Fibroid Management in Midlife

Dr. Ally Murji MD MPH FRCSC
Assistant Professor, University of Toronto
Minimally Invasive Gynecologic Surgery
Mount Sinai Hospital

Learning Objectives

1. Review the work-up symptomatic uterine fibroids in midlife
2. Discuss the options for medical management of fibroids

Disclosure

• I have received a grant(s) or an honorarium from a commercial organization:
  – AbbVie
  – Actavis
  – Bayer
  – Hologic

Prevalence of clinically relevant fibroids

Age (years)
Case
48 yo, G2P2 with heavy menstrual bleeding
Q 24 days, flooding, soaking pads/tampons – CAUSING ANEMIA
Bulk symptoms – urinary urgency and pressure symptoms

Range of Symptoms Associated with Uterine Fibroids*

Nearly half of women with fibroids have significant and often disabling symptoms* Symptomatic fibroids™ can be linked to.3

BLEEDING
BULK
FERTILITY

These have been shown to diminish quality of life3

Get the story straight...

AUB Bleeding Pattern

<table>
<thead>
<tr>
<th>Period Timing?</th>
<th>Complaint?</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGULAR Cyclical Predictable</td>
<td>Heavy Intermenstrual Bleeding</td>
</tr>
<tr>
<td>IRREGULAR Unpredictable</td>
<td>AUB H/L Unpredictable AUB</td>
</tr>
<tr>
<td>AUB-M</td>
<td></td>
</tr>
</tbody>
</table>

Palm

<table>
<thead>
<tr>
<th>Polyp</th>
<th>Adenomyosis</th>
<th>Leiomyoma</th>
<th>Malignancy &amp; Hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulopathy</td>
<td>Ovulatory Dysfunction</td>
<td>Endometrial</td>
<td>Iatrogenic</td>
</tr>
<tr>
<td>Not Yet Classified</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COEIN

Indications for Ebx
- Age > 40
- RF for Endometrial CA
- Failure of medical treatment
- Significant inter-menstrual bleeding
- Consider when infrequent menses suggestive of anovulation

*Not all fibroids are symptomatic

**Symptomatic fibroids™

48 yo with regular heavy bleeding
Exam: Uterus is 16 weeks size
Endometrial biopsy: proliferative endometrium

“Doctor... could these fibroids be cancerous?”

What is the risk of occult sarcoma in symptomatic fibroids?
A) Between 1/300 – 1/500 18%
B) Between 1/500 – 1/1000 31%
C) Less than 1/1000 52%
Cancer risk at fibroid surgery

<table>
<thead>
<tr>
<th>Age</th>
<th>Myomectomy</th>
<th>Myo / Hyst</th>
<th>Any Cancer</th>
<th>Sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>1/2000</td>
<td>1/769</td>
<td>1/2000</td>
<td>1/769</td>
</tr>
<tr>
<td>40 - 49</td>
<td>1/667</td>
<td></td>
<td>1/667</td>
<td></td>
</tr>
<tr>
<td>50 - 59</td>
<td>1/161</td>
<td>1/172</td>
<td>1/161</td>
<td>1/172</td>
</tr>
<tr>
<td>≥ 60</td>
<td>1/29 (3.5%)</td>
<td>1/65 (1.5%)</td>
<td>1/29 (3.5%)</td>
<td>1/65 (1.5%)</td>
</tr>
</tbody>
</table>

Value of Endometrial Sampling

- Retrospective review over 10 years
- Three Cancer Centers in Ontario
- 302 uterine sarcoma (216 LMS / 86 ESS)

25% diagnosed by endometrial sampling

48 yo with HMB + Bulk + Neg Bx

LOCATION, LOCATION, LOCATION

UTERUS WITH FIBROIDS

48 year old with HMB + Bulk + Neg Bx
### Summary of Medical Options

<table>
<thead>
<tr>
<th>Approach</th>
<th>Symptoms</th>
<th>Fibroid shrinkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives</td>
<td>HMB</td>
<td>NO</td>
</tr>
<tr>
<td>Levonorgestrel-releasing IUD</td>
<td>HMB</td>
<td>NO</td>
</tr>
<tr>
<td>Danazol</td>
<td>HMB</td>
<td>NO</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>HMB</td>
<td>NO</td>
</tr>
<tr>
<td>GnRH-A</td>
<td>HMB + Bulk</td>
<td>YES</td>
</tr>
<tr>
<td>Ulipristal Acetate</td>
<td>HMB + Bulk</td>
<td>YES</td>
</tr>
</tbody>
</table>

### 48 yo with HMB + Bulk + Neg Bx

- **SPRM**
- **GnRH-a**

Single or repeated gonadotropin-releasing hormone agonist treatment avoids hysterectomy in premenopausal women with large symptomatic fibroids with no effects on sexual function.

Jan 2014

- ≥ 45 years with symptomatic fibroids
- Comparative cohort: GnRH-a x 6mo vs Hyst
- Medical management at 2 years
  - 12% failed and required surgery; 88% Hyst
  - 22% required additional GnRH-a courses
  - 18% required additional therapies
- Did not examine QoL in the two groups
GnRH Agonist + Add Back
For how long?

SPRM

- How they work?
  - Progesterone hypothesis
  - Ez induces Pg receptor expression
- Compounds that bind to PRs
- Tissue-specific modulation
- Modulate transcription in a positive or negative manner

Ulipristal Acetate: Mechanism of Action

Fibristal™ (ulipristal acetate) is indicated for the treatment of moderate to severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery. The duration of treatment is limited to 3 months.

Health Canada 2013
PEARL III

Long-term treatment of uterine fibroids with ulipristal acetate

June 2014

PEARL III and Extension: Open-Label On-Off Intermittent Use of UPA 10 mg

UPA 10mg: 4 sequential courses of 12 weeks
Each course followed by 10 days of double-blind NETA vs placebo
PEARL III + EXTENSION DURATION: ~22 MONTHS

Donnez et al, FerKlity and Sterility, 2014

209 patients

Pearl III Extension

PEARL III Extension: Patient Flow

Donnez et al, FerKlity and Sterility, 2014

209 patients

NETA, norethindrone acetate; UPA, ulipristal acetate
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41 years</td>
</tr>
<tr>
<td>White race</td>
<td>92%</td>
</tr>
<tr>
<td>BMI</td>
<td>25 kg/m²</td>
</tr>
<tr>
<td>PBAC score</td>
<td>234</td>
</tr>
<tr>
<td>Symptom Severity UFS-QoL</td>
<td>49</td>
</tr>
</tbody>
</table>

Primary Outcome: % amenorrhea after each dose

PEarl III, 2014

Proportion of patients in amenorrhea at the end of each course

PEarl III and Extension: Efficacy on Fibroid Volume Reduction (ITT Population, All Patients)

How distressed were you by:

- Heavy bleeding
- Blood clots
- Duration of period
- Pelvic tightness or pressure
- Frequent urination
- Night time urination
- Fatigue

Quality of Life – Symptom Severity

PEARL III: Endometrium Histology

PAEC (confirmed by at least 2 out of 3 pathologists)

<table>
<thead>
<tr>
<th>Patients having PAEC (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>10.5%</td>
</tr>
<tr>
<td>After 1st UPA course</td>
<td>28.7%</td>
</tr>
<tr>
<td>After 4th UPA course</td>
<td>25.3% (n=22)</td>
</tr>
<tr>
<td>3 months after Course 4</td>
<td>3</td>
</tr>
</tbody>
</table>

PAEC was observed in less than 30% of patients after one menstrual bleed
The frequency of PAEC did not increase after repeated UPA courses
Return to baseline levels after 3 months post-treatment

Limitations of PEARL III

- 10 mg dose
- 3 month duration
- Few ethnic African American (5-9%)
- BMI 25
- Fibroid size restricted to maximum 10cm
- 1/3 of patients did not enroll in Extension Phase
  – Not sure how they would have responded
- OFF LABEL USE
Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids


451 patients
411 patients

PEARL IV

Efficacy: Amenorrhea
(Full Analysis Set)

Proportion of patients in amenorrhea* at the end of treatment course 1 and 2

PEAIRL IV

QUALITY OF LIFE – SYMPTOM SEVERITY

48 yo with HMB + Bulk + Neg Bx

SPRM
- Oral
- Well tolerated
- Rapid control of bleeding
- Sustained effect

GnRH-a
- Excellent volume response
- Long term data & use

PEARL IV

Symptom severity score domains:
1. Bleeding
2. Abdominal pressure
3. Urination frequency
4. Fatigue

44
23

Fewer symptoms

UPA 5 mg
UPA 10 mg

SPRM

GnRH-a

Volume reduction

Long-term data

Exact regimen

PAEC


1. Appropriate work-up of AUB to rule out carcinoma other etiologies
2. Risks of sarcoma in symptomatic fibroids
3. Treat symptoms – Bleeding, BULK, fertility
4. Long term treatment should is the new paradigm especially in perimenopause

Conclusions