Epidemiologic contribution to understanding environmental impact on women’s health:

Study of Environment, Lifestyle & Fibroids (SELF)

Quaker Harmon, MD, PhD
Staff Scientist (she, her)
National Institute of Environmental Health Sciences
Uterine leiomyoma, fibroids

- Non-cancerous smooth muscle tumors of the uterus

Symptoms impact all aspects of life

• Symptoms
  • Heavy menstrual bleeding
  • Pain (during menstrual period, pelvic, back, during sex)
  • Abdominal bloating /pressure
  • Bladder and bowel symptoms
  • Fatigue
  • Difficulty getting pregnant or pregnancy complications

• Leading cause of hysterectomy
Common condition, earlier onset and higher prevalence for Black women.

Laughlin, Baird 2009; Eskenazi 2007; Baird, Dunson 2003

50% of pre-menopausal women without a diagnosis of fibroids had evidence of fibroids on ultrasound.
Few established risk factors, most non-modifiable

- Age
- Race/ethnicity
- Parity (protective)
- Earlier age at menarche

Modifiable risk factors – some supporting data but inconsistent

- Physical activity
- Dietary exposures
- Smoking
- Use of Depo-Provera® (protective, strong support)
Common condition, high burden. Why don’t we know more?

• Animal and human tissue studies
  – Eker rat model
  – Genetic mutations within fibroid tissue

Human studies

Fibroid begins

Fibroid grows

Fibroid big enough to see

Large fibroid causes symptoms (may be diagnosed)

Misclassification of exposure

Non-Case or Controls

Cases

Misclassify non-cases

Too late!
Existing human studies

- Do not learn about the early development of fibroids
- Miss exposures that occur before fibroids develop
- May be difficult to find associations that replicate

- Until we know the natural history, it can be hard to identify important exposures

- We need good study designs to identify causes of fibroids
• Black or African American women ages 23-35
• Detroit, MI area
• No clinical diagnosis of fibroids
**SELF - Study Design**

<table>
<thead>
<tr>
<th>Visit</th>
<th>N</th>
<th>Response</th>
<th>Timeframe</th>
<th>Activities</th>
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</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>1693</td>
<td>88%</td>
<td>2010–2012</td>
<td>Every visit</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>~18-20 mos.</td>
<td>Ultrasound</td>
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<td>Questionnaires</td>
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<td>Clinical Measurements</td>
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<td></td>
<td></td>
<td></td>
<td>Biospecimen</td>
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<tr>
<td>Visit 2</td>
<td></td>
<td>86%</td>
<td>2012–2015</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>~18-20 mos.</td>
<td></td>
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<tr>
<td>Visit 3</td>
<td></td>
<td>91%</td>
<td>2014–2016</td>
<td></td>
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<td>~18-20 mos.</td>
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<tr>
<td>Visit 4</td>
<td></td>
<td></td>
<td>2016–2018</td>
<td></td>
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<td>~18-20 mos.</td>
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What can we do?

• Use ultrasound to detect new fibroids
• Measure fibroid growth
• Measure exposures before fibroids develop
• Many other important outcomes can be studied
• Natural history of a condition is fundamental → population burden, when and who to screen, know when to treat

• Finding exposures which slow the growth of small fibroids → reduce or delay symptoms and the need for invasive treatments

• Identifying exposures which increase the risk of new fibroids or increase the growth of small fibroids → opportunity to avoid or reduce exposure, prioritize screening
Environmental exposures and natural history

• Depo Provera

• Infant soy formula

• Natural history and impact of birth
Demographics at baseline among 1610 participants with at least one follow-up visit

- Mean age 29 Y (SD 3.4)
- 78% have at least some college education
- 60% employed
- 45% household income <$20,000
- 60% have had a birth
Outcome overview

Visit 1 Visit 2
Interval

~18 mos.

- Outcome based on comparison of consecutive ultrasounds
- Fibroid incidence (new fibroids)
- Fibroid growth
Fibroid incidence and growth by age

Cumulative incidence by baseline age

Growth rate by age

↑ incidence with age

↓ growth rates with age

Baird 2020; Wegienka 2022
Depo medroxyprogesterone acetate (DMPA) and fibroids

• An injectable progestin-only contraceptive

Studies of EVER vs. NEVER use of DMPA and fibroids

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimated RR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Lumbiaganon (1985)</td>
<td>0.4 (0.3-0.5)</td>
</tr>
<tr>
<td>Wise (2004)</td>
<td>0.6 (0.4-0.9)</td>
</tr>
<tr>
<td>Harmon (2014)</td>
<td>0.7 (0.6, 0.9)</td>
</tr>
</tbody>
</table>

Cross-sectional OR clinical diagnosis

Use of depo medroxyprogesterone acetate (DMPA)

Years since last use

Use questionnaire data to calculate the number of years since last use of DMPA

40% ever used DMPA
Statistical analysis, overview

- Up to 3 intervals for each participant
- Separate model for fibroid incidence and fibroid growth
- Account for repeated measures by participant and fibroid
- Censor following interventions to treat fibroids

Visit 1

Visit 2

~18 mos.
Fibroid Incidence, N=1232 participants

Visit 1

Visit 2

Eligible
No prior fibroid

Outcome
New fibroid case

Model
Cox Model with age as the time scale
DMPA associated with reduced fibroid incidence

No association

Adjusted for time since last birth, parity, BMI, smoking, income
Fibroid Growth, N=1359 fibroid matches from 433 participants

Visit 1

Visit 2

Eligible
Fibroids matched on position

Outcome
Change in log volume scaled to 18 months

Model
Linear mixed model (fibroid level data)
DMPA associated with reduction in fibroid growth over 18-months

Adjusted for age, time since last birth, number of fibroids, fibroid volume, employment, use of oral contraception, age at menarche
Summary

Exposure to DMPA within 2 years:

**Incidence**: 40% reduction in fibroid incidence

**Growth**: 45% lower growth

**Loss**: 70% higher loss

Important non-contraceptive benefit, needs to be studied in larger populations
Potential to delay symptoms in those with small fibroids
Soy has phytoestrogens

- Isoflavones act as endocrine disruptor
- Postnatal treatment to lab animals
  - alters rodent reproductive tract including uterus
  - increased fibroid development in Eker rats
- Exposure during sensitive developmental windows detrimental effects on reproductive systems
Soy-based infant formula

• Consumed by 12% of U.S. infants

• Contains high levels of phytoestrogens

• Linked to reproductive conditions
  – early/late menarche, menstrual irregularities, endometriosis

• Proliferative vaginal tissue in soy-fed infants

Soy formula assessment

- Participants interviewed their mother when possible (89%)
- Answers from relatives/family friends present during infancy (11%)

35. **Was I ever fed soy formula?**
   - Yes
   - No

36. **About how many months was I fed soy formula?**
   - Less than 1 month
   - 1 to 3 months
   - 4 to 6 months
   - More than 6 months

37. **Did you start giving me soy formula within the first 2 months of my life?**
   - Yes
   - No

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**Composite Variable**
Within 2 months & ≥4 months

More exposed
Increased risk of incident fibroids with soy formula feeding

Adjusted for age (timescale), maternal pre-pregnancy diabetes/GDM, maternal HDP, mother’s age at birth, mother’s educational attainment, birth weight, time since last contraceptive injection, parity, time since last birth, smoking, BMI, and household income.
Summary

• **Increased risk** of ultrasound-identified incident fibroids in adulthood for those fed soy formula *soon after birth and for a longer duration*

• Consistent with prior animal and human studies

• Examine fibroids and other outcomes in larger populations
Association between birth and fibroid growth

• Consistent observational data and animal studies showing that those with a birth are less likely to have fibroids

• Fibroid growth
  – Birth within 5 years reduces fibroid growth by 30% [95% CI (-35%, -9%)]
  – Stronger effects if also breastfeed for 6+ months

• Personal care products
• Sleep quality
• Early-life adversity
• Measured metals, endocrine disrupting compounds
• Inflammation
• Spatial and temporal exposures
• PCOS and hirsutism
• Body mass index
• Menstrual cycle characteristics
• Anti-Müllerian hormone
• Birth outcomes
• COVID experiences
• Infertility
• Vitamin D
• SELF advances the science

• Highly engaged cohort and collaborative science a model for these types of studies

• Starting to use geocoding to capture neighborhood factors, toxic contamination sites, air quality

• Findings need to be replicated in other populations with high-quality study designs

• Life-course disease will require long-term investment
Collaborators and Funding

Current and Recent Trainees

Dr. Christine Langton
Dr. Kristen Moore
Dr. Kristen Upson
Michigan State
Sherice Simpson
Dr. Helen Chin
George Mason

Extramural Collaborators

NICHD Collaborators

Dr. Shyamal Peddada
Dr. Fasil Tekola Ayele

NIEHS Collaborators

Dr. Anne Marie Jukic
Dr. Chandra Jackson
Dr. Symielle Gaston
Dr. Kyla Taylor

American Recovery and Reinvestment Act
Questions
Additional slides
DMPA associated with reduced fibroid incidence

Adjusted for time since last birth, parity, BMI, smoking, income
DMPA associated with increased fibroid loss

Adjusted for age, time since last birth, months between visits, number of fibroids, fibroid volume, BMI, education