• Hospitals and health care systems need to start to address social determinants of health.

CHANGE IN NARRATIVES IN THE FIBROID STORY

• Familial and cultural factors influence how younger enter into care.
• Many families where mothers and grandmothers have experienced fibroids, heavy bleeding can become normalized and women do not always seek care until their fibroids are further along.
• Educating young women about what to expect of their menstrual cycles could help women enter care sooner and with less disease burden.

UNMET NEEDS

• Improved Diagnostic Techniques
• More Effective, Fertility-Preserving, Well-Tolerated Treatments
• Enhanced Patient Education/Empowerment
• Expanded Access to Treatment
• Identification of Best Practices
TANGIBLE SOLUTIONS

- Open, honest, real conversations about racial equity and what it means to have a culture of inclusion.
- Advancing policy solutions and research to better address health disparities.
- Diversifying our practices to better invest in Black and Brown America.
- Earning trust and addressing systemic issues to better foster the inclusion of Black and Brown communities in participating in clinical trials.

Symptoms associated with UF can negatively impact daily living and quality of life (QoL). Symptoms vary by patient, but many women with UF have more than one symptom. Heavy menstrual bleeding (HMB), the most common symptom, occurs in about one-third of patients and can result in life-threatening anemia.

ECONOMIC BURDEN

- The annual cost of UF has been estimated to total 34.4 billion USD, which is more than breast cancer, colon cancer, or ovarian cancer, however less than cardiovascular disease.

HOW TO COLLABORATE WITH PATIENTS, POLICY AND ORGANIZATIONS

- Patient advocacy groups like the White Dress Project and the Fibroid Foundation work to raise awareness of the disease and amplify patient voices.
- Also policy makers such as VP Kamala Harris and Rep. Yvette Clarke earlier this year introduced the Uterine Fibroid Health Act to expand federal research efforts and bring much needed attention to this overlooked disease.

- The study and understanding of health disparities requires dialogue and introspection to our individual belief systems. This will continuance of what we can accomplish to pursue the ultimate goal of eliminating disparities in women’s health.
Multidisciplinary Approach to Fibroids: Case Reviews

Sarah L. (Cohen) Rassier MD, MPH
Director of Fibroid Clinic, Mayo Clinic Rochester MN

Disclosure

I have no financial relationships to disclose

Objectives

- Review expected effects of the non-extirpative fibroid treatments
- Understand counseling on variety of treatment options for individualized care
- Recommend optimal treatment choice for various patient scenarios

Work Up

- Physical exam
  - Uterine size, mobility, where is the bulk?
- Imaging: U/S or MRI
- To assess cavity: Hysteroscopy or saline infusion sonogram
- Labs
  - CBC, iron studies, if indicated TSH, prolactin
- Very low threshold to do endometrial sampling

Treatment Options

- MEDICATIONS
- INTERVENTIONS
- EXTRIPATIVE SURGERY

What are patient goals?

- Which symptoms are most bothersome?
- Interest in future pregnancy?
- Desire to retain uterus
  - Cultural?
  - Long-term health outcomes?
- Size, number and location of fibroids?
Treatment Options

MEDICATIONS
- Interstitial Prostaglandin E2
- GnRH agonist

INTERVENTIONS
- Uterine Artery Embolization
- UFE OUTCOMES
  - Gupta JK, Cochrane Database Syst Rev. 2014
  - >80% improvement in bleeding
  - 30%-50% volume reduction*
  - Risk of non-target embolization (effect on ovarian reserve) similar to hysterectomy
  - Risk of abnormal placentation in future pregnancies

EXTIRPATIVE SURGERY
- Focused Ultrasound Surgery
  - Treatment time depends on fibroid burden
  - <1 week recovery
  - Very low complication rates
    - Abdominal wall inflammation
    - Subcutaneous edema
  - More difficult for insurance coverage

Uterine Artery Embolization
- Can treat wide variety of fibroids
- Less efficacy if >10cm
- Not ideal for large Type 0/1
- 1 night hospital stay for pain control
- Post embolization syndrome
- 1-2 week recovery
- Progressive improvement over 3-6 months

Reintervention risk: UAE vs MMY
- Comparable quality of life, symptom and sexual function scores
- Similar ovarian function and pregnancy loss
- Lower pregnancy rates (2.2x)
- 14-20% reintervention within 5 years
  - For comparison, myomectomy had 12-15% reintervention in similar studies
**Ideal candidate:** single T2 dark fibroid 4-7cm
- Can do multiple fibroids
- Can move bowel to access posterior fibroids
- Lower size limit 2cm
- Upper limit is fundus at umbilicus
- Can’t treat peripherally calcified fibroids
- Avoid hypercellular fibroids
- Limited in patients with extensive abdominal wall scarring

**FUS OUTCOMES**
- 30% of fibroid volume decrease over 6 months
- Promising data on future pregnancy
- Similar sexual function scores as MMY
- Reintervention risk varies widely in literature
  - Some quote similar to MMY, some as high as 50% at 5 years
- Mayo internal data: 23% reintervention at 4 years

**LSC RFA OUTCOMES**
- Laparoscopic recovery: 2-3 weeks, shorter than typical myomectomy
- Similar quality of life, sexual function, symptom severity scores
- Roughly 50-70% volume reduction
- 12% reintervention at 3 years (similar to MMY)
- Okay for future pregnancy, limited data but appears similar to MMY
- Insurance coverage can be limited

**Transcervical radiofrequency ablation**
- RF energy heats fibroid tissue → coagulative necrosis
- Best for fibroids <8cm, type 1-6
- Similar to hysteroscopy
- Recovery 1-2 days

**TC RFA OUTCOMES**
- Can take 3 months to see effects
  - 95% of patients see bleeding improvement at 12 months
  - Most women have >50% decrease in blood loss
  - 50-70% volume reduction
  - 8% reintervention at 3 years
- Not labeled for future pregnancy, limited data but normal pregnancy outcomes have been reported
- Insurance coverage can be limited
### SUMMARY OF FIBROID INTERVENTIONS

<table>
<thead>
<tr>
<th>UAE</th>
<th>FUS</th>
<th>LSC-RIA</th>
<th>UAE-RIA</th>
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<tbody>
<tr>
<td>Longest experience</td>
<td></td>
<td></td>
<td>Newest</td>
</tr>
<tr>
<td>Can treat variety</td>
<td></td>
<td></td>
<td>Better for &gt;8cm fibroids</td>
</tr>
<tr>
<td>1 week recovery</td>
<td>1-2 day recovery</td>
<td>1-2 week recovery</td>
<td>1-2 day recovery</td>
</tr>
<tr>
<td>1 night hospitalization</td>
<td></td>
<td>Requires LSC surgery and GETA</td>
<td></td>
</tr>
<tr>
<td>30-50% volume decrease</td>
<td>30% volume decrease</td>
<td>50-70% volume decrease</td>
<td>50-70% volume decrease</td>
</tr>
</tbody>
</table>

All with lack of indication for use in patients desiring pregnancy, but promising outcomes.

### COMPLEX SCENARIOS – CHOOSE THE BEST OPTION!

**Perimenopausal with heavy menses**

**Perimenopausal, bleeding and bulk; malignant HTN, prior intracranial hemorrhage and DVT**

**Perimenopausal with heavy menses; difficult to biopsy in office**

**61 y/o with bleeding/bulk; 5 prior laparotomies, h/o CVA and MI**
Unable to sample in office, HSC done

45 y/o with primarily bulk symptoms

40 y/o presents with cardiac arrest due to massive PE, 28 wk uterus

Additional cases if time....

References


CULTURAL AND LINGUISTIC COMPETENCY

Assembly Bill 1195 was signed into law on July 1, 2006 requiring local CME providers, such as the AAGL, to assist in enhancing the cultural and linguistic competency of California’s physicians (researchers and doctors without patient contact are exempt). This mandate follows the federal Civil Rights Act of 1964, Executive Order 13166 (2000) and the Dymally-Alatorre Bilingual Services Act (1973), all of which recognize, as confirmed by the US Census Bureau, that substantial numbers of patients possess limited English proficiency (LEP). It is the intent of the Legislature to encourage physicians and surgeons, continuing medical education providers located in California, and the Accreditation Council for Continuing Medical Education to meet the cultural and linguistic concerns of a diverse patient population through appropriate professional development.

**Linguistic Competence:** Providing readily available, culturally appropriate oral and written language services to limited English proficiency (LEP) members through such means as bilingual/bicultural staff, trained medical interpreters, and qualified translators.

**Cultural Competence:** A set of congruent behaviors, attitudes, and policies that come together in a system or agency or among professionals that enables effective interactions in a cross-cultural framework.1

Cultural and Linguistic Competence: The ability of health care providers and health care organizations to understand and respond effectively to the cultural and linguistic needs brought by the patient to the health care encounter.

**Cultural competence** requires organizations and their personnel to:

- Value diversity.
- Assess themselves.
- Manage the dynamics of difference.
- Acquire and institutionalize cultural knowledge.
- Adapt to diversity and the cultural contexts of individuals and communities served.

**California Business & Professions Code §2190.1(c)(3)** states that associations that accredit continuing medical education courses shall develop standards before July 1, 2006, for compliance with the cultural competency requirements. The associations may update these standards, as needed, in conjunction with an advisory group that has expertise in cultural and linguistic competency issues. Cultural competency means a set of integrated attitudes, knowledge, and skills that enables a health care professional or organization to care effectively for patients from diverse cultures, groups, and communities. At a minimum, cultural competency is recommended to include the following: (A) Applying linguistic skills to communicate effectively with the target population. (B) Utilizing cultural information to establish therapeutic relationships. (C) Eliciting and incorporating pertinent cultural data in diagnosis and treatment. (D) Understanding and applying cultural and ethnic data to the process of clinical care, including, as appropriate, information pertinent to the appropriate treatment of, and provision of care to, the lesbian, gay, bisexual, transgender, and intersex communities.

**Title VI of the Civil Rights Act of 1964** prohibits recipients of federal financial assistance from discriminating against or otherwise excluding individuals on the basis of race, color, or national origin in any of their activities. In 1974, the US Supreme Court recognized LEP individuals as potential victims of national origin discrimination. In all situations, federal agencies are required to assess the number or proportion of LEP individuals in the eligible service population, the frequency with which they come into contact with the program, the importance of the services, and the resources available to the recipient, including the mix of oral and written language services. Additional details may be found in the Department of Justice Policy Guidance Document: Enforcement of Title VI of the Civil Rights Act of 1964 [http://www.usdoj.gov/crt/cor/pubs.htm](http://www.usdoj.gov/crt/cor/pubs.htm).

**Executive Order 13166, “Improving Access to Services for Persons with Limited English Proficiency”,** signed by the President on August 11, 2000 [http://www.usdoj.gov/crt/cor/13166.htm](http://www.usdoj.gov/crt/cor/13166.htm) was the genesis of the Guidance Document mentioned above. The Executive Order requires all federal agencies, including those which provide federal financial assistance, to examine the services they provide, identify any need for services to LEP individuals, and develop and implement a system to provide those services so LEP persons can have meaningful access.

**Dymally-Alatorre Bilingual Services Act (Assembly Bill 305)** requires that state agencies that serve a substantial number of non-English-speaking people employ a sufficient amount of bilingual persons in order to provide certain information and render certain services in a language other than English.

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