OPTIONS FOR MANAGEMENT OF UTERINE FIBROIDS

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BACKGROUND

• Fibroids affect*  
  • 60% reproductive age women  
  • 80% of women during lifetime  
  • Fibroids account for 600,000 hysterectomies in US per year†  
  • Public healthcare burden in the US is estimated to be between $5.9-34 billion/year!!  
  • Incidence 3-4 times higher in AA women compared to Caucasian

*Laughlin SK, Semin Reprod Med. 2010; 28:204-217  
†Thynn M. Am J Obstet Gynecol. 2006; 195(4):555  

GENETICS OF LEIOMYOMA

• Benign monoclonal tumors  
• May also occur as part of heritable cancer syndromes  
  • HLRCC (hereditary leiomyomatosis and renal cell cancer) is autosomal dominant  
  • Alport syndrome: X linked progressive nephropathy  
• Up-regulation of genes involved in fibrosis and extracelluar matrix production and transforming growth factor (TGF)β
BACKGROUND

• Fibroids cause
  • Menorrhagia
  • Pelvic pain
  • Pressure symptoms on bladder or bowel
  • Infertility (sole cause in 1-3%)
  • Pregnancy complications
  • Iron deficiency anemia
• Location of fibroids and size matter
  • Submucosal
  • Intramural
  • Subserosal

EFFECT OF FIBROIDS ON FERTILITY

• Submucosal fibroid
  • 70% decrease in implantation and clinical pregnancy rates after IVF*  
• Intramural fibroid
  • Non cavity distorting intramural fibroids adversely affect fertility
    • Related to size of fibroids (>3cm)
    • Decreased implantation, clinical pregnancy and live birth**
• Subserosal fibroid
  • Does not negatively affect clinical pregnancy but may influence mode of delivery

*Somigliana E Hum Reprod Update. 2007;13:465-76
**Sunkara SK Hum Reprod. 2010;25:418-19

DIAGNOSIS

• Clinical examination
  • Essential to determine route of surgery
• Endometrial sampling
  • Important in most women
  • Risk factors for fibroids are similar to those of endometrial hyperplasia
    • Low parity
    • Obesity
    • AA race
• Sonohysterography
• Hysterosalpingography
• Hysteroscopy
**IMAGING - ULTRASOUND**

- Ultrasonography
  - Transvaginal sonography
  - Sufficient for diagnosis in a vast majority of patients not considering uterine preservation
  - Saline sonohysterography outlines submucous fibroids

**IMAGING - MRI**

- Useful for precise anatomic mapping
- Especially useful to evaluate large uterus
- Obesity does not obscure
- Detects co-existing disease such as adnexal mass
- Distinguishes between adenomyosis and leiomyoma
- Outlines distortion of pelvic anatomy due to fibroids

**MEDICAL MANAGEMENT**

- Managing excessive bleeding
- Managing pelvic pressure/pain
- Managing anemia due to chronic blood loss
- Pre-operative shrinking of fibroids

There are currently no FDA approved agents for long term treatment of uterine fibroids.
### MEDICAL MANAGEMENT

- **GnRH analogues**
  - Pre-operative Depot Leuprolide 3.75mg/month for 3 months is the only FDA approved GnRH analogue
  - 35-65% reduction in size of fibroids and uterus can be achieved
  - Amenorrhea
  - Reduces intra-operative blood loss, decreases hospital stay and helps convert some laparotomies into minimally invasive procedures
  - Re-growth of fibroids to pre-treatment size within months of cessation of GnRH therapy
  - May make surgical planes indistinct: myomectomy may be difficult

- **GnRH Analogue with Add-back**
  - Progesterone
    - Relieves symptoms of hot flashes
    - Uncertain if it helps or opposes the effect of GnRH
  - Estrogen
    - Risk of unopposed estrogen effect on endometrium
  - Estrogen-Progesterone
    - Comparable to Progesterone only add-back

- **Tibolone**
  - Not available in the US
  - Selective tissue estrogenic activity modulator
  - Long term (24 months) use as add-back reduced hot flashes, prevented bone loss
  - Raloxifene
    - More significant reduction in size of leiomyoma than GnRH alone
MEDICAL MANAGEMENT

- **GnRH antagonist**
  - Does not have the immediate flare effect of GnRH analogues
  - Needs daily injection
- **Selective Estrogen Receptor Modulator***
  - Currently no evidence that they are effective
  - **Raloxifene**
    - Decreases collagen synthesis in leiomyomata
  - **Tamoxifen**
    - Not ideal since it will increase risk of endometrial cancer
    - May be a better choice in patients with history of breast cancer

* Deng L. The Cochrane Library, 2012, issue 10

MEDICAL MANAGEMENT

- **Aromatase inhibitors**
  - Currently available: letrozole and anastrozole
  - Significantly block ovarian and peripheral estrogen production
  - Reduction of leiomyoma size similar to GnRH analogue
  - Rapid onset of action without flare
  - Oral medication

MEDICAL MANAGEMENT

- **Selective Progesterone receptor modulators**
  - Currently available: Mifepristone, ulipristal,
  - Investigational: telapristone, asoprisnil
  - Can cause endometrial thickening and hyperplasia
  - **Mifepristone**
    - Improves fibroid specific quality of life without reducing fibroid size*
    - Endometrial hyperplasia, risk is increased 1.6-55 fold*
  - **Ulipristal**: oral daily dose equivalent to GnRH analogue**

* Tristan M. The Cochrane Library, 2012 Issue 8
** Croxton J. Drugs. 2012; 72 (8):1073-85
**MEDICAL MANAGEMENT**

- Levonorgestrel IUS
  - FDA does not approve use in patients with uterine anomalies or distortion
  - Effective in reducing bleeding without reduction in myoma size *
  - Consider in pre-menopausal patients with menorrhagia
- Other agents
  - Danazol: no proven effectiveness
  - Gestrinone: side effect of androgen excess symptoms
- Acupuncture
  - Cochrane review** shows no effect but there were no RCTs

*Maruo T. Contraception. 2007; 75:99-103
**Zhang Y. The Cochrane Library. 2012; Issue 1

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**UTERINE FIBROID EMBOLIZATION**

- Performed by interventional radiologists
- Small particles of polyvinyl alcohol used to occlude blood supply to fibroids
- MRI used to map the uterus prior to procedure

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**UTERINE FIBROID EMBOLIZATION**

- **Indications**
  - Symptomatic fibroids
  - Future fertility not desired
  - Wish to avoid surgery
  - Poor surgical risk
- **Contraindications**
  - Gynecologic cancer not ruled out
  - Pregnancy
  - Allergy to contrast
  - Coagulopathy
  - Renal insufficiency
UTERINE FIBROID EMBOLIZATION

- Adverse effects
  - Post-procedure pain
  - Post embolization syndrome
  - Fever
  - Nausea
  - Fatigue
  - Pain
  - Passage of fibroids through cervix 5%**
  - Premature menopause*
    - 1-2% under 45 years
    - 15-20% over 45 years
  - Re-intervention rate 5.3%**

*Stovall D. Menopause 2011;18(4):437-444
**Toor SS. AJR 2012; 199:1153-1163

UTERINE FIBROID EMBOLIZATION

- Effectiveness
  - Symptomatic improvement 78-90%*
  - Less blood loss compared to abdominal hysterectomy*
  - Shorter hospital stay*
  - Quicker return to work*
  - Cost $20,000 (compared to hysterectomy 17,800)**
  - If pregnancy does occur there is increased risk of miscarriage of up to 60%**

*Toor SS. AJR 2012; 199:1153-1163
**Stovall D. Menopause 2011;18(4):437-444

MR GUIDED FOCUSED ULTRASOUND

- Performed by radiologists
- High intensity US is focused on fibroids
- Temperature 65°C-85°C
- Takes several hours
- Patient has to lay still and prone
- No more than 2 sessions in a 2 week period
- Not for postmenopausal women
MR GUIDED FOCUSED ULTRASOUND

Indications
- Symptomatic fibroids
- Uterine size less than 24 week size

Contraindications
- Desire for future fertility
- Subserous or pedunculated fibroids
- Presence of any metal implant
- Presence of IUD
- Myoma close to bladder, bowel, sacral nerves
- Adenomyosis
- Inability to lie prone
- Weight >250 lbs
- Abdominal surgical scars
- Severe anemia

Adverse effects
- Pain
- Potential bowel or bladder injury
- Skin burns
- Nerve injury

Effectiveness
- 85-95% symptom relief in 12 months*
- 21% recurrence of symptoms at 12 months*
- If pregnancy occurs there is increased risk of spontaneous loss (28%)**
- Cost: $12,000*


ENDOMETRIAL ABLATION

Treats menorrhagia
Applicable
- if cavity is not distorted
- if submucous fibroid is less than 3.5cm
Effectiveness data is mixed with DUB treatment
Cost $3,000-8,000
MYOMECTOMY

- Open procedure through laparotomy
- Laparoscopic myomectomy
- Single port laparoscopy
- Robotic laparoscopic myomectomy
- Hysteroscopic myomectomy

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MYOMECTOMY

- Indications
  - Desire to preserve fertility
  - Desire to preserve uterus
  - pedunculated subserous fibroid
  - Small symptomatic submucous fibroids
- Effectiveness
  - No difference between open and laparoscopic route for fertility
  - No RCT available to assess hysteroscopic route and fertility

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HYSTERECTOMY

- Minimally invasive approach
  - Vaginal hysterectomy
  - Laparoscopic assisted vaginal hysterectomy
  - Total laparoscopic hysterectomy
  - Single-port laparoscopic hysterectomy
  - Robotic assisted total laparoscopic hysterectomy
- Open (Laparotomy)
  - Total hysterectomy
  - supracervical hysterectomy
SUMMARY

- Only symptomatic fibroids need treatment
- Current data does not support using UAE, MRgFUS in patients desiring future fertility
- No RCT data showing myomectomy improves fertility
- If surgery is chosen, minimally invasive option results in quicker recovery and less blood loss.
- Hysterectomy offers the best long term solution when fertility is not desired