Endometriosis: A Fundamental Example for Women’s Health Discovery

NICHD Council Meeting
June 11, 2019

Stacey Missmer, Sc.D.
Michigan State University College of Human Medicine
Harvard T.H. Chan School of Public Health
Harvard Medical School
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
Major Health Issue

1 in 10 women have endometriosis during their reproductive years
35–50% of women with pelvic pain or infertility

190 Million women worldwide

U.S. costs for diagnosis, treatment, and quality of life / work productivity = $69 Billion
Similar to Crohn’s, Rheumatoid Arthritis, and Diabetes Mellitus

Higher risk of ovarian cancer, autoimmune disease, CVD

World Bank. Population Projection Tables
Missmer SA. Int J Epidemiol 2009
Symptoms

- Severe menstrual cramping (dysmenorrhea)
- Pelvic pain not associated with menses
- Painful intercourse (dyspareunia)
- Painful urination (dysuria)
- Painful defecation (dyschezia)

- U.S. Interview Survey (n = 31,617)
  - Mean number of “bed” days = 18 / year

GSWH - QOL Impact

Activities negatively impacted by symptoms (n=2,753 women in eight countries)

- Sexual life: 50%
- Relationship: 36%
- Family: 34%
- Performance at work/school/university: 35%
- Housekeeping: 34%
- Attendance at work/school/university: 32%
- Social activities: 29%
- Sports: 21%
- Other: 9%

Age at first consultation for symptoms

- 18% <20 years
- 64% <30 years

- 18% Age 10–19
- 46% Age 20–29
- 31% Age 30–39
- 7% Age 40–49

Impact of Pain

**Adults**
- No/mild pain interfering with work/school: 60%
- Moderate/severe pain interfering with work/school: 40%

**Adolescents**
- No/mild pain interfering with work/school: 33%
- Moderate/severe pain interfering with work/school: 67%

Adolescent QOL

**SF-36**: Girls with endometriosis did not differ on mental health domains, except for Social Functioning which was significantly lower than the norm.

Gallagher JS, et al. J Adolesc Health 2018
Retrograde Menstruation – Sampson 1927

Pathogenic Hypotheses

- Retrograde Menstruation
  - “Excessive” (e.g., outflow obstruction)
  - “Normal”
- Other Pathways (e.g., Coelomic metaplasia)
- Immune Dysfunction
- Hormonal Stimulation
- Endometriosis

Health Across the Lifespan

Pre-Illness History
- Fetal Development
- Birth
- Childhood
- Adolescence
- Adulthood

Illness Onset →
- Menopause
- Older Aging

Courtesy of Dr. Janet Rich-Edwards, Harvard University
Health Across the Lifespan

- Fetal Development
- Birth
- Childhood
- Adolescence
- Adulthood
- Menopause
- Older Aging

Pre-Illness History 

Illness Onset
Health Across the Lifespan

Pre-Illness History

Illness Onset ➔ Adolescence

Adulthood

Menopause

Older Aging

Fetal Development

Birth

Childhood
Health Across the Lifespan

Pre-Illness History

Illness Onset

Fetal Development

Birth

Childhood

Adolescence

Adulthood

Menopause

Older Aging
Health Across the Lifespan

Low Birthweight
DES
?Premature Delivery?

Health Across the Lifespan

Pre-Illness History
- Fetal Development
- Birth
- Childhood
- Adolescence
- Adulthood

Illness Onset
- Menopause
- Older Aging

Shorter Menstrual Cycles
- Lower BMI
- Lower WHR
- Nulliparity
- Dysplastic Nevi / Moles

Questions:
- ?Dioxin?
- ?Sedentary?
- Red meat, trans fat, cruciferous
- No or short duration Lactation

Global Study of Women’s Health: 
Endometriosis average diagnostic delay

Symptoms start
26

First consultation
27

Diagnosis!
33

1 year
6 years

7 years

Average of 8 clinicians before Gyn specialist referral

Major Clinical Obstacles

- Currently, diagnosis requires surgery
- Imaging only effective for large and deep infiltrating lesions
- No blood, urine, or other biomarkers
- Many PCPs unaware of disease
- Reluctance to perform surgery without severe disease
- Symptoms are nonspecific or associated with other disorders
  - May be mistakenly dismissed as “normal” menstrual pain
  - Family and friends’ attitudes towards menstrual pain
  - Embarrassment specific to pelvic pain
- Survey of N = 7,025 women
  - 65% misdiagnosed
  - 46% saw ≥ 5 MDs to get correct diagnosis

Ohio Reproductive Medicine
What is endometriosis?

Endo appearance (red, yellow, clear, white, brown, blue/black)
  – Continuum or distinct disease?

Superficial Peritoneal (SPE), Deep, Endometrioma

Propensity for scarring/adhesion

Infertility risk

Molecular / somatic phenotypes?
Appearance at surgery

Adhesions

“Powder-burn” Lesion

“Chocolate” Ovarian Cyst

St. Charles Endometriosis Program
Martin D, 1997
Giudice LC, NEJM 2010
rASRM Staging

Stage I

Stage IV

Surgically visualized disease:
• Does NOT correlate with symptoms
• Does not predict treatment response
Breast Cancer

ER+

Luminal A
- Slow growing
- Less aggressive
- High survival
- Responds to endocrine therapy

Luminal B
- High proliferation rate
- Worse prognosis than LumA
- Responds to endocrine therapy

HER2 type
- High proliferation
- More likely to be node +
- Responds to targeted therapy

ER-

Basal
- Younger age at diagnosis
- High grade
- Lack of targeted therapy

Adapted from Dr. Rulla Tamimi, Harvard University
Current therapeutic options are limited
  Primarily hormonal pathways with impactful side effects
  Limited geographic and economic access to expert surgeons
Informative Subtypes Discovery

Obvious Heterogeneity of
• Lesions
• Symptoms
• Co-Morbidities
• Treatment response

What peripheral and tissue markers and characteristics define them? Do they have different risk factors? Pathophysiology? Can we maximize treatment response through personalized medicine? Do they have different long-term health outcomes?
WERF EPHect
Endometriosis Phenome and Biobanking Harmonization Project
STANDARDIZED DATA AND SAMPLE COLLECTION TOOLS

- Surgical
- Clinical
- Fluids
- Tissue
25 centers in 17 countries
12 emerging centers in 9 additional countries
Endometriosis

Surgical / Imaging Phenotype
Lifestyle exposures
Hormonal indicators / markers
Epigenetics
Omics
Inflammatory indicators / markers
Cancers
Auto-immune diseases & allergies
Metabolic traits (fat distribution, cardiovascular disease)
Menstrual & Reproductive History
Pain History
Family History

Adapted from Krina Zondervan, Oxford
The Future for Endometriosis Discovery

• 2003 - 15 years since discovery of Triple Negative Breast Cancer
  – informative subtypes advanced risk understanding, drive personalized treatment and save lives

• WILL be true for endometriosis
Vision: Stratified and Precision Medicine

One-size fits-all medicine

Stratified medicine

Precision medicine

Stratification
Patients are grouped by: Disease Subtypes Demographics Clinical features Biomarkers

Personalisation
Patient individual: Preferences, Clinical features Medication history Environment Behaviours & habits Biomarker

Adapted from Manchester Precision Medicine Institute
Vision: Rapid Accurate Diagnosis

• Ideally in hands of first line health care practitioners
• Define magnitude of undiagnosed women / true prevalence
• Shorten time interval from diagnosis to begin effective treatment
• May successfully modify infertility or co-morbidity risk
• A biomarker may elucidate physiologic pathways that will catalyze novel treatment development or prevention potential
• Utilize the millions of samples and decades of data poised for discovery

Adapted from H. Taylor, AbbVie Biomarker Symposium, WCE 2017
What is endometriosis?

- Prevalent, impactful disease affecting millions of women
- Identifying critical windows of etiologic physiology may allow prevention and cure
- Informative subtypes that predict risk, treatment selection, and prognosis must be defined
- Large, collaborative, diverse studies with **multidisciplinary** teams will drive forward
- Fundamental questions for encouraged investigators
Thank you!

Boston Center for Endometriosis

Nurses’ Health Study

The Women’s Health Study

From Adolescence to Adulthood

Endometriosis CaRe

OXFORD Care & Research

WERF ePHect Endometriosis Phenome and Biobanking Harmonisation Project
<table>
<thead>
<tr>
<th>Nº</th>
<th>Research Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Can a cure be developed for endometriosis?</td>
</tr>
<tr>
<td>2</td>
<td>What causes endometriosis?</td>
</tr>
<tr>
<td>3</td>
<td>What are the most effective ways of educating healthcare professionals throughout the healthcare system resulting in reduced time to diagnosis and improved treatment and care of women with endometriosis?</td>
</tr>
<tr>
<td>4</td>
<td>Is it possible to develop a non-invasive screening tool to aid the diagnosis of endometriosis?</td>
</tr>
<tr>
<td>5</td>
<td>What are the most effective ways of maximising and/or maintaining fertility in women with confirmed or suspected endometriosis?</td>
</tr>
<tr>
<td>6</td>
<td>How can the diagnosis of endometriosis be improved?</td>
</tr>
<tr>
<td>7</td>
<td>What is the most effective way of managing the emotional and/or psychological and/or fatigue impact of living with endometriosis (including medical, non-medical and self-management methods)?</td>
</tr>
<tr>
<td>8</td>
<td>What are the outcomes and/or success rates for surgical or medical treatments which aim to cure or treat endometriosis, rather than manage it?</td>
</tr>
<tr>
<td>9</td>
<td>What is the most effective way of stopping endometriosis progressing and/or spreading to other organs (e.g. after surgery)?</td>
</tr>
<tr>
<td>10</td>
<td>What are the most effective non-surgical ways of managing endometriosis-related pain and/or symptoms (medical/non-medical)?</td>
</tr>
</tbody>
</table>

Courtesy of Dr. Andrew Horne, University of Edinburgh
<table>
<thead>
<tr>
<th>№</th>
<th>Research Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Is it possible to develop a non-invasive screening tool to aid diagnosis of endometriosis?</td>
</tr>
<tr>
<td>2</td>
<td>What causes endometriosis?</td>
</tr>
<tr>
<td>3</td>
<td>How can endometriosis be prevented?</td>
</tr>
<tr>
<td>4</td>
<td>What are the most effective non-surgical ways of managing endometriosis-related pain and/or symptoms (medical/non-medical)?</td>
</tr>
<tr>
<td>5</td>
<td>Is endometriosis a single disease or are there different disease subtypes which represent different, but related, pathological entities?</td>
</tr>
<tr>
<td>6</td>
<td>How can the diagnosis of endometriosis be improved?</td>
</tr>
<tr>
<td>7</td>
<td>How can we prevent endometriosis in women and/or young girls with a family history of the disease?</td>
</tr>
<tr>
<td>8</td>
<td>What is the natural history of endometriosis (e.g. how, and how quickly, does it progress and spread)?</td>
</tr>
<tr>
<td>9</td>
<td>Is there a link between endometriosis and auto-immune diseases, and endometriosis and/ or inflammatory disorders (e.g. MS, Lupus, RA, osteoarthritis, asthma, eczema and thyroid) and if so why?</td>
</tr>
<tr>
<td>10</td>
<td>What can be done to stop endometriosis from recurring (e.g. after treatment)?</td>
</tr>
</tbody>
</table>

Courtesy of Dr. Andrew Horne, University of Edinburgh