Fibroid Treatment Dilemmas

Alison F. Jacoby, MD
Director, Comprehensive Fibroid Center
University of California, San Francisco
Objectives

- Help women with symptomatic fibroids choose between different treatment options
- Know the evidence to support the use of Mirena® IUD, endometrial ablation, UAE and myomectomy
- Review current literature about fibroid impact on fertility and pregnancy outcomes
Case 1

AF is a 44 yr old G0 who presents with a 9 month history of heavy periods lasting 10-12 days/month. She smokes 1 pack/day. Her hematocrit is 32%. A pelvic US shows a 12 x 6 x 6 cm uterus w/ several 3-4 cm intramural fibroids. At least one has a submucosal component. A saline sonohysterogram shows a 3 cm fibroid extending 30% into the cavity. She wants to avoid major surgery.

What are her treatment options?
Case 1

Submucous fibroid and menorrhagia

Potential treatment options:

1. Birth control pills
2. Mirena® IUD
3. Endometrial ablation
4. Hysteroscopic myomectomy
5. UAE
What is the evidence to support these treatments?...
Submucous Fibroid Classification

Type 0 fibroid
Mirena® in Contraception Trials

- Less bleeding
- Less anemia
- Less dysmenorrhea
- Fewer incident fibroids

Sivin 1994, Hidalgo 2002
Mirena® IUD for Fibroids

- 2 prospective, before-and-after studies
  - n=69 and n=32
- Sono confirmed fibroids
- Uterine size ≤12 wk size
- Normal cavity
Mirena® IUD for Fibroids

Grigoreva V, Fertil Steril 2003;79:1194

- Bleeding results:
  - Mean baseline PBAC score- 97
  - Mean 12 month PBAC score- 16
  - Amenorrhea rate- 40%

Mercorio, Contraception 2003;67:277

- 60% completed 12 months
  - Mean baseline PBAC score- 310
  - Decreased bleeding
  - 74% still had PBAC score > 100

- 40% withdrew by 6 months
  - 4 IUD expulsions (12%)
  - 7 persistent menorrhagia, requested surgery (22%)
  - 2 lost to follow-up
Mirena® IUD for Fibroids

- Decreases bleeding in women with fibroids
  - ≤ 12 week size uterus
  - No submucous component

- Level of evidence: II-3
- Strength of recommendation: B
  - Moderate effect
  - Less effective as bleeding becomes heavier
Endometrial Ablation in the Presence of Fibroids

- Thermachoice
- Novasure
- Microsulis
- Hydrothermablator
## Endometrial Ablation in the Presence of Submucous Fibroids

<table>
<thead>
<tr>
<th>Device</th>
<th>FDA Approval</th>
<th>Published Evidence</th>
<th>Fibroid Type</th>
<th>Diameter (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ThermoChoice™ (thermal balloon)</td>
<td>No</td>
<td>Yes (Level I)</td>
<td>II</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>Hydro ThermAblator™ (circulating hot fluid)</td>
<td>No</td>
<td>Yes (Level II-3)</td>
<td>I, II</td>
<td>≤ 4</td>
</tr>
<tr>
<td>Her Option™ (cryotherapy)</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Novasure™ (radiofrequency energy)</td>
<td>No</td>
<td>Yes (Level II-2)</td>
<td>I, II</td>
<td>≤ 3</td>
</tr>
<tr>
<td>Microsulis Endometrial Ablation™ (microwave)</td>
<td>Yes</td>
<td>Yes (Level I)</td>
<td>I, II</td>
<td>≤ 3</td>
</tr>
</tbody>
</table>

ACOG Practice Bulletin, 81, May 2007
Thermal Balloon Ablation and Fibroids

- **RCT** of 96 Turkish women with fibroids and menorrhagia
  - Age ≥ 40
  - Uterine size ≤ 12 wk with IM/SS myoma < 5 cm or SM type II fibroid < 3 cm
  - PBAC score ≥ 150
  - 45 underwent thermal balloon ablation under local
  - 48 underwent rollerball ablation under general

Soysal ME Gynecol Obstet Invest 2001;51:128
# Thermal Balloon Ablation and Fibroids

<table>
<thead>
<tr>
<th></th>
<th>PBAC Initial</th>
<th>PBAC 12 m</th>
<th>P value</th>
<th>Hgb Initial</th>
<th>Hgb 12 m</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermal Balloon Ablation</td>
<td>384</td>
<td>41</td>
<td>&lt;0.0001</td>
<td>10.0</td>
<td>12.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Roller-ball Ablation</td>
<td>385</td>
<td>40</td>
<td>&lt;0.0001</td>
<td>9.8</td>
<td>12.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Soysal ME Gynecol Obstet Invest 2001;51:128
Thermal Balloon Ablation and Fibroids

- Amenorrhea rates: 11% TBA, 19% RBA
- Hysterectomy rates: 9% in each group
- Thermal balloon ablation group
  - Fewer complications
  - Shorter operative time
  - Performed comfortably under local anesthesia

Soysal ME Gynecol Obstet Invest 2001;51:128
Microsulis™ Endometrial Ablation and Fibroids

- FDA Pivotal Trial: RCT
  - 71 subjects with menorrhagia
  - Randomized to Microsulis™ or rollerball ablation
  - Size: ≤ 3 cm
  - Location: Submucous, type I and II

FDA Pivotal Trial data, Filing date 7/14/03
## Microsulis™ Endometrial Ablation and Fibroids

<table>
<thead>
<tr>
<th></th>
<th>Amenorrhea Rates (%)</th>
<th>Clinical Success (%) (PBAC score ≤ 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microsulis Endometrial Ablation</strong> (microwave)</td>
<td>61</td>
<td>68</td>
</tr>
<tr>
<td><strong>Rollerball Ablation</strong></td>
<td>39</td>
<td>77</td>
</tr>
</tbody>
</table>

Comparable results to subjects without fibroids

FDA Pivotal Trial data, Filing date 7/14/03

**Fibroid Inclusion Criteria:**
- ≤ 3 cm
- Type I and II SM fibroids
Endometrial ablation in the presence of submucous fibroids

- Decreases bleeding in women with fibroids
  - ≤ 12 week size uterus
  - Type I and II submucous fibroids
  - Size ≤ 3 cm

- Level of evidence: I- Thermachoice, Microsulis
  II-3- Novasure and Thermablator

- Strength of recommendation: A
  - Moderate effect
  - Comparable to rollerball ablation
Hysteroscopic Myomectomy
Hysteroscopic Myomectomy

- Predictors for resolution of menorrhagia:
  - Complete surgical resection
    - Type 0 > Type I > Type II
    - Fibroid size
  - Uterine size
  - Number of fibroids

Emanuel MH et al Obstet Gynecol 1999;93:743-8
Hysteroscopic Myomectomy

- Decreases bleeding in women with fibroids
  - Effectiveness decreases over time
  - Most efficacious for type 0 and type I submucous fibroids

- Level of evidence: II-2
- Strength of recommendation: B
  - Accepted method for management of AUB caused by SM fibroids
Uterine Artery Embolization

Pre-UAE

Post-UAE
Reduction in Menorrhagia after UAE

- Ravina: 89%
- Worthington: 88%
- Goodwin: 88%
- Hutchins: 86%
- Pelage: 90%
- Spies: 90%
- Pron: 83%
Reduction in Bulk Symptoms

- Worthington: 94%
- Goodwin: 91%
- Hutchinson: 68%
- Spies: 91%
- Pron: 84%
Fibroid Size Reduction after UAE

- Ravina: 31%
- Worthington: 46%
- Goodwin: 43%
- Hutchins: 48%
- Pelage: 52%
- Spies: 38%
- Pron: 35%
Long term outcomes after UAE

182 of 200 pts (91%) completed 5 yr follow-up:

- Sustained symptom control - 73%
- Failure or recurrence - 25%

- Major interventions - 20%
  - 25 hysterectomies
  - 8 myomectomies
  - 3 repeat UAE’s

Predictors of success

The Fibroid Registry:

In multivariate analyses, predictors of improvement in symptom and QoL scores included:

- Heavy bleeding as a presenting symptom ✓
- Submucous location ✓
- Older age
- Lower BMI
- Low initial symptom score

Spies J et al Obstet Gynecol 2008;111:22-33
Predictors of failure

- Increased fibroid size\(^1\), \(^2\), \(^3\)
- Multiple fibroids\(^2\), \(^4\)
- Adenomyosis\(^2\)
- Hypovascularity of fibroid\(^4\)
- Location in LUS or cervix\(^1\)
- Less volume reduction after 1 yr\(^3\)

\(^1\) Spies J et al Obstet Gynecol 2008;111:22-33
\(^2\) Marret H et al BJOG 2005;112:461-465
\(^3\) Spies J et al Obstet Gynecol 2005;106:933-9
\(^4\) Isonishi S et al Am J Obstet Gynecol 2008;198:270
Uterine Artery Embolization

Outcomes:
- Decreases bleeding, dysmenorrhea and urinary symptoms
- RCT’s of UAE + hysterectomy and UAE + myomectomy:
  - Shorter hospital stays, faster return to activities following UAE

Level of evidence: I

Strength of recommendation: A

"Based on long- and short-term outcomes, UAE is a safe and effective option for appropriately selected women who wish to retain their uteri."

ACOG Practice Bulletin 96, 2008
Case 1: Submucous fibroid and menorrhagia

Potential treatment options:

- Birth control pills
  - Smoker age $\geq 35$ yrs
- Mirena IUD
  - No data for submucosal fibroids
- Endometrial ablation $\checkmark$
- Hysteroscopic myomectomy
  - Better for type 0 and I fibroids
- UAE $\checkmark$
Case 2

A 39 yr old G1P1 with known fibroids for several years, now has worsening urinary frequency, pelvic pressure and discomfort lying prone. On exam, the fundus is palpable at the umbilicus. A pelvic US shows 3 fibroids: 10 cm SS fundal, 6 cm IM posterior and 4 cm IM anterior. She desires future childbearing.

What treatments would you recommend?
Case 2: Large uterus w/ bulk symptoms

Potential treatment options:

1. GnRH agonist x 6 months
2. Myomectomy
3. UAE
4. Hysterectomy
   1. Fibroids too large for other options
Myomectomy
How well does myomectomy work?

- Resolution of symptoms:
  - Menorrhagia: 81%
  - Bulk symptoms: 70-80%

- Predictors for recurrence:
  - Number of fibroids
  - Uterine size
  - Parity after myomectomy
  - Use of GnRH agonist
  - Route of myomectomy
How well does myomectomy work?

Recurrence of fibroids after myomectomy

- Review of 41 studies, published from 1924-1998
- Poor methodology
  - Various techniques to assess recurrence
    - US at regular intervals, Clinical exam with oriented US, recurrence of symptoms, etc
  - Sample bias due to cases lost to follow-up
  - Failure to define follow-up period

Fauconnier A Human Repro Update 2000; 6(6): 595-602
How well does myomectomy work?

Recurrence of fibroids after myomectomy

- Cumulative risk of clinically significant recurrence:
  - ~10% at 5 yrs

- Cumulative risk of US detected recurrence:
  - 51% at 5 yrs
  - Represents the prevalence rate of fibroids after myomectomy
  - Significance is questionable since many will remain asymptomatic

Fauconnier A Human Repro Update 2000; 6(6): 595-602
How well does myomectomy work?

Recurrence of fibroids after abdominal myomectomy

<table>
<thead>
<tr>
<th></th>
<th>Single Fibroid</th>
<th>Multiple Fibroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence Rate (%)</td>
<td>27</td>
<td>59</td>
</tr>
<tr>
<td>Re-operation Rate</td>
<td>11</td>
<td>26</td>
</tr>
</tbody>
</table>

• 125 myomectomy cases from 1944-1962
• Follow-up > 5 yrs
• Cited in ACOG Practice Bulletin, August, 2008
Is abdominal myomectomy more risky than hysterectomy?

- 3 studies show similar rates of complications
- 1 study shows myomectomy less morbid
  - Less blood loss, fever and fewer bladder, bowel, ureteral injuries compared to hysterectomy

Iverson RE et al Obstet Gynecol 1996;88:415-9
Abdominal Myomectomy

- **Outcomes:**
  - Decreases bleeding and bulk symptoms
  - High rates of recurrence and re-operation

- **Level of evidence:** II-2

- **Strength of recommendation:** A
  
  “Safe and effective alternative to hysterectomy for treatment of women with symptomatic leiomyomas.” ACOG Practice Bulletin 96, 2008
Is UAE a good option?

- Reserve for women who have completed childbearing
  
  “There is insufficient evidence in the current literature to ensure safety in women desiring to retain fertility. Therefore, the procedure should be considered investigational or relatively contraindicated in women wishing to retain fertility.”

  ACOG Committee Opinion, Number 293, February 2004
## UAE vs. Myomectomy

<table>
<thead>
<tr>
<th></th>
<th>UAE</th>
<th>Myomectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate (%)</td>
<td>50</td>
<td>78</td>
</tr>
<tr>
<td>Miscarriage rate (%)</td>
<td>64</td>
<td>23</td>
</tr>
<tr>
<td>Delivery rate (%)</td>
<td>19</td>
<td>48</td>
</tr>
</tbody>
</table>

Mara et al Cardiovasc Intervent Radiol 2008;31:73-85
Case 2:
Large uterus w/ bulk symptoms

Potential treatment options:
- GnRH agonist x 6 months
  Temporary solution only
- Myomectomy
- UAE
  Avoid if future childbearing desired
- Hysterectomy
  Refer if not comfortable performing myomectomy for large fibroids
Case 3

MJ is a 38 y.o woman recently diagnosed with an 8 cm posterior intramural fibroid. The endometrial stripe appears displaced anteriorly. She has no fibroid symptoms. She hasn’t tried to become pregnant, but wants to know how the fibroid will impact her fertility and pregnancy outcomes.

How would you advise her?
Asx IM fibroid and pregnancy

Counseling options:

A. Attempt pregnancy without pre-treatment
B. Prophylactic myomectomy
C. Perform saline sono or diagnostic hysteroscopy to better evaluate the cavity
The BIG Questions:

- Do uterine fibroids decrease fertility?
- Does removal enhance fertility?
Impact of Fibroids on Fertility

- What does the literature tell us for women who haven’t yet tried to conceive?
  - No Studies

- What data is available?
  - Studies of women with infertility
Updated systematic review

- 23 studies included in data analysis
  - 1 RCT, 9 prospective, 13 retrospective
  - 15 had age matched controls
  - 7 examined effect of myomectomy
  - Fibroid size ranged from 1-10 cm
  - Fibroid number ranged from 1-8

Fibroids and Infertility

Conclusions:

- Subserosal fibroids do not affect fertility and removal does not show benefit.
- Submucosal fibroids lower fertility rates and removal increases conception and live birth rates.
- Results from 2001 and 2009 systematic reviews are in agreement.

Fibroids and Infertility

However, in contrast to the 2001 systematic review, the 2009 review shows that:

- Intramural fibroids appear to decrease fertility and there is no clear evidence that myomectomy is beneficial.

Caveats

- Data is still sparse and methodological issues limit confidence in conclusions.

Fibroids and Pregnancy Outcomes

Qidwai I, Caughey AB, Jacoby AF. Obstet Gynecol 2006;107:376-82

- Retrospective cohort study
- Subjects: 401 women with fibroids detected on routine 2nd trimester ultrasounds from 1994-2003 who subsequently delivered at UCSF
- Controls: 25,000 women delivering at UCSF during same time period
Fibroids and Pregnancy Outcomes

- Presence of fibroids associated with:
  - Preterm delivery (AOR 1.45, 95% CI 1.08-1.96)
  - Placenta previa (AOR 1.86, 95% CI 1.02-3.39)
  - Breech presentation (AOR 1.64, 95% CI 1.11-2.40)
  - Cesarean delivery (AOR 1.57, 95% CI 1.16-2.13)
  - Post-partum hemorrhage (AOR 2.57, 95% CI 1.54-4.27)

Qidwai I, Caughey AB, Jacoby AF. Obstet Gynecol 2006;107:376-82
Fibroids and Pregnancy Outcomes

- Presence of fibroids **not** associated with:
  - PPROM
  - Placental abruption
  - Operative vaginal delivery
  - Chorioamnionitis
  - Endometritis

Qidwai I, Caughey AB, Jacoby AF. Obstet Gynecol 2006;107:376-82
Asx IM fibroid and pregnancy

Counseling options:

✓ Attempt pregnancy without pre-treatment
  Discuss increased risk for infertility, SAB and adverse pregnancy outcomes

✓ Prophylactic myomectomy
  “Proxy literature” does not support

✓ Perform saline sono or diagnostic hysteroscopy to better evaluate the cavity
  If a submucosal component is identified, may justify myomectomy
Conclusions
Conclusions

- Evidence supports use of Mirena® IUD, endometrial ablation and UAE in addition to traditional hysterectomy and myomectomy.

- Use GnRH agonists to facilitate a surgical procedure, not as a stand alone treatment.

- Subserosal fibroids have no effect on fertility and should only be removed for symptoms.

- Submucosal fibroids affect pregnancy rates and benefit shown for removal.

- Intramural fibroids may diminish pregnancy rates and myomectomy may not reverse this effect but more research needed.
Thank you
Novasure™ and Fibroids

- Prospective, single-arm study of 65 Canadian women with fibroids and menorrhagia
  - Pre- and post-menopausal women enrolled
  - Type I and II submucous fibroids, ≤ 3 cm
- Menstrual questionnaire at screening and 12 mo
- Success defined as return to normal bleeding

Sabbah R, J Minimally Invas Gynecol 2006;13(5):467
Novasure™ and Fibroids

- Success rate- 95%
- Amenorrhea rate- 69%
- Satisfaction rate- 95%
- Decrease in premenstrual sx and dysmenorrhea

Sabbah R, J Minimally Invas Gynecol 2006;13(5):467
Hydrothermablator™ and Fibroids

- Retrospective, observational study
- 22 US women
- Age 34-60 yrs
- Presence of submucous fibroid ≤ 4 cm
- Pretreatment with lupron, danazol or norethindrone
- Office procedure with local anesthesia
- 12 m follow-up

Glasser MH J Am Assoc Gynecol Laparosc 2003;10:521
Hydrothermablator™ and Fibroids

- Success rate-91%
  - Amenorrhea rate- 55%
  - Failure rate- 9%

- No objective documentation of menorrhagia

- Observational study with small numbers

Glasser MH J Am Assoc Gynecol Laparosc 2003;10:521
Fibroids

Myomectomy

Reproductive Age

Post-Reproductive

Fibroids

Hysterectomy
Case 3

Jane is a 47 year-old woman with a history of fibroids. Last year, you documented a 12 week size uterus. This year, it’s 20 week size. A pelvic US shows multiple fibroids, the largest of which is a 10 cm. On an US 3 yrs ago, it measured 5 cm. Although she has no symptoms, the rapid growth is worrisome for leiomyosarcoma.

What would you do next?
What is the incidence of sarcoma?

- Retrospective study of 1332 women
  - Hysterectomy or myomectomy for fibroids
  - 1 leiomyosarcoma (0.08%)
  - 2 endometrial stromal sarcomas (0.15%)
- Incidence 0.23%
- Actual incidence much lower
  - ~20% of women w/ fibroids undergo surgery

Parker et al, Obstet Gyn 1994;83:414-8
Case 3
What would you do next?

- Order a pelvic MRI to rule out sarcoma
- Biopsy the large mass
- Schedule an abdominal myomectomy and consent for hysterectomy too
- Schedule a hysterectomy with Gyn Onc back-up
- Counsel about fibroids and follow for symptom development
What is the incidence of sarcoma?

- During study period, 9 women had pre-op diagnosis of sarcoma
  - Age: 64-86 yrs
  - Presentation: vaginal bleeding, pelvic pain
  - 1 endometrial stromal sarcoma
  - 8 mixed mesodermal tumors

Parker et al, Obstet Gyn 1994;83:414-8
Does “rapid growth” predict sarcoma?

Rapid growth defined as $\geq 6$ wk increase in uterine size within 1 yr

- 0/198 had sarcoma
- 0/17 post-menopausal women had sarcoma
  - 10/17 were on HRT

Parker et al, Obstet Gyn 1994;83:414-8
Abdominal Myomectomy: Safety and feasible with large fibroids

Retrospective chart review by 1 gynecologist

- N=91 women
- Uterine size ≥ 16 wk (range 16-36 wk, mean 21 wks)
- Pfannestiel incisions

Results

- # fibroids removed: 1-25, mean 7
- Fibroid weight: 100 to 2500 gm, mean 668 gm
- OR time: 120-390 min, mean 236 min
- EBL: 50-3000 cc, mean 800 cc
- LOS: 1-5 days, mean 1.8 days
- None converted to hysterectomy
- No sarcomas

West S et al Fertil Steril 2006;85 (1): 36
Disclosures

- No financial associations to disclose
- Alert: Off label use for devices will be discussed