New Treatments For Fibroids
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Disclosure
• Co-Investigator, The FIRSTT Study
  NIH/NICHD
  A Randomized Trial of MRgFUS vs UAE
• Principal Investigator, The ULTRA Trial
  Halt Medical under Contract with UCSF
  *Investigator Initiated Research (IIR)
  *Study design, implementation, analysis, and publication are independent of sponsor

Impact of Fibroids
• 30% of premenopausal women
• #1 reason for hysterectomy
  (250,000/year)
• $34 billion/year to care for women with fibroids
• $17 billion for lost work and disability after surgery

Outline
• Medical Management
  • Antifibrinolytics
  • Hormonal modulations
• MR Guided Focused Ultrasound
• Radiofrequency ablation
  • Laparoscopic
  • Hysteroscopic
A 40 year old P2 presents with heavy menstrual bleeding and 2 intramural fibroids not contacting endometrium, 5cm and 4cm. Hb=11.5. Would you offer her tranexamic acid (lystedda) for heavy menstrual bleeding?

A. Yes  
B. No

Antifibrinolytic: Tranexamic Acid

- Immediate release formula available outside of U.S. for 40 years (over the counter in Europe)
- GI side effects limited use (nausea, abdominal pain)
- 2009 FDA approves modified release formula (Lysteda) for treatment of heavy menstrual bleeding

Antifibrinolytic: Tranexamic Acid

- Nonhormonal
- Binds to plasmin to inhibit fibrinolysis

Tranexamic Acid: RCT

- Placebo controlled trial (n=297)
- 35% of participants had fibroids
  - Excluded if number/size of fibroids required surgery based on surgeon opinion
- Starting EBL per menses 153-178cc
- Tranexamic acid tid up to 5 days per menses 3.9g/day or 1.95g/day or placebo
- Results reported for 3 cycles

Freeman et al, AJOG, 2011, pg 319. e1-7
Tranexamic Acid: RCT Results

- Freeman et al, AJOG, 2011, pg 319. e1-7

Tranexamic Acid: RCT Adverse Events

- Potential risk of thromboembolism (n=0)
  - Not observed in trials of tranexamic acid
  - Patients at risk have been excluded (including those on OCPs)
  - Contraindicated: hx or current thromboembolic disease
- Ocular events (n=3, 1%, 1 in placebo)
  - blurred vision/lenticular opacities
- Headache, GI symptoms, muscle/back pain

Tranexamic Acid: Limitations

- Little known about fibroid subgroup (location/size)
- No comparison to OCPs or other medications
- May be effective for women with fibroids, more studies needed
  - 1300mg tid as needed day 1-5 for heavy bleeding
  - Patient can usually tell on day 1 if there is improvement

Medical Management: Hormonal Manipulation

- Estrogen
- Progesterone

Drug Targets: Decrease levels
Selectively block action

Freeman et al, AJOG, 2011, pg 319. e1-7
Progesterone Receptor Modulators (PRM)

- Inhibits ovulation, decreases fibroid volume
- Does not decrease estrogen like GnRH antagonist
- Ulipristal
  - Studied as 5-10mg tabs
  - Only available as 30mg tabs in U.S.

Ulipristal Trials

<table>
<thead>
<tr>
<th></th>
<th>Ulipristal vs. Placebo</th>
<th>Ulipristal vs. Lupron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amenorrhea</td>
<td>82% U10mg N=94</td>
<td>6.3% Placebo N=48*</td>
</tr>
<tr>
<td></td>
<td>90% U10mg N=95</td>
<td>99% Lupron N=93</td>
</tr>
<tr>
<td>Menstrual bleeding</td>
<td>93%</td>
<td>19%</td>
</tr>
<tr>
<td>became normal</td>
<td></td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99%</td>
</tr>
<tr>
<td>Change in fibroid</td>
<td>-12%</td>
<td>+3%</td>
</tr>
<tr>
<td>volume</td>
<td></td>
<td>-22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-44%</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>10%</td>
<td>40%</td>
</tr>
</tbody>
</table>

PRM Risk

- Potential for increased risk of hyperplasia or cancer
- Mixed results in studies with EMBs
- NIH Pathology Panel classified new pattern of endometrial changes: PRM-associated endometrial changes (PAEC)
- 10-15% of patients develop PAEC
- More long-term study needed to assess natural progression of this entity

Other Medications

- **Antiprogestin Mifepristone**
  - Decreases fibroid size/bleeding
  - 10% endometrial hyperplasia/PAEC?
  - Not available as needed for fibroids (5-50mg)
- **GnRH agonist Elagolix**
  - Trial for FDA approval (recruiting, NCT01441635)
- **Estrogen Receptor Modulator Raloxifene:**
  - Preliminary studies with conflicting results, concern re: VTE
- **Aromatase Inhibitors: Anastrozol and Letrozole**
  - Initial studies promising

New fibroid devices that are used in surgery or radiology performed procedures must be shown to be effective with comparative trials prior to FDA approval.

A. True  
B. False

Fibroid Devices

- Unlike new drugs, FDA does not require comparative trials for new devices

- **FDA approves new device for fibroids**
- **Insurance considers device experimental:** Need RCTs, Declines coverage
- **Limits ability to obtain gold standard evidence**
- **Limits access to effective treatments**

- **RCTs conducted with support from:** Industry (concern re: bias), NIH (too $$ to pay for device)

MR Guided Focused Ultrasound (MRgFUS)

FDA approved 2003, still no completed comparative trials
What is MRgFUS?

- Focused ultrasound beam heats tissue to 150-185°F
- Coagulative necrosis occurs

FDA approved 2003, still no completed comparative trials

What is MRgFUS?

- Shave from umbilicus to pubic bone
- Patient lies prone for 3-5 hours in MRI
- Conscious sedation
- Foley
- Hand held automatic stop button

What is MRgFUS?

A. B. C. D.

MRgFUS vs. UAE

<table>
<thead>
<tr>
<th></th>
<th>UAE</th>
<th>MRgFUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ioinizing radiation</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hospital admission</td>
<td>X (75%)</td>
<td></td>
</tr>
<tr>
<td>Return to normal activities</td>
<td>7-10 days</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Potential for ovarian failure</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Post-procedure fever/infection</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Current Evidence on MRgFUS

- Largest study 359 women in U.S.A and abroad
- Single arm, all women underwent MRgFUS
- Pivotal trial for FDA approval
- Industry sponsored

MRgFUS Symptom Improvement

- Symptomatic improvement in women with fibroids
- 44% decrease in symptoms
- 38% average reoperation rate

MRgFUS Fibroid Shrinkage: 12 months

- 20% average shrinkage
- Residual ratio (%)

MRgFUS Reoperation: 6-24 months

- 38% average reoperation rate
- Average treatment NPV ratio (%)
More Recent Studies

- FDA has approved larger fibroid treatment areas

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>NPV</th>
<th>Shrinkage</th>
<th>Reoperation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gorny 2011</td>
<td>130</td>
<td>45%</td>
<td>N/A</td>
<td>7.4% at 12 mo</td>
</tr>
<tr>
<td>LeBlang 2010</td>
<td>80</td>
<td>55%</td>
<td>31% at 6 mo</td>
<td>N/A</td>
</tr>
<tr>
<td>Funaki 2009</td>
<td>91</td>
<td>40%</td>
<td>at 24 mo</td>
<td>15% at 34 mo</td>
</tr>
</tbody>
</table>

Adverse Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>33%</td>
</tr>
<tr>
<td>Back or leg pain with sonications</td>
<td>13%</td>
</tr>
<tr>
<td>Nausea or emesis</td>
<td>11%</td>
</tr>
<tr>
<td>Bladder or catheter pain</td>
<td>14%</td>
</tr>
<tr>
<td>Abnormal vaginal discharge</td>
<td>11%</td>
</tr>
<tr>
<td>Skin burns</td>
<td>5%</td>
</tr>
</tbody>
</table>

Pregnancy after MRgFUS

- Olive D, Obstet Gynecol, March 2008
- Parker W, Obstet Gynecol, Nov 2007

- 54 pregnancies (51 women)
- Delivered 41% (22/54)
- Ongoing 20% (11/54)
- Antepartum hospitalization 18% (4/22)
- TAB 13% (7/54)
- SAB 26% (14/54)
- Placenta previa 9% (2/22)
- Term (14/15)

Access to MRgFUS

- Available in 9 states, 12 sites
- 9/12 academic medical centers
- In California: UCSF, UCLA, UCSD, Stanford
- Reimbursement is major challenge
- Some sites offer treatment in research protocol

Rabinovici, et al, Fertility and Sterility, January 2010
The PROMISE Trial

- Pilot randomized, placebo-controlled trial
- Goal: to assess feasibility of larger trial

Randomized
N=20

MRgFUS
N=13

Sham MRgFUS
N=7

3 month change in:
Fibroid Symptoms, Fibroid Size, Hematocrit

Jacoby VJ, Kohi M, Poder L, Jacoby A, Coakley F, under consideration

Change in UFS-QOL Symptom Severity Score

Baseline 4 weeks 12 weeks

MRgFUS Placebo

-13 -31

Upcoming Trials

- Placebo-controlled trial for new MR Focused Ultrasound Device underway (Sonavelle device, Philips, NCT01504308)

- The FIRSTT Study: A Randomized Trial of MRgFUS versus UAE (NCT NCT00995878)
  - NIH funded
  - Mayo Clinic (PI E. Stewart), UCSF, Duke
  - Final results expected 2015-16

Radiofrequency Ablation
The Radiofrequency Ablation Device

- FDA approved for fibroids November 2012 (Acessa)
- Generator with Foot Pedal
- Laparoscopic Ultrasound
- 3mm RF Handpiece

Radiofrequency Ablation

- Fibroids identified with ultrasound
- Radiofrequency (RF) probe placed under ultrasound guidance
- Monopolar RF energy delivered to fibroids
- Tissue heats to 100° C to cause coagulative necrosis
- Fibroid cells reabsorbed

Advantages of Acessa over Current Treatment

<table>
<thead>
<tr>
<th></th>
<th>Hospital Stay</th>
<th>Recovery Time</th>
<th>Blood Loss</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiofrequency Ablation</td>
<td>0</td>
<td>5-9 days</td>
<td>32 cc</td>
<td>Minimal</td>
</tr>
<tr>
<td>Open Hysterectomy</td>
<td>2-3 nights</td>
<td>4-6 weeks</td>
<td>300-500cc</td>
<td>Moderate</td>
</tr>
<tr>
<td>Laparoscopic or Vaginal Hysterectomy</td>
<td>1 night</td>
<td>4 weeks</td>
<td>200cc</td>
<td>Minimal-Moderate</td>
</tr>
<tr>
<td>Open Myomectomy</td>
<td>2-3 nights</td>
<td>4-6 weeks</td>
<td>250-500cc</td>
<td>Moderate</td>
</tr>
<tr>
<td>Laparoscopic Myomectomy</td>
<td>0-1</td>
<td>2-4 weeks</td>
<td>200cc</td>
<td>Minimal-Moderate</td>
</tr>
</tbody>
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RF Ablation: Eligibility

- Premenopausal
- Can tolerate laparoscopic procedure
- Uterus < 14 or 16 weeks size uterus
- ≤6 total fibroids
- No single fibroid >7 or 10cm
RF Ablation: Current Evidence

- Largest study, n=135
- Industry funded, FDA pivotal trial
- Single arm, all women treated with RF ablation
- 2 year follow-up

Chudnoff et al, Green Jo, May 2013
Guido et al, Health and Quality of Life Outcomes 2013; 11:139

<table>
<thead>
<tr>
<th>UFS-QOL</th>
<th>Symptom Severity Score</th>
<th>Quality of Life Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>-52%</td>
<td>+50%</td>
</tr>
<tr>
<td>12 months</td>
<td>-57%</td>
<td>+53%</td>
</tr>
<tr>
<td>24 months</td>
<td>-59%</td>
<td>+53%</td>
</tr>
</tbody>
</table>

Chudnoff et al, Green Jo, May 2013

RF Ablation: Current Evidence

- Uterine Volume
- Fibroid Volume

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<thead>
<tr>
<th>UFS-QOL</th>
<th>Uterine Volume</th>
<th>Fibroid Volume</th>
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<td>-45%</td>
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Chudnoff et al, Green Jo, May 2013

RF Ablation: Current Evidence

- Adverse events: 4%
- Pregnancy ("not recommended" per FDA)
  - 1 pregnancy, term, C section
  - Postpartum hemorrhage, 6 U PRBC
  - 48 hours later, passage of degenerating fibroid
- Re-intervention
  - <1% at 1 year, 5% at 2 years

Chudnoff et al, Green Jo, May 2013
Guido et al, Health and Quality of Life Outcomes 2013; 11:139
**RF Ablation: Upcoming Studies**

- The ULTRA trial
  - 5 UC sites (the UC Fibroid Network)
  - Single arm study, 3 years of follow-up
  - Preliminary data for RCT of RF ablation vs. myomectomy
- Vizablate (NCT01226290):
  - Hysteroscopic RF ablation

**Conclusions**

- Several new effective medications, limited availability
- Surgical treatments focused on minimally invasive approaches that leave fibroids in utero
- Long-term studies are needed to confirm the durability of these treatments