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

Women’s Risk of Endometriosis (WREN) Study

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Endometriosis

# Endometriosis

- Chronic pelvic pain
- Acyclic pelvic pain
- Painful menstrual periods
- Painful bowel movements
- Painful urination
- Pain during intercourse
- Fatigue

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Endometriosis: Pathogenesis

Separate etiologic pathways?
- Peritoneal endometriosis
- Ovarian endometriosis
- Deep infiltrating endometriosis

Multiple factors involved
- Anatomical
- Hormonal
- Immunological
- Genetic
- Environmental

Estrogen
- Regulates key pathological processes

Endometriosis: Environmental chemicals

Endocrine-disrupting chemical

"...is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action."

Endocrine disrupting chemicals
Endocrine disrupting chemicals

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Endocrine disrupting chemicals

- Pesticides, PCBs, metals, BPA, phthalates
- PFAS
- BPA
- Phthalates, triclosan, metals
- Flame-retardant chemicals
Endocrine disrupting chemicals

Endometriosis: Major challenge

Definitively diagnosed by surgical visualization

Prospective cohort study

Population

Cases

Time passes

Screen
Screen
Screen

Image (modified) from: https://healthjade.com/laparoscopy/
Endometriosis: Major challenge

Definitively diagnosed by surgical visualization

Image (modified) from: https://healthjade.com/laparoscopy/
Women’s Risk of Endometriosis (WREN) Study

Endometriosis cases
- Ages 18-49
- Diagnosed years 1996-2001
- Surgically-confirmed

Population controls
- Ages 18-49
- Randomly selected enrollees
- Age-matched to cases

Eligibility criteria:
- Pre-menopausal
- Ages 18-49
- Intact uterus
- At least one ovary
- No prior endometriosis diagnosis
- Enrolled >6 months before reference date

Date of first visit for symptoms leading to endometriosis diagnosis
Women’s Risk of Endometriosis (WREN) Study

Endometriotic disease case definition

Focus on endometriosis with
- Tissue invasiveness
- Interference with physiologic processes

Benefits
- ↑ likelihood of observing true etiologic associations
- ↓ frequency of undiagnosed disease in study population

Data on:
- Ovarian endometriosis
- Non-ovarian pelvic endometriosis

Table 1. Proposed Standard Definition of Endometriotic Disease for Epidemiologic Studies of Endometriosis

<table>
<thead>
<tr>
<th>Status</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
</table>
| Definite disease | Ovarian endometriomas of any size  
Pelvic endometriotic implants of any size >5 mm deep  
Pelvic endometriotic implants of any size with adhesions not attributable to another cause |
| Possible disease | Pelvic endometriotic implants not meeting above criteria, plus one or more of the following symptoms:  
- Infertility  
- Moderate to severe dysmenorrhea (painful menstrual periods)  
- Moderate to severe dyspareunia (pain during intercourse)  
- Moderate to severe pelvic pain |

Women’s Risk of Endometriosis (WREN) Study

WREN participants:
310 Endometriosis cases
727 Population controls

In-person structured interview
- Conducted by trained female interviewers
- At participant home or Fred Hutch
- Questions covered range of health histories
  - e.g., menstruation, reproductive, pregnancy, contraception
- Methods employed to aid recall
Women’s Risk of Endometriosis (WREN) Study

11 Organochlorine pesticides (OCPs)
34 Polychlorinated biphenyl congeners (PCBs) (non-dioxin-like)

Bisphenol A (BPA)

8 Phthalate metabolites

Science to Achieve Results (STAR) grant R829438

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University of Washington
Doctoral Dissertation Small Grants Program

Icons from Fengquan Li, DinosoftLab, faisalovers, Isabel Foo, Visualeat, and Jonathan Li at the Noun Project
# Women’s Risk of Endometriosis (WREN) Study

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=310)</th>
<th>Controls (n=727)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR)</td>
<td>39 years (IQR: 33-44)</td>
<td>39 years (IQR: 33-44)</td>
</tr>
<tr>
<td>White race</td>
<td>85%</td>
<td>83%</td>
</tr>
<tr>
<td>College graduate</td>
<td>46%</td>
<td>41%</td>
</tr>
<tr>
<td>Income ($≥70,000)</td>
<td>23%</td>
<td>28%</td>
</tr>
<tr>
<td>BMI (≥30)</td>
<td>21%</td>
<td>20%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>48%</td>
<td>30%</td>
</tr>
</tbody>
</table>


Icons from Alexa, Deemak Daksina, Adrien Coquet, Nikita Kozin, dDara, and Yeong Rong Kim at the Noun Project
Women’s Risk of Endometriosis (WREN) Study

Detected in 100% of participants

Women’s Risk of Endometriosis (WREN) Study

- **Organochlorine pesticides**
  - 2x over risk
  - Q3 vs Q1: OR 2.5, 95% CI: 1.2, 5.2
  - Q4 vs Q1: OR 2.5, 95% CI: 1.1, 5.3

- **PCBs (Polychlorinated biphenyls)**
  - 30% suggested risk
  - Q3 vs Q1: OR 2.5, 95% CI: 1.2, 5.2
  - Q4 vs Q1: OR 2.5, 95% CI: 1.1, 5.3

- **Phthalate metabolites**
  - 70% suggested risk
  - MEHP: Q4 vs Q1: OR 0.3, 95% CI: 0.1, 0.7
  - Log-linear ↑: OR 1.3, 95% CI: 0.8, 2.2

- **Bisphenol A (BPA)**
  - 3x suggested risk
  - Q2 vs Q1: OR 3.0, 95% CI: 1.2, 7.3
  - Q3 vs Q1: OR 3.0, 95% CI: 1.1, 7.6

**Endometriosis**

**Ovarian endometriosis**

**Non-ovarian pelvic endometriosis**


Icons from Lia Rahdiah, Foodicons, Collection, Eucalyp, IconMark, Arthur Shlain, Kelly Ness, Sahab Uddin, Vectorstall, Hermine Blanquart, Visualeat, Justin Blake, and Jonathan Li at the Noun Project.
Women’s Risk of Endometriosis (WREN) Study

- **Soy formula**
  - Infant feeding
  - $2x$ over
  - OR 2.4, 95% CI: 1.2, 4.9

- **In utero DES** (diethylstilbestrol)
  - $2x$ suggested
  - OR 2.0, 95% CI: 0.8, 4.9

- **Nightshift work**
  - 50% higher
  - OR 1.48, 95% CI: 0.96, 2.29


Icons from Flatart, arif fajar yulianto, fibo junior, Hermine Blanquart, and Justin Blake at the Noun Project
Women’s Risk of Endometriosis (WREN) Study

Limitations

- Biologic sample collection after case diagnosis
- Single sample for non-persistent chemicals (BPA, phthalates)
- Research conducted before recent developments in mixtures analyses
- Undiagnosed disease among controls

Strengths

- Population-based sampling
- Collection of biologic samples
- Years of biologic sample collection (before EDCs widely known)
- Data on ovarian and non-ovarian pelvic endometriotic lesion location
Findings across studies

Reassessing the evidence for the link between dioxin and endometriosis: from molecular biology to clinical epidemiology
Sun-Wei Guo1,2, Peter Simsa2,2, Cleophas M. Kyamara2, Attila Mihalyi, Vilmos Fulop, Essam-Eldin R. Othman3, and Thomas M. D’Houge1,3

Review
Dioxin-like PCBs and Endometriosis
Kaylon L. Bruner-Tran and Kevin G. Odion
Women’s Reproductive Health Research Center, Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville, TN, USA

Role of environmental organochlorinated pollutants in the development of endometriosis
M.G. Porpora, S. Resta, E. Fugetta, P. Storelli, F. Meggiori, L. Manganaro, E. De Felip
Department of Obstetrics-Gynecology and Urology, “Sapienza” University of Rome, Rome (Italy)

Environmental Risk Factors for Endometriosis: a Critical Evaluation of Studies and Recommendations from the Epidemiologic Perspective
Kristen Upson

Consistencies within population-based studies

Human epidemiological evidence about the associations between exposure to organochlorine chemicals and endometriosis: Systematic review and meta-analysis
German Cano-Sanchez, Stéphane Plotto, Komodo Matta, Evdochia Aduanassi, Genevieve Buck Louis, Jaime Mendiola, Emilie Darai, Jean Squiffleet, Bruno Le Bizec, Jean-Philippe Autrique

Discrepant Results

2008
2009
2010
2013
2016
2017
2019
2020

Reasons for disparate results

- Study population differences
- Exposure measurement
- Confounder adjustment
- Undiagnosed disease in controls

Reasons for disparate results

- Study population sampling
- Sample collection at diagnosis
- Statistical analysis issues
- Single disease entity

Recommendations

1. Population-based sampling
   - Novel avenues:
     - Build capacity to collect endometriosis data in large, epidemiologic cohort studies

2. Exposure during etiologically-relevant window
   - Novel avenues:
     - Archived newborn dried blood spots
     - Baby teeth
     - Link with existing data (e.g., air pollution)

3. Disaggregating endometriosis
   - Novel avenues:
     - Collect operative and pathology reports

4. Environmental exposures unique to menstruators
   - Novel avenues:
     - Menstrual product use
     - Menstrual blood loss
     - Hormonal contraceptive use

5. Team science
   - Novel avenues:
     - Epidemiology
     - Biostatistics
     - Toxicology
     - Exposure science
     - Gynecology
Women’s Risk of Endometriosis (WREN) Study

WREN Researchers

- Victoria Holt, PhD, MPH
- Delia Scholes, PhD
- Jennifer Marino, PhD, MPH
- Britton Trabert, PhD, MS
- Kristen Upson, PhD, MPH

WREN Collaborators

- Holly Harris, MPH, ScD
- Anneclaire De Roos, PhD, MPH
- Russell Dills, PhD
- Sheela Sathyanarayana, MD, MPH
- Dana Barr, PhD
- Holger Koch, PhD

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- **National Institute of Nursing Research** F31NR009164 (Marino)
- **National Institute of Environmental Health Sciences** R03ES019976 (Holt)
- **University of Washington Department of Epidemiology** Doctoral Dissertation Small Grants Program (Upson)

**Eunice Kennedy Shriver National Institute of Child Health and Human Development** T32HD052462 (Williams)
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