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

Michael C. Lu, MD, MPH
Associate Professor
Department of Obstetrics & Gynecology
David Geffen School of Medicine at UCLA
Department of Community Health Sciences
Center for Healthier Children, Families and Communities
UCLA School of Public Health

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


**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


**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


**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


**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

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

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

Preterm Birth
- Air pollution: Positive findings for sulfur dioxide & particulates; inconsistent findings for carbon monoxide, hydrocarbons, 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

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

Summary
- Early puberty: BPA, cigarette smoke, organochlorine pesticides (e.g. DDT/DDE), DES, PCBs, phthalates, some phytoestrogens
- Impaired fertility or infertility: BPA, cigarette smoke, DES, PCBs
- Menopause: BPA
- Neurodevelopment: BPA & some phytoestrogens, DDT, other pesticides, DES, dioxins, PCB
- Polycystic ovarian syndrome (PCOS): BPA
- Uterine fibroids: DES, BPA, some organochlorine pesticides
- Spontaneous abortion: DES, BPA, DDT, DDE, methoxychlor
- Preterm Birth: Sulfer dioxide, particulates, DDT, lead
- Endometriosis: Organochlorines such as DDT, methoxychlor, dioxin, PCBs, phthalates, BPA
- Breast cancer: BPA, cigarette smoke, DES, pesticides DDT & estradiol

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
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.

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.

Epigenetics

- Same Genome, Different Epigenome


Prevention Begins Before Conception: Dioxins

- Endocrine disruptor

- Developmental neurotoxicant & immunotoxicant

- Bioaccumulates 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

Research Priorities

- Human and animal studies that are longitudinal, including prenatal exposure
- Incorporate semen analysis into CDC’s NHANES study
- Biopsy collection & banking should be incorporated into epidemiological study designs
- Development of biomarkers of exposure and precocial 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 transgene analysis, epigenetics, regulation effects, nontraditional dose-response curves, crosstalk among endocrine systems and receptors
- Develop systems to identify new emerging contaminants
- Enhanced collaboration among researchers and between researchers and granting agencies
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

- 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. "SD... 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