Fibroids in the Perimenopausal Woman:

Can We Make It to Menopause Without Surgery?

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Disclosures

- Menogenix: Stock Options, Scientific Advisory Board
- Ogeda/Astellas: Scientific Advisory Board

Learning Objectives

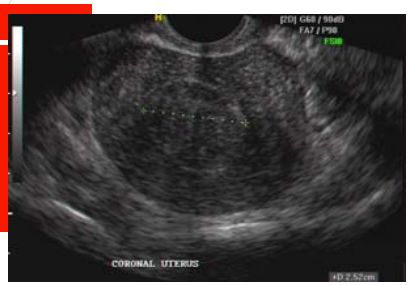
At the end of this talk, the learner is expected to:

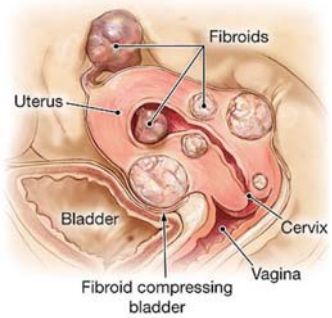
- Describe the natural history of uterine fibroids over the female life span
- Offer a selection of non-surgical management options for perimenopausal patients with fibroids
- Recommend surgery in appropriate cases

Prevalence and Natural History of Fibroids

- Estimates range from 20-80% depending on screening method
- Racial differences in prevalence and severity
- Differential growth based on size (smaller fibroids grow faster) and location (intramural fibroids grow faster; Mavrelos)
- Not known to occur prior to puberty; believed to regress after menopause
- Estrogen AND progesterone sensitive

Mavrelos, Ultrasound Ob Gyn 2010; 35:238; Stewart, UptoDate





Van Voorhis. JAMA 2009;301:82-93

At Menopause

- Expectation is that fibroids will regress or disappear
- Can become problematic during hormone therapy, if needed
- Fibroids that grow after menopause should be removed

Leiomyosarcoma

- Most feared consequence of 'watchful waiting' strategy
- Wide reported variation
- Molecular signature of sarcomas differ from leiomyoma
- We need better diagnostics

Case Study

- 49 year old woman with unmanageably heavy menses, Hgb 8 gm/dl, fatigue:
  - 8cm transmural mass on ultrasound
  - Appears to impinge on the uterine cavity
  - Additional intramural and subserosal masses

What Would You Do Next?

Temporizing Measures

- OCPs: menstrual suppression
- LNG IUD
- Selective Progesterone Receptor Modulators (SPRMs)
- Embolization
- Focused ultrasound
- GnRH agonist
- GnRH agonist + AI

OCPs and Fibroids

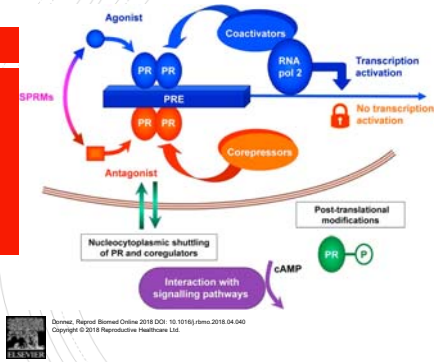
- Reduces menstrual flow
- Especially helpful given continuously
- Oral, transdermal, vaginal combined hormonal contraception
- Serves the need for both contraception and bleeding/fibroid symptom control

ACOG Practice Bulletin

LNG-IUD

- Limited studies but effective in reducing menorrhagia
- Does not appear to change fibroid size
- Relatively high continuation rate in two small trials (>80%)
- Also provides contraception

Sangkomkanhang, Cochrane Database Syst Rev 2013 Feb 28;(2): CD008994. doi: 10.1002/14651858. CD008994.pub2; Seno, Clin Exp Ob Gyn 2015; 42:224; Machado, Gyn Endo 2013; 29: 492



Donnez, Reprod Biomed Online 2018 DOI: 10.1016/j.rbmo.2018.04.040
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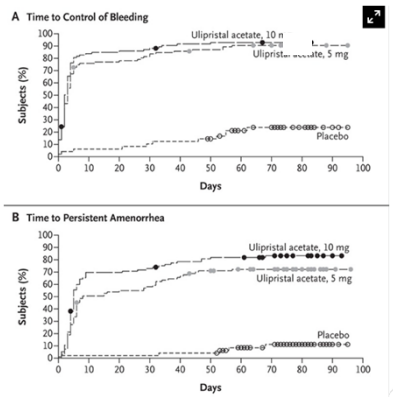
Clinical Data Summary Ulipristal PEARL Studies >1000 Women

- PEARL I: hemoglobin normalized
- PEARL II: fewer side effects than GnRHa, faster control of bleeding: 80% amenorrhea
- PEARL III: effective up to 6 months, prolonged symptoms control/fibroid shrinkage after stopping
- PEARL IV: use for up to 4 cycles
- 5mg/day for up to 4 months; repeat cycles appropriate as needed

Powell, Womens Health (Lond) 2016; 12:544

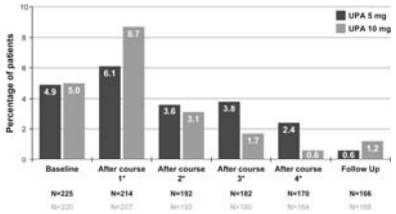
Excellent Bleeding Control and Amenorrhea Rates

Donnez,NEJM2012;366:409



Ullipristal Endometrial Thickness>16mm

Donnez, Fertil Steril 2016; 105:165



Ullipristal: Clinical Considerations

- 5mg daily dose for 3 months; can repeat x 3 or more
- Cystic/stromal non-physiologic changes in endometrium: 8%-16 of women, reversible
- Avoid in patients with hepatic impairment, glucocorticoid dependent conditions
- Avoid pregnancy!
- Fibroids 3-12cm studied
- Limited data on African-American women

Hrgovic, J Clin Pharm Ther 2018; 43: 121

Ullipristal: Liver Toxicity

- 5 cases identified
- 1 fatal
- 2 recovered
- 1 required liver transplant
- EMA review:
- FDA withholding approval pending evaluation of data

GnRHa + AIs

- N=10, Age ≥47, perimenopausal
- At least 3 fibroids, >5cm, HMB and anemia
- 11.25mg GnRHa (triptorelin) + letrozole 2.5mg
- Add-back hormone given (CEE+MPA)
- Small reduction in fibroid volume
- Hematologic normalization
- Up to 3 years treatment

Moradan J Menopausal Med 2018; 24:62

Symptoms related to uterine leiomyoma represented by numeric scale.

	Average	SD	Minim.	Maxim.	Mean
T1	5.5	1.00	4.0	7.0	6.0
T2	4.4	0.82	3.0	6.0	4.0
T3	3.6	0.68	3.0	5.0	3.5

View Table in HTML

Note: SD = Standard deviation.

Hilario, Fertil Steril 2009; 91:240

Is DMPA an Effective Choice?

- DMPA
- Will result in amenorrhea
- Can reduce fibroid size because of low E2
- Less desirable in perimenopause because of adverse effects on BMD—without recovery time

Uterine Artery Embolization (UAE)

- Chief Advantages: Fast recovery time, may be done with local/epidural anesthesia/no need for OR
- Chief Disadvantage: 15-32% need for surgery within 2 years for UAE versus 7% for myomectomy/hysterectomy
- More minor complications than surgical options
- Likely better outcomes for women closer to menopause

Gupta, Cochrane Database Syst Rev. 2014 Dec 26;(12):CD005073

Focused Ultrasound

- High intensity ultrasound beam—thermal destruction of fibroid tissue; MRI guidance
- Effective with low morbidity in selected patients
- Cannot be done if: bowel imposition, >5 fibroids, adenomyosis
- Multiple sessions may be required
- Cost-effectiveness not well established
- COMPARE-UF Registry: patient centered outcome database, in progress

Stewart E, Am J Obstet Gynecol 2018; 219: 95e.1

Which is Better: UAE or Focused US?

- FIRSTT Trial (Fibroid Interventions: Reducing Symptoms Today and Tomorrow)
- RCT (N=57) = 'comprehensive cohort' (N=83) design
- UAE: worse post-procedure pain; longer recovery time (8 [6-14]vs 4 [2-7]days); more post-procedure opioids (75 vs 21%) and other pain meds

Barnard, Am J Obstet Gynecol 2017; 216: 500.e1

What Happens With HT?

- Few studies directly address this issue
- Among 32 women taking E+P, fibroid volume went from 20+/-25 cc to 29 +/-56cc at 6 months, NS but 9 with 'clinically significant' growth (Chang)
- 60 women on HT: 'no increase' (24+/-20cc to 29+/-30cc) over 12 months; greatest growth seen in those with fibroids >3cm at baseline (Colacurci)
- CEE+bazedoxifene may be an alternative HT for women with fibroids

Chang, J Meno Med 2013; 19:123; Colacurci Maturitas 200; 35: 167

Summary

- Uterine fibroids are very common tumors that extract a large toll on female QOL
- Fibroids that persist/grow in the perimenopause are amenable to a variety of treatments
- Inexpensive options (hormonal contraception, LNG-IUD) can control HMB and avoid pregnancy
- Ulliprista acetate, the newest modality, controls bleeding and also reduces fibroid size
- Medically inducing earlier menopause (with GnRHa) may only be needed in limited cases
- HT is not contraindicated in the presence of fibroids; for women with fibroid growth or bleeding, SERMs may be beneficial