Disparities in Causes and Cures for Heavy Menstrual Bleeding

Preserving the future: Uterine Fibroid Therapy for the 21st Century

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Disclosures

- William H. Catherino has the following relevant financial or non-financial interest(s) to disclose:
  - Advisory Board
    - Abbvie
    - Allergan
    - Bayer
    - EMD Serono
    - Myovant

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Commercial Support was not received for this activity
Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Review the impact of uterine fibroids on active duty and veteran women
2. Recognize the limitations of investigating uterine fibroids
3. Summarize the recent advances for investigating uterine fibroids
Military Women’s Health Research

- Cooperative Inter-Agency Effort to Promote DHA and USU Goals for Women’s Health

- Goal: Enhance research on causes, prevention, mitigation, and treatment of disease impacting women’s health and readiness
Heavy Menstrual Bleeding

• Excessive menstrual blood loss that interferes with physical, emotional, social and material quality of life
• Impacts up to 30% of women in their lifetime
• Accounts for 18-30% of gynecologic visits
• Estimated annual direct costs = $1,000,000,000
• Estimated indirect costs = $12,000,000,000
  – Lost days of work and quality of life

Farquar and Brown Cochrane Database Syst Rev 2009;4:CD000154
Liu Value Health 2007;10:183-94
Causes of HMB

• Common Causes
  – Uterine Fibroids
  – Uterine Polyps
  – Ovulatory Disorders

• Rare Causes
  – Adenomyosis
  – Endocrine Disorders
  – Iatrogenic
  – Malignancy
  – Coagulopathy
  – Not Yet Classified
Fibroids in Active Duty Women

“Incidence rates of uterine fibroids by age group and race/ethnicity, active component, U.S. Armed Forces, 2001-2010”

Cumulative Incidence of Fibroids over Reproductive Lifespan

Laughlin Seminars Reprod Med 2010;28: 214
What are Uterine Fibroids?

- Hormonally sensitive benign tumors that produce an abundance of fibrosis
- Account for 50% of all hysterectomy procedures
- Grow in the presence of estrogen and progesterone
Fibroids Increase Miscarriage Rate

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
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<td>Gianaroli et al., 2005</td>
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<td>Girgin et al., 2005</td>
<td>0.499</td>
<td>0.274</td>
<td>0.910</td>
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<td>Khalaf et al., 2006</td>
<td>0.474</td>
<td>0.301</td>
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<td>Farhi et al., 1995</td>
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<td>Ramzy et al., 1998</td>
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<td>0.619</td>
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<td>Jun et al., 2001</td>
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<td>Yarali et al., 2002</td>
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<td>Ng et al., 2002</td>
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<td>Oliveria et al., 2004</td>
<td>1.154</td>
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<td>Guven et al., 2013</td>
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<td>0.737</td>
<td>0.647</td>
<td>0.840</td>
<td>-4.591</td>
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</tbody>
</table>

Odds of miscarriage decreased with no myoma compared to myoma
Not Impacting the Cavity
OR = 0.737 [0.647, 0.840]
# Obstetric Complications of Fibroids

<table>
<thead>
<tr>
<th>Complication</th>
<th>Fibroid</th>
<th>No Fibroid</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal labor</td>
<td>49.6%</td>
<td>22.6%</td>
<td>2.2</td>
</tr>
<tr>
<td>Cesarean Section</td>
<td>46.2%</td>
<td>23.5%</td>
<td>2.0</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>13.8%</td>
<td>10.7%</td>
<td>1.5</td>
</tr>
<tr>
<td>Breech position</td>
<td>9.3%</td>
<td>4.0%</td>
<td>1.6</td>
</tr>
<tr>
<td>pp Hemorrhage</td>
<td>8.3%</td>
<td>2.9%</td>
<td>2.2</td>
</tr>
<tr>
<td>PROM</td>
<td>4.2%</td>
<td>2.5%</td>
<td>1.5</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>1.7%</td>
<td>0.7%</td>
<td>2.0</td>
</tr>
<tr>
<td>Abruption</td>
<td>1.4%</td>
<td>0.7%</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Biderman-Madar Arch Gynecol Obstet 2005;272:218
Coronado Obstet Gynecol 2000;95:764
Navid Ayub Med Coll Abbottabad 2012;24:90
Stout Obstet Gynecol 2010;116:1056
Ciavattini J Matern Fetal Neonatal Med 2015;28:484-8
Sheiner J Reprod Med 2004;49:182
Qidwai Obstet Gynecol 2006;107:376
Fibroids

• Cause heavy menstrual bleeding
• Cause pelvic pain
• Cause pelvic pressure
• Cause infertility
• Cause miscarriages
• Cause pregnancy complications
# Treatment options for Uterine Leiomyomas

<table>
<thead>
<tr>
<th>Surgical</th>
<th>Radiologic / Minimally Invasive</th>
<th>Medical</th>
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</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td>Uterine Artery Embolization</td>
<td>Oral Contraceptive Pills</td>
</tr>
<tr>
<td>Open Myomectomy</td>
<td>MRI-Guided HiFU</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>L/S Myomectomy</td>
<td>Endometrial Ablation</td>
<td>GnRH Analogues</td>
</tr>
<tr>
<td>Robotic Myomectomy</td>
<td>L/S Radiofrequency Ablation</td>
<td>Aromatase Inhibitors</td>
</tr>
<tr>
<td>H/S Myomectomy</td>
<td>Uterine Artery Obstruction</td>
<td>SPRMs</td>
</tr>
</tbody>
</table>

- Damages uterus
- Starves uterus
- Hormonal regulation
- Pain control
Why Such Poor Options After 150 Years of Study?

• The disrespected uterus

• Symptom taboo

• Poor models

• Poor focus
Available Models

• 150 years: Surgical specimens
• 35 years: Cell culture
• 30 years: Explant cultures
• 25 years: Animal models
  – Limitations
    • Typically failed by 4 weeks
    • Did not represent human disease
Mouse Xenograft Model

Mouse skin and hair

Leiomyoma xenograft
Gross Impact of Gonadal Hormones

Original Cultures

Placebo

Estradiol

Progesterone

Estradiol + Progesterone
Impact of Gonadal Hormones on Collagen

Placebo

Estradiol (E2) Progesterone (P4) E2P4
Microscopic Impact of Gonadal Hormones

<table>
<thead>
<tr>
<th>SMCα</th>
<th>Ki67</th>
<th>FN1</th>
<th>ERα</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

Tissue Xenografts
- No Hormone
- Estradiol exposure

3D Xenografts
- No Hormone
- Estradiol exposure
Morcellation and the FDA

- 1:350 have unsuspected sarcoma
- Risk of upstaging and worsening prognosis
- Discourages the use of laparoscopic power morcellation
Growth in 3D Format
Leiomyoma cells

Leiomyosarcoma cells
Summary

• Uterine fibroids are highly prevalent and symptomatic, directly impacting readiness

• Available therapies are poor due to limited understanding

• Cutting-edge advances supported by the Military Women’s Health Research allow for rapid advances in treatment options for suffering women and active duty partners
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