대한산부인과내분비학회 제20차 학술대회 및 연수강좌



내분비 교란 물질과 여성의 생식기능



2018.01.07 <mark>동아대학교 의과대학</mark> 조연진

Endocrine Disrupting Chemicals (EDCs)

 "항상성을 유지하거나 발달 과정을 조절하는데 필요한 신체 내 호르몬의 자 연적인 생성, 분비, 이동, 대사, 결합, 작용, 제거의 과정에 문제를 유발하는 외부 물 질"로 정의하였습니다.

U.S. Environmental Protection Agency (EPA)

Estrogen receptors (ERs)

androgen receptors (ARs)

progesterone receptors (PRs)

Nuclear receptors, nonnuclear steroid hormone receptors, nonsteroid receptors, orphan receptors, enzymatic pathways involved in steroid biosynthesis/metabolism

Silent Spring by Rachel Carson

- The woman and the book that warned against the environmental and health impact of industrial chemicals and launched the environmental movement
- Originally published in a series in the New Yorker in the summer of 1962, read and commented on by J.F.K, instant best seller



Economic Burden of EDCs

THE LANCET **Diabetes & Endocrinology**

ORIGINAL ARTICLE

Volume 4, Issue 12, December 2016, Pages 996-1003

240 hillion \$ 222% of aross GDD **NEWS & VIEWS** Expos nature popula ENDOCRINOLOGY REVIEW Teresa M A Pierre Bour Leonardo Tr

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Articles

Female Reproductive Disorders, Diseases, and Costs of Exposure to Endocrine Disrupting Chemicals in the European Union

> EDCs were estimated to result in 145,000 cases of Endometriosis annually €1.5 billion annually

JCEM OF CLINICAL ENDOCRINOLOG

Persistent Chemical vs Non-persistent Chemcals





(e.g. cosmetics)



Hormones vs EDCs

Hormones	EDCs				
Act via receptors	Some act on hormone receptors				
Tissue specific receptor classes	Likely isoform-specific interactions				
Active at low doses	Some act at low doses, others variable				
Blood levels do not always reflect activity					
No bioaccumulation	Possible bioaccumulation				
Non-linear dose response relationships					
High dose effects not same as low dose					
Tissue and life-stage specific effects					
Developmental effects permanent					
Programs brain and endocrine system for adult function	Interferes with programming processes				

WHO State of the Science of Endocrine Disrupting Chemicals - 2012

EDCs and Reproduction

- Nontraditional dose-response dynamics
- Direct effect
- HPO axis
- Epigenetic, transgeneration effects



Skinner & Guerrero-Bosagna, 2009

PCB (polychlorobiphenyl)



PCB (polychlorobiphenyl)

- Association between PCB exposure and time to pregnancy
 - Compared with time to pregnancy for women in the lowest exposure category, time to pregnancy increased for women in the highest exposure category in PCBs
 Law et al., Am J Epidemiol 2005
- Decreased fecundability in female offspring of fisheaters was found to be associated with PCB exposure in utero Han et al. Environmental Health 2016
- Increasing quartiles of PCB-153 and the sum of all measured PCB congeners (ΣPCBs) were associated with significantly elevated dose-dependent odds of failed implantation in IVF

Meeker et al., Environ Health Perspect 2011

2,3,7,8,-tetrachloro-dibenzo-p-dioxin (TCDD)

- TCDD, Dioxin like PCB
 - Agent Orange exposure in South
 Vietnam
 - paper bleaching, smelting, and the manufacture of herbicides and pesticides
 - Impair follicle growth, increase atresia, and reduce oocyte quality in the postnatal ovary
 - Lower pregnancy rate



Pesticides – DDT

- 1,1,1-trichloro-2,2'bis(p-chorophenyl) ethane
 - 1874 first synthesized





cation malaria in

untry erm count, IUGR

Nonyl-phenols and octyl-phenols

- Detergent by-products: food chain and consumer products, estrogenic and/ or anti-androgenic effects, interaction with PR
 - Unexplained pregnancy loss, preterm birth, low birth weight



BPA Bisphenol A



- 1891 synthetic estrogen replaced by DES
- 1949s epoxy resin in plastics, canned foods, receipts
- BPA and reproduction
- BPA linked to many reproductive disorders : early puberty, PCOS, endometriosis, infertility, thyroids disease, poor outcome with IVF

(Lamb et al., 2008)

BPA Bisphenol A



- Legislation
 - 2008
 - Canada limited BPA and labeled it as reproductive toxin
 - California banned baby bottles with BPA
 - FDA stated that BPA is safe at current estimated levels
 - 2011 FDA banned it from baby bottles
 - 2012 FDA states low levels are safe
 - 우리나라? : 소변에서 검출되는 BPA 0.75ug/L (2012) → 1.09ug/L (2015)

Phthalates : DEHP, MEHP, DPB....



- Plasticizer (plastics, toys, IV bags, etc)
- consumer products (e.g. perfume, lotion, soap, make-up etc)
- 18 billion pounds produced /year, 95% of pregnant women have phthalates in their system (Berman 2009)
- Associated with developmental abnormalities of male reproductive system, miscarriage, endometriosis, low sperm counts, poor IVF outcomes

Phthalates: DEHP, MEHP, DPB....



- The Environment and Reproductive Health (EARTH) Study
 - Low oocyte yield, clinical pregnancy, and live birth following
 ART in high DEHP group

Hauser et al., Environ Health Perspect 2016

• The phthalate metabolite MEHP was associated with higher occurrence of pregnancy loss

Toft et al., Environ Health Perspect 2012

Phthalates



- Europe has banned >1300 chemicals from beauty products
- US limited 1938 chemicals in beauty and health products in 2016
 12세 이하 어린이가 사용하도록 만들어진 제품에 한해 Phthalate계 가소제 사용 규제
- Hong kong
 - 완구 및 아동용품 내 Phthalate계 가소제 규제 시행

Organophosphate Flame Retardants (PFRs)



Effects of EDC on Ovarian Steroidogenesis



Endocr Rev 2015 ; An Endocrine Society Scientific Statement

Effects of EDCs on Menstrual cycle

Influence of various compounds on menstrual cycles.

Compound	Cycle leng	th Cycle ir	Cycle irregularities			
POCs	Shorter					
PCBs	Longer		Yes			
PCBs and PCDFs	Shorter		Yes			
Dioxins and dioxin-like PCBs	Longer (for P	CBs)	Yes			
F						
Interfere with r	nenstrual cvc	licity through	n multiple			

pathways, resulting in irregular periods, shorter or longer cycles and changes in duration of bleeding and/or pain

Mendola, Messer & Rapazzo,2008; Mendola & Buck Louis, 2010

Effects of EDC on miscarriage

• Maternal conjugated BPA was associated with a higher risk of aneuploid and euploid miscarriage (relative risk 1.97 vs 3.33)

Lathi et al., FS 2012

- Rodents
 - DEHP exposure for 8 weeks caused a 100% pregnancy loss
 - Neonatal life exposure of BPA decreased implantation sites
 - Prenatal exposure significantly reduced fertility index and the ability of mice to maintain pregnancies in the F3 generation

Schmidt et al., Environ Health Perspect 2012 Gore et al., Endocrine reviews 2015

EDC and Early menopause/POI (1)

• Women occupationally exposed to chemicals during their reproductive life are at greater risk of POI than women of reproductive age in other occupations

Gallicchio et al., Hum Reprod 2009

- Cross-sectional survey using the NHANES, **Early Menopause** in U.S. Women
 - 15 specific EDCs (i.e. PCB, DDE, dioxin, phthalate metabolites) and earlier age at menopause-3.8 years earlier in women with the highest EDC level
 - Women with high levels of phthalate metabolites had an earlier mean age at menopause compared to women with low levels of phthalate metabolites

Grindler et al., PLoS one2015

EDC and Early menopause/POI (2)

	-		-		-				
EDC	Compound Name	N*	Threshold analysis EDC > 90th percentile†			Dose-respo	nse analysis		
					Log EDC‡		EDC decile§		
			Average change in age of menopause beta (SE) in years	P	Average change in age of menopause beta (SE) in years	Р	Average chang age of menopa beta (SE) in ye	jein P use ars	
PCBs	PCB-74	268	-1.98 (1.00)	0.058	-1.47 (0.603)	0.021	-0.28 (0.214)	0.20)1
	PCB-99	248	-3.08 (0.915)	0.002	-1.51 (0.504)	0.006	-0.37 (0.180)	0.05	51
	PCB-105	249	-1.86 (0.677)	0.010	-1.46 (0.467)	0.004	-0.36 (0.126)	0.00	8
	PCB-118	249	-2.46 (0.826)	0.006	-1.02 (0.446)	0.029	-0.37 (0.189)	0.06	52
	PCB-138	250	-2.21 (0.764)	0.007	-1.58 (0.429)	0.001	-0.71 (0.186)	<0.0	001
	PCB-153	250	-1.89 (0.799)	0.025	-1.40 (0.473)	0.006	-0.61 (0.200)	0.00)5
	PCB-156	268	-0.52 (0.863)	0.553	-1.92 (0.617)	0.004	-0.52 (0.169)	0.00)4
	PCB-170	268	-0.85 (0.962)	0.385	-1.21 (0.574)	0.045	-0.26 (0.231)	0.27	72
	PCB-183	249	-2.29 (0.817)	0.009	-1.58 (0.618)	0.016	-0.31 (0.145)	0.04	10
Pesticides	p,p'-DDE	268	-1.42 (0.926)	0.136	-0.67 (0.320)	0.046	-0.34 (0.162)	0.04	13
	Beta-hexachloro- cyclohexane	177	-1.90 (1.03)	0.075	-0.70 (0.138)	<0.001	-0.32 (0.078)	0.00)4
	Mirex	177	-1.39 (0.823)	0.103	-0.54 (0.084)	<0.001	-0.12 (0.049)	0.02	21
Dioxin/ furan	1,2,3,4,6,7,8-hepta- chlorodibenzofuran	212	-1.77 (0.697)	0.024	-0.72 (0.567)	0.178	-0.22 (0.193)	0.11	4
Phthalate	Mono-(2-ethyl-5- hydroxyhexyl)phthalate	153	-3.80 (0)	<0.001	-0.35 (0)	<0.001	-0.17 (0)	<0.0	001
	Mono-(2-ethyl-5- oxohexyl)phthalate	153	-3.17 (0)	<0.001	-0.28 (0)	<0.001	-0.22 (0)	<0.0	001

Grindler et al., PLoS one2015

EDC and Early menopause/POI (3)

• DEHP : potentially interfere with normal ovarian function, cause POI



Pocar et al., Toxicol Appl Pharmacol 2017

Effects of EDC on Endometriosis (1)

Experimental Data

Endometriosis in rhesus monkeys

(Macaca mulatta) following chronic Number of rhesus monkeys with varying degrees of endometriosis (based on revised American Fertility Society scale) after 4-year dietary exposure to TCDD.

	None	Т	Ш	Ш	IV
Control	4	2	0	0	0
High dose (25 ppt)	1	0	1	1	4

Note: Data from Rier et al. (109).

Rier et al, Fundam Appl Toxicol 1993 Yang et al., Toxicol Sci 2000

Human data

↑ plasma concentrations of DEHP in

women with endometriosis *vs.* controls

↑ levels of phthalates (DnBP, BBP,

DnOP, DEHP) in Indian women with

endometriosis vs. controls

Cobellis et al., Hum Reprod 2000 Reddy et al., BJOG 2006

Effects of EDC on Endometriosis (2)

 Women with advanced stages of endometriosis had significantly higher plasma levels of MEHP and DEHP than women without advanced stages of endometriosis

Kim et al., FS 2011

- A cross-sectional study of urinary phthalates (NHANES)
 - positive association between MBP and an increased risk of endometriosis

Weuve et al., Environ Health Perspect 2010

• In the Natural History, Diagnosis, and Outcomes Study (ENDO study), six phthalate metabolites were significantly associated with **2-fold increased** odds of endometriosis in population group.

Buck Louis et al., FS 2013

• It is important to note that **not all epidemiological** studies have shown that phthalate exposure increased the risk of endometriosis

EDCs and Reproduction

Endocr Rev 2015 ; An Endocrine Society Scientific Statement



How to Avoid?



- Counseling on **pesticides** avoidance
 - Organic diet / Wash, scrub all products / Peel
 - Higher consumption of high-pesticide residue fruit and vegetables were associated with lower probabilities of pregnancy and live birth following infertility treatment with ART
 - High pesticide residue food : fresh apple/pear, grape, potatoes, peach, strawberry, spinach, green peppers
 - Low pesticide residue food : dried plums, onions, advocado, corn, cabbage, orange juice...

Chiu et al., JAMA 2017

How to Avoid?



- Counseling on **BPA** avoidance
 - Glass, porcelain, stainless steel containers, esp for hot food or liquids
 - Avoid food in microwave plastic containers
 - Reduce use of can food /Water bottles with BPA free
 - Wooden toy / Ask for BPA free dental sealants
 - Opt for email receipt

How to Avoid?

- PHTHALATES
- Counseling on **Phthalate** avoidance
 - Organic fresh/frozen fruits and veggies
 - Avoid plastic storage for food/drink
 - Avoid fragance or perfume
 - Throw away soft plastic toys
 - Wash hands frequently
 - Vacuum/wet dust
 - Medical professional : wear gloves



Summary

Growing evidence suggests that EDCs are etiologically involved in female reproduction problems.

- Robust scientific evidence has emerged over the past 20 years, demonstrating that preconception and prenatal exposure to toxic environmental agents can have a profound and lasting effect on reproductive health across the life course
- Evidence based recommendation for preventing exposure must include policy change

ACOG and ASRM committee opinion 2013 Endocrine Society committee 2015

Summary

- Be aware
- Take away
- It's O.K. to say
 - We are **still learning** and until we know, **limit exposure**.





ASRM 2017