New Treatments For Fibroids

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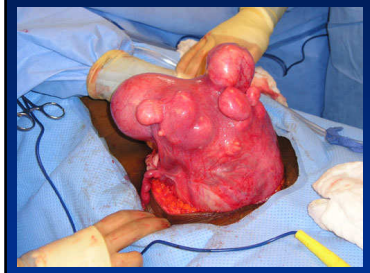
Disclosure

- 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



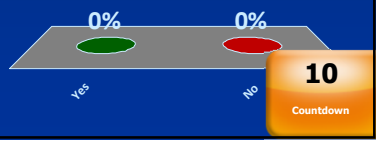
- 30% of premenopausal women
- #1 reason for hysterectomy (250,000/year)
- $34 billion/year to care for women with fibroids
- **$17 billion for lost work and disability after surgery**

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 (lysteda) for heavy menstrual bleeding?

A. Yes
B. No

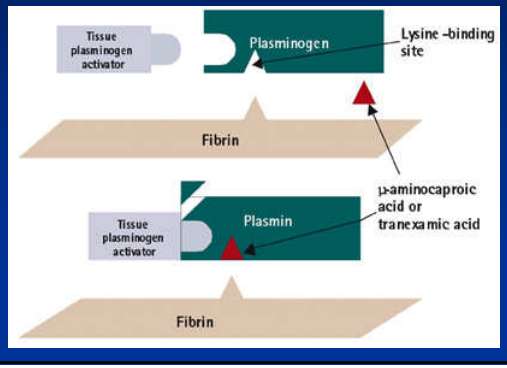


Antifibrinolytic: Tranexamic Acid

- 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

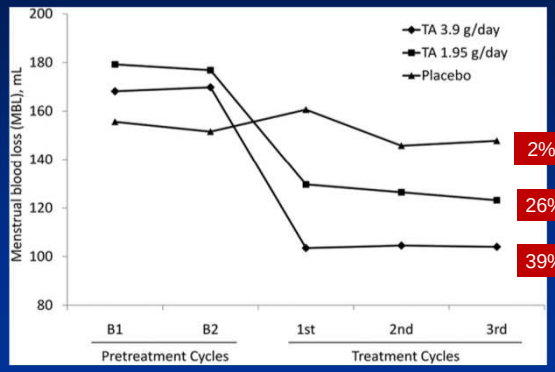


Tranexamic Acid: RCT

- 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



2% decrease

26% decrease

39% decrease

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

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

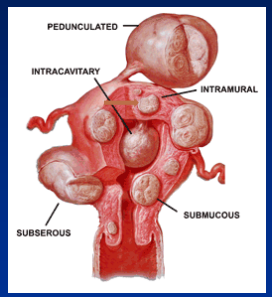
Tranexamic Acid: Limitations

- 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

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

Medical Management: Hormonal Manipulation

Estrogen



Progesterone

Drug Targets: Decrease levels

Selectively block action

Progesterone Receptor Modulators (PRM)

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

Progesterone Receptor Modulators: Ulipristal

- Two randomized trials, industry funded
- Placebo vs. Ulipristal (n=242)
- Lupron vs. Ulipristal (n=307)
- Participants had heavy bleeding, anemia, uterus <16 weeks, planning surgery
- 13 weeks of medication

Donnez et all, NEJM, 2012; 366: 409-420.

Ulipristol Trials

	Ulipristal vs. Placebo		Ulipristal vs. Lupron	
	U 10mg N=94	Placebo N=48*	U 10mg N=95	Lupron N=93
Amenorrhea	82%	6.3%	90%	80%
Menstrual bleeding became normal	93%	19%	98%	99%
Change in fibroid volume	-12%	+3%	-22%	-44%
Hot flashes			10%	40%

*p<.05 compared with U 10mg

PRM Risk

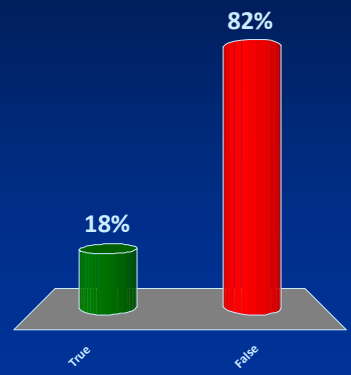
- Potential for increased risk of hyperplasia or cancer
- Mixed results in studies with EMBs
- NIH Pathology Panel classfied new pattern of endometrial changes: **PRM-associated endometrial changes (PAEC)**
- 10-15% of patients develop PAEC
- More long-term study needed to assess natural progression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

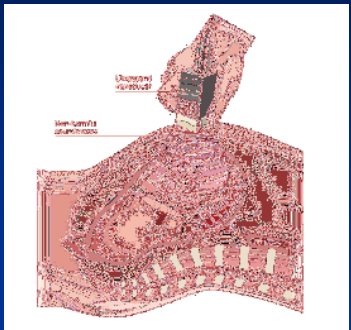
RCTs conducted with support from:
Industry (concern re: bias)
NIH (too $$ to pay for device)

MR Guided Focused Ultrasound (MRgFUS)

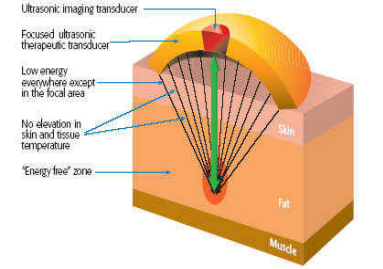
FDA approved 2003, still no completed comparative trials

What is MRgFUS?

FDA approved 2003, still no completed comparative trials

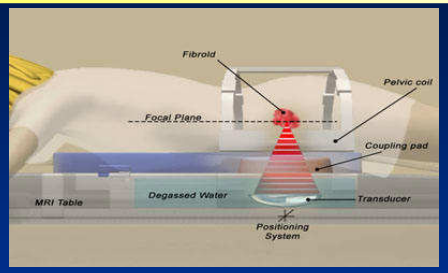


Diagnostic ultrasound waves



- Focused ultrasound beam heats tissue to 150-185^0 F
- Coagulative necrosis occurs

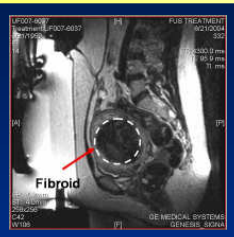
What is MRgFUS?

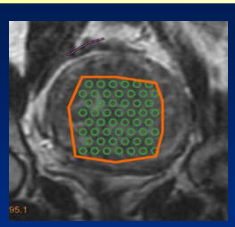


- Shave from umbilicus to pubic bone
- Patient lies prone for 3-5 hours in MRI
- Conscious sedation
- Foley
- Hand held automatic stop button

What is MRgFUS?

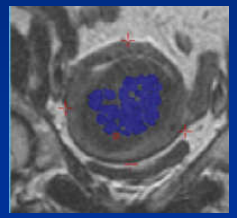
A.





B.

C.



nonperfused volume (NPV)

D.

MRgFUS vs. UAE

	UAE	MRgFUS
Ioinizing radiation	X	
Hospital admission	X (75%)	
Return to normal activities	7-10 days	1-3 days
Potential for ovarian failure	X	
Post-procedure fever/infection	X	

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

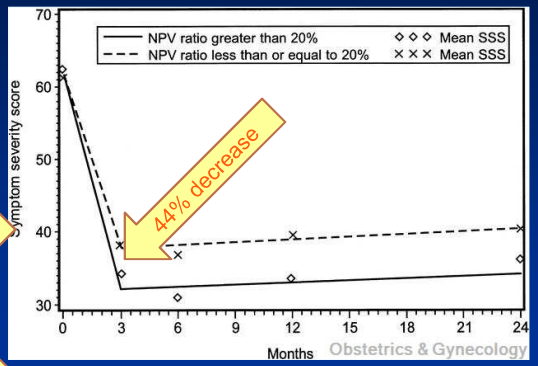
Stewart EA, Gostout B, et al, Obstet Gynecol, Aug 2007

MRgFUS Symptom Improvement

Symptoms

Fibroids

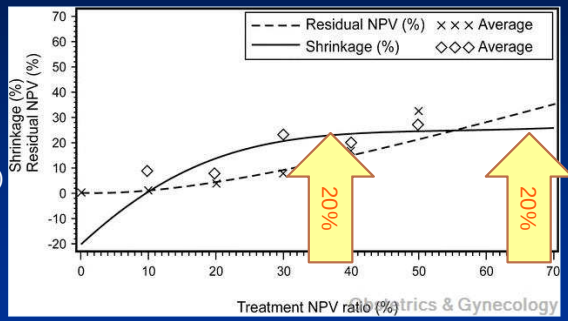
No fibroids



Stewart EA, Gostout B, et al, Obstet Gynecol, Aug 2007

MRgFUS Fibroid Shrinkage: 12 months

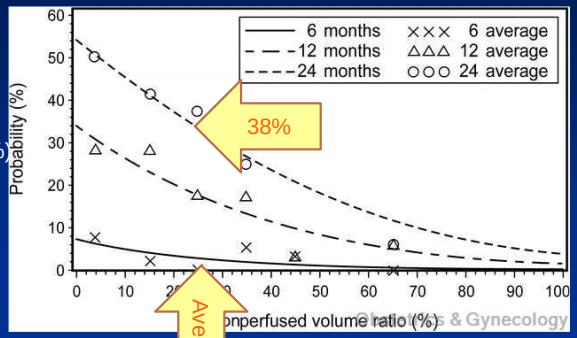
Fibroid Shrinkage (%)



Stewart EA, Gostout B, et al, Obstet Gynecol, Aug 2007

MRgFUS Reoperation: 6-24 months

Reoperation (%)



Stewart EA, Gostout B, et al, Obstet Gynecol, Aug 2007

More Recent Studies

•FDA has approved larger fibroid treatment areas

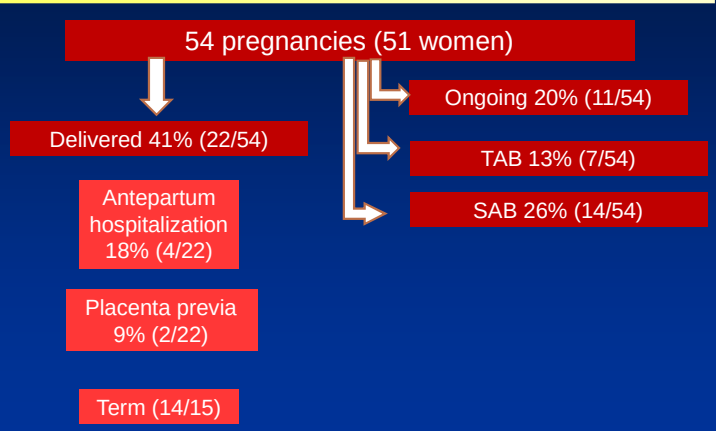
Study	N	NPV	Shrinkage	Reoperation
Gorny 2011	130	45%	N/A	7.4% at 12 mo
LeBlang 2010	80	55%	31% at 6 mo	N/A
Funaki 2009	91		40% at 24 mo	15% at 34 mo

Adverse Events

Outcome	Percent
Abdominal pain	33%
Back or leg pain with sonications	13%
Nausea or emesis	11%
Bladder or catheter pain	14%
Abnormal vaginal discharge	11%
Skin burns	5%

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

Pregnancy after MRgFUS



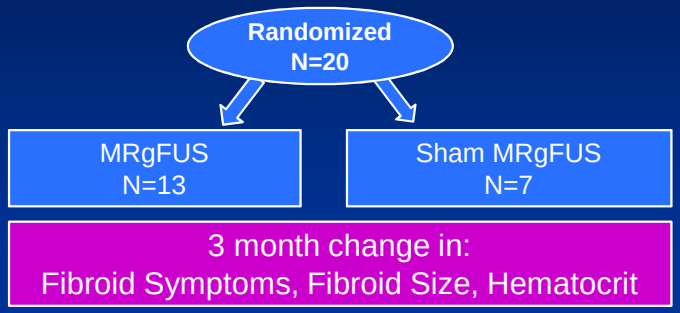
Rabinovici, et al, Fertility and Sterility, January 2010

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

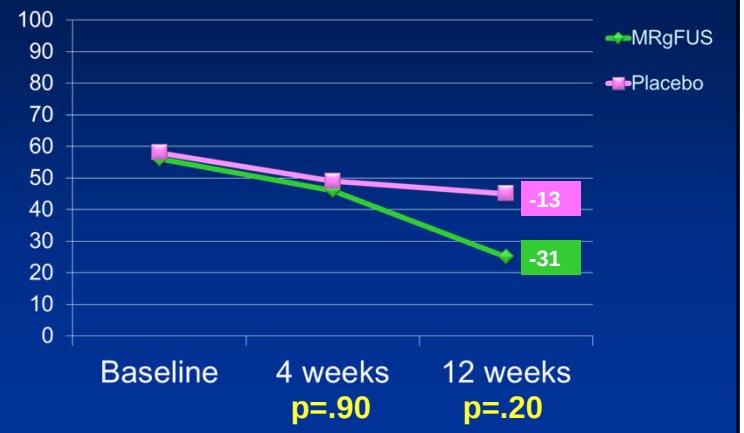
The PROMISe Trial

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



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

Change in UFS-QOL Symptom Severity Score



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

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

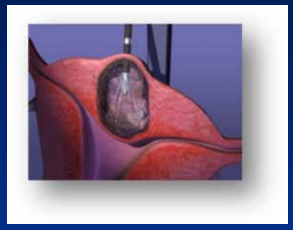
- FDA approved for fibroids November 2012 (Acessa)

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 100^0 C to cause coagulative necrosis
- Fibroid cells reabsorbed

Advantages of Acessa over Current Treatment

	Hospital Stay	Recovery Time	Blood Loss	Pain
Radiofrequency Ablation	0	5-9 days	32 cc	Minimal
Open Hysterectomy	2-3 nights	4-6 weeks	300-500cc	Moderate
Laparoscopic or Vaginal Hysterectomy	1 night	4 weeks	200cc	Minimal-Moderate
Open Myomectomy	2-3 nights	4-6 weeks	250-500cc	Moderate
Laparoscopic Myomectomy	0-1	2-4 weeks	200cc	Minimal-Moderate

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

RF Ablation: Current Evidence

	UFS-QOL	
	Symptom Severity Score	Quality of Life Score
3 months	-52%	+50%
12 months	-57%	+53%
24 months	-59%	+53%

Chudnoff et al, Green Jo, May 2013

RF Ablation: Current Evidence

	UFS-QOL	
	Uterine Volume	Fibroid Volume
3 months	-15%	-40%
12 months	-25%	-45%

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