Advancing NIH Research on the Health of Women: A 2021 Conference

Fortifying Opportunities to Advance Female-Specific Chronic Disease Research

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October 20, 2021
Disclosures

- President-Elect, World Endometriosis Society
- Trustee, World Endometriosis Research Foundation
- Member, Interdisciplinary Network on Female Pelvic Health, Society for Women’s Health Research
- Past Chair, American Society for Reproductive Medicine Endometriosis Special Interest Group
- International Advisor, European Society of Human Reproduction and Embryology Special Interest Group for Endometriosis and Endometrial Disorders
- Member, International Endometriosis Advisory Committee, AbbVie
- Statistical Editor – *Human Reproduction*
- Field Chief Editor – *Frontiers in Reproductive Health*
- Research Grant Recipient – NIH, DoD, AbbVie, Marriott Family Foundations

The views expressed in this presentation are the presenters and do not represent any private or public institution, professional society, or the US federal government.
## Chronic Debilitating Conditions

### Female Specific
- Gyn Cancers
- Menstrual abnormalities
- Fibroids
- **Endometriosis**
- Adenomyosis
- Infertility
- Miscarriage
- PCOS
- Pelvic Floor d/o
- Menopause
- PID

### Female Prevalent
- Depression
- Migraine
- Breast Cancer
- Autoimmune
- Rheumatoid Arthritis
- Multiple Sclerosis
- STIs
- Chronic Fatigue
- Fibromyalgia
- Osteoporosis
- Candidiasis

### Poorly Understood in Women
- Violence
- Dementia
- Osteoarthritis
- Endocrine d/o
- Metabolic d/o
- Blood d/o
- Immune d/o
- Recurrent UTIs
- HIV
- Neuropathy
- Incontinence
- Chronic pain

### Morbid in Women
- Heart Disease
- Low back pain
- COPD
- Drug use d/o
- Stroke
- Diabetes
- Obesity
- Influenza
- Pneumonia
What is Endometriosis?

Endometrial-like tissue (glands and stroma) growing outside of the uterus
   -- Peritoneal cavity, but also distal sites (e.g. lung, heart, brain)

Estrogen-dependent, progesterone-resistant, inflammatory disorder

Zondervan, Becker, Missmer. *NEJM* 2020
Diagnostic Obstacles in Female-Specific Conditions

• Symptoms are nonspecific or associated with other disorders
  • Circuitous path
  • Mistakenly dismissed as “normal” menstrual pain
  • Embarrassment specific to menstruation and pelvic pain

65% Misdiagnosed
Median see 5+ MDs before correct diagnosis

Zondervan, Becker, Missmer. *NEJM* 2020
Mihalyi A, et al. *Hum Reprod* 2010
WaterAid – No Shame Campaign 2017
Treatment Obstacles in Female-Specific Conditions

Zondervan, Becker, Missmer. NEJM 2020
Figure 2: Theoretical effects of endometriosis on life-course trajectory. Life exposures and their influences on a patient's attainments in life, education, family, career, etc. A comparison of untreated or persistently symptomatic endometriosis vs no endometriosis.

Missmer S, et al. *Int J Gen Med* 2021
Treatment Obstacles in Female-Specific Conditions

Zondervan, Becker, Missmer. NEJM 2020
Moving Beyond Reflexive and Prophylactic Gynecologic Surgery

Elizabeth A. Stewart, MD; Stacey A. Missmer, ScD; and Walter A. Rocca, MD, MPH
Treatment Obstacles in Female-Specific Conditions

Zondervan, Becker, Missmer. *NEJM* 2020
### Coexisting Conditions and Subsequent Disorders

- **Gynecologic**
  - Uterine fibroids, adenomyosis
- **Pain**
  - Fibromyalgia, migraine
- **Central sensitization**
- **Gastroenterologic**
  - Irritable bowel syndrome, ulcerative colitis
- **Genitourinary**
  - Interstitial cystitis
- **Mental health**
  - Depression, anxiety
- **Immunologic**
  - Rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, allergies, asthma
- **Cancer**
  - Ovarian cancer, melanoma, thyroid cancer
- **Cardiovascular disease**

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**Figure 2. Multisystemic Endometriosis Phenome.**

- Zondervan, Becker, Missmer. *NEJM* 2020
- Missmer S. *Int J Epidemiol* 2009
Research Obstacles in Female-Specific Conditions

Requires:
- Detailed clinical and phenotypic data
- Collected from many women
- Tied to critical lifecourse windows

RARELY exist in biobanks or in eMR!

Exist in longstanding prospective cohorts

Environmental / Behavioral exposures

Inflammatory indicators / markers

Adapted from Krina Zondervan, Oxford
Current Members

The NCI Cohort Consortium membership is international in scope. It includes investigators responsible for more than 61 high-quality cohorts who are studying large and diverse populations in more than 15 different countries.

The purple regions on the map below represent the locations of populations that NCI Cohort Consortium members are currently studying.

Map of NCI Cohort Consortium Membership by Continent, 2021
Research Obstacles in Female-Specific Conditions

Requires:
Detailed clinical and phenotypic data
Collected from many women
Tied to critical lifecourse windows

RARELY exist in biobanks or in eMR!

Exist in longstanding prospective cohorts
BUT Don’t have pain or endometriosis data

Environmental / Behavioral exposures

Inflammatory indicators / markers
Research Obstacles in Female-Specific Conditions

Krumsieck et al, 2016
Publicly available datasets... No endometrium

- Link genetic results to levels of gene and protein expression
- Examine the environment’s impact on this (‘epigenetics’) 
- Target tissue: endometrium and constituting cells
Mirin 2020. Gender disparity in NIH funding

2019 NIH Funding ($ Millions)

2015 U.S Disability Adjusted Life Year (DALY) ($log_{10}$)

(DALY = index of disease burden and combines prevalence, morbidity and mortality)

Courtesy of Dr. Ron Chandler, MSU
Need to Advance Female-specific Chronic Disease Research

- Adding women to a study is not the same as studying women
- Intermittent research in women’s health insufficient
- Female-specific (and female-dominant) conditions result in life-long disability

Recommendations:
- Establish a National Institute of Women’s Health
- Specifically address female-specific and female-dominant disorders across the lifecourse
- Collaborate with other institutes whose missions involve exposures or diseases that impact women
  - Build female-specific foundational normative and chronic condition databases
  - Design trials directly related to the disease and symptom experience in women
Following are extra slides for potential questions
Figure 1 Connections between endometriosis-associated impairments and life impacts.

Impact Factors by Field

• Reproductive Medicine
  • AJOG (Gray) 6.50
  • Fertility and Sterility 6.31
  • Human Reproduction 5.73
  • Ultrasound in ObGyn 5.57
  • Obstetrics and Gynecology (Green) 5.52
Impact Factors by Field

• Cancer (173)
  • Lancet Oncology (4) 33.75
  • Journal of Clinical Oncology (5) 32.96
  • JNCI (12) 11.58
  • Cancer Research 9.73
  • European Journal of Cancer 7.28
  • British Journal of Cancer (45) 5.79
Impact Factors by Field

• Cardiology (139)
  • Circulation 23.60
  • European Heart Journal 22.67
  • Circulation Research (5) 14.47
  • Hypertension 6.29
  • J Am Soc Echocardiography (21) 5.51
Endometriosis rASRM Staging

Stage I

Stage IV

Surgically visualized disease:

- Does NOT correlate with symptoms
- Does not predict treatment response
Endometriosis and Ovarian Cancer Risk

- 24 studies
- All studies: 1.93 (1.68-2.22)
- High level of heterogeneity: $I^2=78\%$, $P<0.0001$

Kvaskoff, et al. *Hum Reprod Update* 2021
Endometriosis rASRM Staging

Zondervan, Becker, Missmer. NEJM 2020
## Endometriosis x Ovarian Cancer Subtypes

<table>
<thead>
<tr>
<th>Cancer Type or Site</th>
<th>Ovarian (n=23,210)</th>
<th>Peritoneal (n=20,187)</th>
<th>Deep (n=2,372)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Cervix uteri*</td>
<td>15</td>
<td>0.96</td>
<td>0.54–1.58</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>4</td>
<td>0.91</td>
<td>0.25–2.32</td>
</tr>
<tr>
<td>Invasive squamous cell cancer</td>
<td>4</td>
<td>0.55</td>
<td>0.15–1.41</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>1.80</td>
<td>0.72–3.70</td>
</tr>
<tr>
<td>Corpus uteri*</td>
<td>33</td>
<td>1.12</td>
<td>0.77–1.57</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>27</td>
<td>1.12</td>
<td>0.74–1.62</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>1.13</td>
<td>0.41–2.46</td>
</tr>
<tr>
<td>Ovary</td>
<td>64</td>
<td>2.56</td>
<td>1.98–3.27</td>
</tr>
<tr>
<td>Serous</td>
<td>20</td>
<td>1.62</td>
<td>0.99–2.49</td>
</tr>
<tr>
<td>Mucinous</td>
<td>5</td>
<td>1.29</td>
<td>0.42–3.01</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>17</td>
<td>4.72</td>
<td>2.75–7.56</td>
</tr>
<tr>
<td>Clear cell</td>
<td>14</td>
<td>10.1</td>
<td>5.50–16.9</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>2.16</td>
<td>0.93–4.26</td>
</tr>
<tr>
<td>Other female genital organs</td>
<td>21</td>
<td>1.09</td>
<td>0.68–1.67</td>
</tr>
<tr>
<td>Vulva</td>
<td>7</td>
<td>0.87</td>
<td>0.35–1.78</td>
</tr>
<tr>
<td>Vagina</td>
<td>4</td>
<td>1.92</td>
<td>0.52–4.90</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>1.11</td>
<td>0.53–2.03</td>
</tr>
<tr>
<td>Not included above*</td>
<td>82</td>
<td>0.75</td>
<td>0.60–0.92</td>
</tr>
<tr>
<td>Cervix uteri, noninvasive neoplasms*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline tumor of ovary</td>
<td>20</td>
<td>1.63</td>
<td>1.00–2.52</td>
</tr>
</tbody>
</table>

- Endometrioma ↑ OvCa risk, clear-cell, endometrioid, serous
- SPE ↑ OvCa risk, endometrioid, clear-cell
- Deep × OvCa risk

Saavaleinen, et al. *Obstet Gynecol* 2018