Endocrine disrupting chemicals and endometriosis

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Endometriosis is an estrogen dependent gynecologic disease with lasting implications for many women's fertility, somatic health, and overall quality of life. Growing evidence suggests that endocrine disrupting chemicals (EDCs) may be etiologically involved in the development and severity of disease. We weigh the available human evidence focusing on EDCs and endometriosis, restricting to research that has individually quantified chemical concentrations for women, included a comparison group of unaffected women, and used multivariable analytic techniques. Evidence supporting an environmental etiology for endometriosis includes metals/trace elements, dioxins, and other persistent organic pollutants, as well as nonpersistent chemicals, such as benzophenones and phthalates. To address the equivocal findings for various EDCs, future research directions for filling data gaps include [1] use of integrated clinical and population sampling frameworks allowing for incorporation of new diagnostic modalities; [2] the collection of various biologic media, including target tissues for quantifying exposures; [3] study designs that offer various comparison groups to assess potentially shared etiologies with other gynecologic disorders; and [4] novel laboratory and statistical approaches that fully explore all measured EDCs for the assessment of mixtures and low dose effects and the use of directed acyclic graphs and supporting causal analysis for empirically delineating relationships between EDCs and endometriosis. (Fertil Steril® 2016;106:959–66. ©2016 by American Society for Reproductive Medicine.)

Key Words: Chemicals, endocrine disruptors, endometriosis, environment, pesticides

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Endometriosis is commonly said to be a clinical enigma, in that numerous etiologic agents have been investigated to delineate its underlying pathophysiology to no avail. Commonly defined as the presence of endometrial glands and stroma outside the endometrial cavity (1), an environmental origin for endometriosis arose during the past few decades with some, albeit inconsistent, findings supporting a possible association.

Although the exact timing of onset and rate of progression of endometriosis are unknown, some researchers suggest that it may have a developmental or in utero origin. Evidence in support of a developmental origin for endometriosis stems from three bodies of observational evidence: müllerianosis (2), detection in fetuses (3), and lean body habitus up to the timing of diagnosis (4, 5). As an estrogen dependent disease, possible in utero estrogenic exposures have been posited to be associated with endometriosis. For example, exposures reported to be associated with a hig her risk of endometriosis include diethylstilbestrol (6, 7) and pregnancy complications such as prematurity or diminished birth weight (6–8). Conversely, exposure to maternal cigarette smoking, which may be accompanied by lowered circulating estrogens, is reported to be associated with a reduced risk of endometriosis in some (9) but not all studies (10).

Questions have arisen about the role of endocrine disrupting chemicals (EDCs), defined as any exogenous chemical or mixture of chemicals that can interfere with any aspect of hormone action (11), in the context of endometriosis following findings from primate and experimental research. Specifically, a dose dependent relation was observed between 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and dioxin-like polychlorinated biphenyls (PCBs) and peritoneal endometriosis in rhesus monkeys (12, 13). Mechanistic research suggested that EDCs such as TCDD may induce proliferation of endometrial endothelial cells that are relevant for endometrial angiogenesis (14), or that EDCs may affect developing uterine tissue for eventual aberrant growth following estrogenic exposure later in life (15).

Although there is some evidence suggesting a role between EDCs and endometriosis in women, it is important to consider important methodologic challenges that preclude a

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TABLE 1

Literature focusing on persistent and nonpersistent endocrine disrupting chemicals and endometriosis.

Class of EDC, authors and y (reference)	Sampling framework	Biologic media	Endometriosis diagnostic method	(%) Endometriosis (sample size [n])	Significant positive association (odds ratio > 1.00)	Significant negative association (odds ratio < 1.0)	No association
Persistent chemicals							
Metals/trace elements							
Heilier et al. 2006 (29)	Clinical	Blood Urine	Surgical visualization	83% (144)			✓ cadmium, lead
Jackson et al. 2008 (30)	US population	Blood	Self-report	2% (2812)	✓ cadmium		
Pollack et al. 2013 (31)	Clinical and population	Blood	Surgical visualization and MRI (population)	41% (473) clinical 11% (127) population	✓ chromium, copper	✓ cadmium	
Dioxins (PCDD, PCDFs, TCDD)							
Eskenazi et al. 2002 (32)	Population	Serum	Self-report	3% (601)			✓
Pauwels et al. 2001 (33)	Clinical	Serum	Surgical visualization	61% (69)			✓
Fierens et al. 2003 (34)	Population	Serum	Self-report	7% (142)			✓
Heilier et al. 2005 (35)	Clinical	Serum	Surgical visualization	35% (71)	✓ Dioxin, TEQ		
Simsa et al. 2010 (36)	Clinical	Plasma	Surgical visualization	48% (202)	✓ Σ TEQ		
OCPs							
Porpora et al. 2009 (37)	Clinical	Serum	Surgically visualized	51% (158)			✓ HCB, DDE
Cooney et al. 2010 (38)	Clinical	Serum	Surgical visualization	38% (84)	✓ HCB		
Buck Louis et al. 2012 (39)	Clinical and population	Fat and serum	Surgical verification and MRI	41% (473) 11% (127)	✓ γ-HCH clinical β-HCH population		
Upson et al. 2013 (40)	Population	Serum	ICD-9 codes for surgical visualization	33% (878)	✓ β-HCH		
PBDEs							
Buck Louis et al. 2012 (39)	Clinical and population	Fat and serum	Surgical verification and MRI	41% (473) 11% (127)		✓ #47	
PCBs							
Lebel et al. 1998 (41)	Clinical	Plasma	Surgically visualized	55% (156)			✓
Buck Louis et al. 2005 (42)	Clinical	Serum	Surgically visualized	38% (84)	✓ Anti-estrogenic		
Porpora et al. 2006 (43)	Clinical	Serum	Surgically visualized	50% (80)	✓ #101, 105, 118, 138, 153, 156, 167, 170, 180)		
Porpora et al. 2009 (37)	Clinical	Serum	Surgically visualized	51% (158)	✓ #118, 138, 170		

Smarr. EDCs and endometriosis. Fertil Steril 2016.