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

Women's Risk of Endometriosis (WREN) Study

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Advisory Committee on Research on Women's Health October 18, 2022



Endometriosis



Image modified from: Zondervan KT, Becker CM, Missmer SA. Endometriosis. N England Journal of Medicine 2020;382: 1244-1256.

Endometriosis



Chronic pelvic pain Acyclic pelvic pain

Painful menstrual periods



Painful urination



Fatigue



Pain during intercourse

Image modified from: Zondervan KT, Becker CM, Missmer SA. Endometriosis. *N England Journal of Medicine 2020;382: 1244-1256.* Icons from ProSymbols, Sasha Sash, fauzan akbar, LUTFI GANI AI, and Ayub Irawan at the Noun Project



Separate etiologic pathways?

- Peritoneal endometriosis
- Ovarian endometriosis
- Deep infiltrating endometriosis

Multiple factors involved

- Anatomical
- Genetic
- Hormonal
- Environmental
- Immunological

Estrogen

 Regulates key pathological processes

Endometriosis: Environmental chemicals

POSITION STATEMENT

Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society

R. Thomas Zoeller, T. R. Brown, L. L. Doan, A. C. Gore, N. E. Skakkebaek,

A. M. Soto, T. J. Woodruff, and F. S. Vom Saal

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





Icons from Simon Child, Jason Dilworth, Eucalyp, IconMark, Arthur Shlain, Kelly Ness, Sahab Uddin, Vectorstall, WiStudio, Mehmet Gozetlik, Mahmure Alp, Made by Made, Iconfeld, DPIcons, Awesome, alerma at the Noun Project



WiStudio, Mehmet Gozetlik, Mahmure Alp, Made by Made, Iconfeld, DPIcons, Awesome, alerma at the Noun Project

Endocrine disrupting chemicals



Pregnant women (n = 54; each vertical bar is one study participant)

Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003-2004. *Environ Health Perspect 2011;119: 878-885.*

Endometriosis: Major challenge

Definitively diagnosed by surgical visualization



		/
Population		Cases
	Time passes	
Screen	Screen	Screen

Prospective cohort study

Endometriosis: Major challenge

Definitively diagnosed by surgical visualization





Upson K. *Curr Epidemiol Rep 2020;7: 149-170.*

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







R01 HD033792

Eunice Kennedy Shriver National Institute of Child Health and Human Development



Eligibility criteria:

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

Endometriosis cases

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

Population controls

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

Date of first visit for symptoms leading to endometriosis diagnosis



Victoria Holt, PhD



FRED HUTCH



Endometriotic disease case definition

Focus on endometriosis with

- Tissue invasiveness
- Interference with physiologic processes

Benefits

- ↓ 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		
Status	Signs and Symptoms	
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 	



WREN participants:

310 Endometriosis cases727 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







Icons from Fengquan Li, DinosoftLab, faisalovers, Isabel Foo, Visualeat, and Jonathan Li at the Noun Project





Upson K, et al. Fertil Steril 2015;104: 964-971 e965.

Icons from Alexa, Deemak Daksina, Adrien Coquet, Nikita Kozin, dDara, and Yeong Rong Kim at the Noun Project



Detected in 100%

of participants

Trabert B, et al. *Environ Health Perspect 2010;118: 1280-1285.* Upson K, et al. *Environ Health Perspect 2013;121: 1319-1324.* Upson K, et al. *Environ Res 2013;126: 91-97.* Upson K, et al.. *Hum Reprod 2014;29: 2457-2464.*







Icons from Lia Rahdiah, Foodicons, Collection, Eucalyp, IconMark, Arthur Shlain, Kelly Ness, Sahab Uddin, Vectorstall, Hermine Blanguart, Visualeat, Justin Blake, and Jonathan Li at the Noun Project





Upson K, et al. Fertil Steril 2015.

Marino JL, et al. Epidemiology 2008;19: 477-484.

Icons from Flatart, arif fajar yulianto, fibo junior, Hermine Blanquart, and Justin Blake at the Noun Project



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





Environmental Risk Factors for Endometriosis: a Critical Evaluation

Heilier JF, et al. *Chemosphere 2008;71: 203-210;* Guo SW et al. *Mol Hum Reprod 2009;15: 609-624;* Bruner-Tran et al. *Systems biology in reproductive medicine 2010;56: 132-146;* Porpora MG, et al. *Clin Exp Obstet Gynecol 2013;40: 565-567;* Smarr MM, et al. *Fertil Steril 2016;106: 959-966;* Yao M, et al. *Environmental pollution 2017;229: 837-845;* Cano-Sancho G et al. *Environment international 2019;123: 209-223;* Upson K. et al. *Curr Epidemiol Rep 2020;7: 149-170.*



Heilier JF, et al. Chemosphere 2008;71: 203-210; Guo SW et al. Mol Hum Reprod 2009;15: 609-624; Bruner-Tran et al. Systems biology in reproductive medicine 2010;56: 132-146; Porpora MG, et al. Clin Exp Obstet Gynecol 2013;40: 565-567; Smarr MM, et al. Fertil Steril 2016;106: 959-966; Yao M, et al. Environmental pollution 2017;229: 837-845; Cano-Sancho G et al. Environment international 2019;123: 209-223; Upson K. et al. Curr Epidemiol Rep 2020;7: 149-170. Icon from Cuputo at the Noun Project

Recommendations



Population-based sampling

Novel avenues:

• Build capacity to collect endometriosis data in large, epidemiologic cohort studies

Novel avenues:

- Archived newborn dried blood spots
- Baby teeth
- Link with existing data (e.g., air pollution)

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Disaggregating endometriosis

etiologically-relevant window

Novel avenues:

Collect operative and pathology reports

Environmental exposures unique to menstruators

Exposure during

Novel avenues:

- Menstrual product use
- Menstrual blood loss
- Hormonal contraceptive use

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Team science

- Epidemiology Exposure science
- Biostatistics
- Gynecology
- Toxicology



WREN Researchers

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Further information:



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