

Reproductive Health & the Environment: What Does the Current Research Tell Us?

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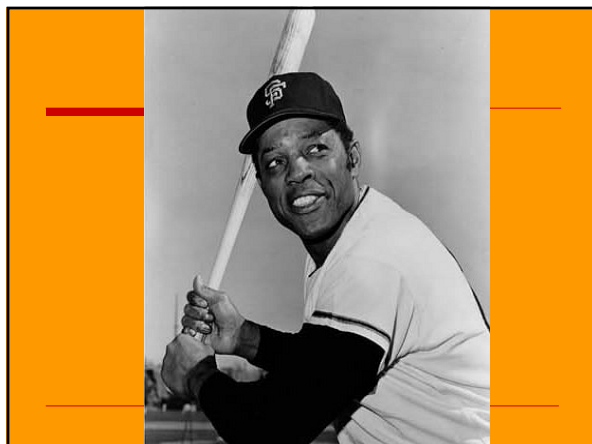
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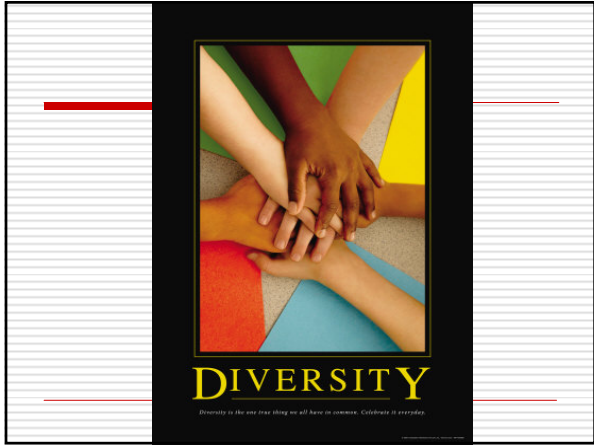
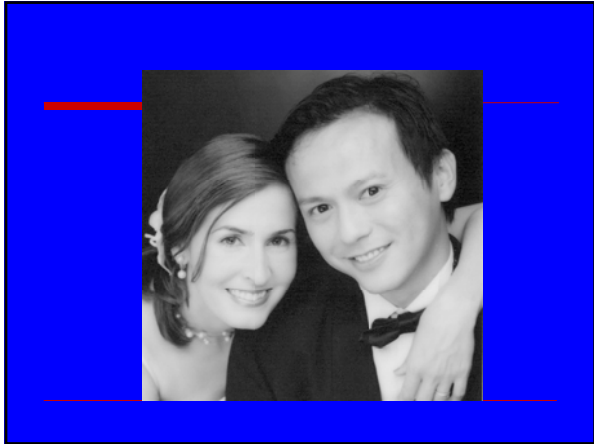
Advocacy through Education:
Women's Reproductive Health &
The Environment in Los Angeles County
November 16, 2010

Acknowledgment

- The Iris Cantor-UCLA Women's Health Education & Resource Center
- Los Angeles County Department of Public Health Office of Women's Health

E Pluribus Unum





"Just Like Every Other Kid in LA"

What a pediatrician said about Sasha's asthma

Reproductive Health & the Environment

Early Puberty

- ❑ Age of puberty onset has declined in developed nations
- ❑ Early puberty is associated with depression, sexual victimization, substance abuse, & adult breast cancer
- ❑ Early puberty has been linked to PCBs, PBBs, cigarette smoke, & organochlorine pesticide exposure in the womb or in early life
- ❑ Growing body of evidence linking early puberty to cumulative exposures to estrogen-like substances e.g. phthalates, BPA, DES, & some phytoestrogens
- ❑ Cumulative estrogenic exposures can promote early puberty by accelerating maturation of hormonal axis or by acting directly on development of ovaries and breasts

Woodruff et al Fert Steril 2008;89:e1-20; Howdeshell et al Nature 1999;401:763-4; Windham et al Am J Epidemiol 2006;163:662-71; Ouyang et al Occup Environ Med 2005;62:378-4; Guette et al Environ Health Perspect 2006;114:471-5; Krsinic et al Hum Reprod 2001;16:1020-6; Vasiliki et al Hum Reprod 2004;19:1556-12; Colon et al Environ Health Perspect 2000;108:895-900; Brown et al Environ Health Perspect 1995;103:768-73; From-Trueter et al Am J Dis Child 1996;140:1262-7; Hanson et al Arch Environ Contam Toxicol 1987;16:255-62; Denham et al Pediatrics 2005;115:e127-34; Blanck et al Epidemiology 2000;11:641-7

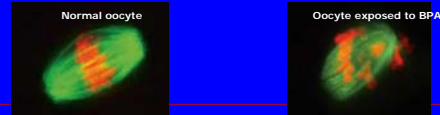
Impaired Fertility & Infertility

- ❑ Endocrine disruptors such as BPA, cigarette smoke, DDT, DES, PCBs have been linked to impaired fertility
- ❑ Male factor infertility
- ❑ Female factor infertility by disrupting ovarian & uterine development and functions

Woodruff et al Fert Steril 2008;89:e1-20; Sugitara-Ogasawara Hum Reprod 2005;20:2325-2329; Hruska et al Clin Obstet Gynecol 2000;43:821-9; Younglai et al Hum Reprod Update 2005;11:43-57; Cohn et al Lancet 2003;361:2205-6; Vanders et al Ann Epidemiol 2005;15:209-16; Longnecker et al Environ Res 2002;92:122-33; Paroz et al Fert Steril 2005;84:1649-56; Sharrara Fert Steril 1998;70:613-22; Miller et al Toxicol Appl Pharmacol 2004;198:111-31; Toft Reprod Toxicol 2004;19:5-26; Crain et al Fert Steril 2008;90:911-40

Aneuploidy

- ❑ A condition in which a cell has extra or missing copies of specific chromosomes (e.g. Trisomy 21)
- ❑ Exposure to BPA in the womb or as adult can lead to production of eggs & embryos with abnormal number of chromosomes
- ❑ Prenatal exposure leads to altered synapsis & recombination during meiosis
- ❑ Adult exposure leads to altered spindle formation & chromosomal alignment during meiosis



Woodruff et al Fert Steril 2008;89:e1-20; Crain et al Fert Steril 2008;90:911-40; Hunt et al Curr Biol 2003;13:546-53; Katsube et al Biol Cell 1999;91:6

Polycystic Ovarian Syndrome (PCOS)

- ❑ PCOS characterized by hyperandrogenism, anovulation or oligoovulation, and polycystic ovaries
- ❑ Women with PCOS found to have higher levels of BPA
- ❑ PCOS has been linked to excessive androgen exposure in the womb

Woodruff et al Fert Steril 2008;89:e1-20; Ikezaki et al Hum Reprod 2002;17:2839-41; Takeuchi et al Endocr J 2004;51:145-9; Crain et al Fert Steril 2008;90:911-40

Endometriosis

- ❑ Animal studies have linked endometriosis to adult exposures to DDT, methoxychlor, dioxin, PCBs
- ❑ Human studies have linked endometriosis to adult exposures to dioxin, phthalates, PCBs
- ❑ Organochlorines can interfere with hormonal regulation (e.g. reduced PR expression) & immune function to promote endometriosis
- ❑ In utero exposures are also associated with endometriosis
 - ❑ DES daughters have 80% higher risk of developing endometriosis
 - ❑ Prenatal exposure to dioxin shown to promote endometriosis in mice

Woodruff et al Fert Steril 2008;89:e1-20; Cibellis et al Hum Reprod 2003;18:1152-5; Reddy BJOC 2006;113:515-20; Porpora et al Chemosphere 2006;63:1361-7; Hoffman et al Ann Epidemiol 2007;17:503-10; Mousner et al Fert Steril 2002;80:1441-6; Book et al Pediatr (Chic) 1998;102:1443-4; Crain et al Fert Steril 2008;90:911-40

Fibroids

- ❑ Animal studies have linked uterine fibroids to DES, BPA and some organochlorine pesticides
- ❑ DES exposure during sensitive periods of development turns on estrogen sensitive genes
- ❑ DES daughters have twofold increased risk of fibroids
- ❑ In utero or neonatal exposures to BPA, at levels to which women are currently exposed, also increase the risk of fibroids in adult mice
- ❑ In vitro studies show DES and organochlorines induce proliferation of fibroid cells

Woodruff et al Fert Steril 2008; 89: e1-20; Backlin et al Vet Path 2003; 40: 175-80; Hodges Ann NY Acad Sci 2001; 948: 100-11; Newbold et al Reprod Toxicol 2007; 24: 253-8; Wise et al Obstet Gynecol 2005; 105: 167-72; Crain et al Fert Steril 2008; 90: 911-40

Spontaneous Abortion

- ❑ Spontaneous abortion can be caused by aneuploidy, uterine anomalies, & endocrine or immune disruption
- ❑ May also be caused by poor implantation
 - Early gestation exposure to BPA causes poor placentation
 - Early gestation exposure to methoxychlor reduces proliferation & induces apoptosis
 - Early gestation exposure to synthetic estrogen induces trophoblast degeneration
- ❑ Poor implantation has also been implicated in preeclampsia, IUGR and preterm birth

Woodruff et al Fert Steril 2008; 89: e1-20; Crain et al Fert Steril 2008; 90: 911-40; Longnecker et al Lancet 2001; 358: 110-4; Bamigboye et al Cochrane Database Syst Rev 2003; CD004353; Derfoul et al J Cell Biochem 2003; 89: 755-70; Tachibana et al Reprod Dev 2007; 53: 509-14; Crain et al Fert Steril 2008; 90: 911-40

Preterm Birth

Air pollution	Positive findings for sulfur dioxide & particulates; inconsistent findings for carbon monoxide, nitrous oxides, ozone
Water pollution	No association with THM or other chlorination disinfection by-products
Agricultural chemicals	Inconsistent findings; DDT associated with preterm birth OR 2.5-3.1
Polychlorinated biphenyls	Inconsistent findings for PCBs
Dioxins	Inconsistent findings for TCDD
Environmental tobacco smoke	Passive smoking consistently associated with preterm birth OR 1.2-2.4
Metals & metalloids	Lead consistently associated with preterm birth; inconsistent findings for aluminum, cadmium, arsenic

Institute of Medicine. Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Board on Health Sciences Policy. Bohman RE, Butler AS (eds). Preterm birth: Causes, consequences, and prevention. Washington DC: The National Academies Press; 2007.

Breast Cancer

- ❑ Mammary gland tumors have been linked to more than 200 chemicals, including BPA, cigarette smoke, DES, & pesticides DDT and atrazine
- ❑ DES daughters have increased risk of breast cancer
- ❑ In utero exposure to BPA is associated with increased density of mammary gland tissue, a risk factor for breast cancer, which is not manifested until after puberty
- ❑ In human studies, no link was found between adult exposure to DDT, but among women who were exposed to high levels of DDT under the age of 14, there was a fivefold increased risk of breast cancer

Woodruff et al Fert Steril 2008; 89: e1-20; Lee et al Inhalation Toxicology 2006; 18: 1053-70; Vandenberg et al Endocrinology 2007; 148: 116-27; Durando et al Environ Health Perspect 2007; 115: 80-6; Martin et al Breast Cancer Res 2008; 10: 201; Palmer et al Com Epidemiol Biomarkers Prev 2006; 15: 1599-14; Trossi et al Int J Cancer 2007; 121: 356-60; Cohen et al Environ Health Perspect 2007; 115: 1406-14; McElroy et al J Expo Sci Environ Epidemiol 2007; 17: 207-14; Crain et al Fert Steril 2008; 90: 911-40

Summary

Early puberty	BPA, cigarette smoke, organochlorine pesticides (e.g. DDT/DDE), DES, PBBs, PCBs, phthalates, some phytoestrogen
Impaired fertility or infertility	BPA, cigarette smoke, DDT, DES, PCBs
Aneuploidy	BPA
Menstrual irregularities	BPA & some phytoestrogens, DDT, other pesticides, DES, dioxins, PCBs
Polycystic ovarian syndrome (PCOS)	BPA
Uterine fibroids	DES, BPA, some organochlorine pesticides
Spontaneous abortion	BPA, DES, DDT/DDE, methoxychlor
Preterm Birth	Sulfur dioxide, particulates, DDT, lead
Endometriosis	Organochlorines such as DDT, methoxychlor, dioxin, PCBs, phthalates, DES
Breast cancer	BPA, cigarette smoke, DES, pesticides DDT & atrazine

Male Reproductive Health & the Environment

- ❑ Cryptorchidism, hypospadias, testicular germ cell cancer, infertility are on the rise
- ❑ Testicular dysgenesis syndrome may have a common fetal origin due to "abnormal testis development"
- ❑ In utero exposure to DBP reduces Sertoli cells
- ❑ Adult exposure to phthalates, PCBs, heavy metals, DBCP, pesticides linked to decreased sperm quality

Woodruff et al Fert Steril 2008; 89: e1-20; Crain et al Fert Steril 2008; 90: 911-40; Skakkebaek et al Hum Reprod 2001; 16: 972-8; Sharpe et al Fert Steril In press; Hauser et al Epidemiol 2006; 17: 682-91

No "Safe" Dose

- ❑ Very low levels of BPA can harm reproductive health in female mice and their offspring
- ❑ Mice exposed to extremely low levels of DES in the womb grew to be extremely obese in adulthood, whereas mice exposed to higher levels of DES actually lost weight



Barrett J, Gonzalez S, Sarantis H, Varshavsky J, Giri, disrupted. Hormone disruptors and women's reproductive health. Bolinas, CA: Collaborative on Health and Environment. 2009. www.healthandenvironment.org

Timing Matters

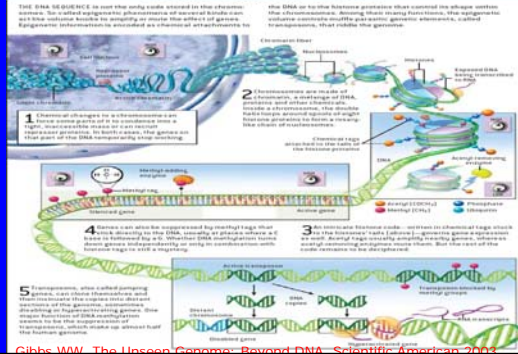
- ❑ **Programming:** The process whereby a stimulus or insult, at a sensitive or 'critical' period, has lasting or lifelong impact on health or function.
- ❑ **Critical or sensitive windows of susceptibility:** Time-sensitive interval when exposures to a stimulus or insult can disrupt or interfere with the physiology of a cell, tissue, or organ



Woodruff et al Fert Steril 2008;89:e1-20; Crain et al Fert Steril 2008;90:911-40

Epigenetics

VOLUME CONTROLS FOR GENES



Clebbe MW. The Hissop Genome: Beyond DNA. Scientific American 2014

Epigenetics

Same Genome, Different Epigenome



R.A. Waterland, R.A. Jirtle, "Transposable elements: targets for early nutritional effects on epigenetic gene regulation," *Mol Cell Biol*, 23:5293-300, 2003. Reprinted in the New Scientist 2004

Prevention Begins Before Conception: Dioxins

- ❑ Endocrine disruptor
- ❑ Developmental neurotoxicant & immunotoxicant
- ❑ Bioaccumulate in animal fat
 - Long half life: 7 years
 - Crosses the placenta easily
- ❑ Prevention
 - Low animal fat diet for children & young women
 - Quit feeding animal fat to animals

Schettler, T, Solomon G, Valenti M, Huddle A. Generations at risk: Reproductive health and the environment. Cambridge, MA: MIT Press. 2000.

Research Priorities

- ❑ Human and animal studies that are longitudinal, including prenatal exposures
- ❑ Incorporate semen analysis into CDC's NHANES study
- ❑ Biomarker collection & banking should be incorporated into epidemiological study designs
- ❑ Development of biomarkers of exposure and preclinical indicators of disease & better biomarkers of human fertility
- ❑ Strategies to address regulatory obstacles (e.g. HIPPA)
- ❑ Increased funding for emerging areas of research: epigenetics, fetal programming and transgenerational effects, low-dose effects, nontraditional dose-response curves, crosstalk among endocrine systems and receptors
- ❑ Develop systems to identify new emerging contaminants
- ❑ Enhanced collaborations among researchers and between researchers and granting agencies

Adapted from Woodruff et al Fert Steril 2008;89:e1-20

Southern California Environmental Health Sciences Center

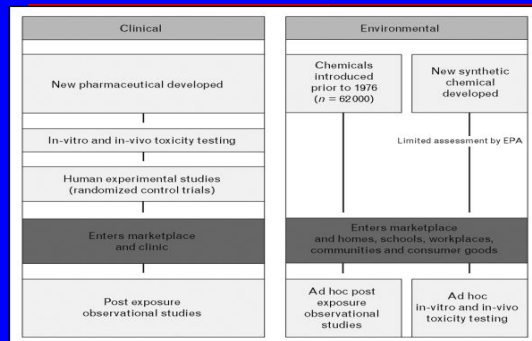
- Collaboration between UCLA & USC
- Established in 1996 to promote environmental health research in Southern California
- Center studies have included improved approaches for assessing exposure to automobile exhaust, toxicologic assessment of toxic air contaminants, and the measurement of particles of all sizes.
- In one major study, Center investigators are studying 6,000 children living in Southern California who breathe some of the most polluted air in the United States.

National Children's Study

- Longitudinal study – from before birth to 21 years of age
- Cohort of 100,000 children from 100 Study Locations
- Study how children's genes and their environments interact to affect their health and development
- In Los Angeles,
 - 4,000 children
 - 56 neighborhoods
 - 67 birth hospitals
 - Followed for 21+ years

Policy

Reproductive environmental health.
Suttler, Patricia; Guzman, Elena; Woodruff, Tracy
Current Opinion in Obstetrics & Gynecology, 22(6):517-524, December 2010.
DOI: 10.1097/GCO.0b013e3181e2830e59



Policy

- 2007: REACH
 - European Community Regulation on chemicals and their safe use (EC 1907/2006)
- 2009: Essential Principles for Reform of Chemicals Management Legislation
 - US EPA to help inform legislative efforts to reauthorize and strengthen the effectiveness of chemical regulations

"Now that *you're* here,
the word of the Lorax seems perfectly clear.
UNLESS someone like you
Cares a whole awful lot,
Nothing is going to get better.
It's not.
"SO...
Catch!" calls the Once-ler.
He lets something fall.
"It's a Truffula Seed.
It's the last one of all!
You're in charge of the last of the Truffula Seeds.
And Truffula Trees are what everyone needs.
Plant a new Truffula. Treat it with care.
Give it clean water. And feed it fresh air.
Grow a forest. Protect it from axes that hack.
Then the Lorax
And all of his friends
May come back."

- Dr. Seuss, *the Lorax*