The Effects of Endocrine Disruptors on Childhood Obesity

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March 4th, 2015
Endocrine disruptor

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Endocrine disrupting chemical (EDC)
Learning Objectives

1. Know the definition of Endocrine Disrupting Chemicals (EDCs)
2. Review the evidence regarding the effects of EDCs on obesity in children and adolescents
3. Discuss potential mechanisms of how EDCs lead to obesity and other metabolic dysfunction
DES is a known endocrine disruptor

**Diethylstilbestrol (DES)**

- Synthetic estrogen prescribed to pregnant women between the 1940s and 1970s
- In 1971, DES was found to cause vaginal adenocarcinoma in women born to mothers exposed to DES
- Reproductive anomalies found in “DES daughters” and “DES sons”
- Findings confirmed by animal studies


Newbold. Hormones. 2010
What are endocrine disruptors?
Endocrine Disruptor Definition

“An endocrine disruptor is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.”

Which contain EDCs?
Some EDCs persist in nature

• **Persistent Organic Pollutants (POPs)**
  – Pesticides (DDT – banned in 1972)
  – Dioxins
  – PCBs (banned in 1977-79)
  – Flame retardants

• **Short-lived pollutants**
  – BPA
  – Phthalates
Concerns regarding EDCs are based on 3 strands of evidence

1. High incidence and increasing trends of many endocrine-related disorders in humans
2. Observations of endocrine-related effects in wildlife populations
3. Identification of chemicals with endocrine disrupting properties linked to disease outcomes in laboratory studies

Bergman et al. Environmental Health Perspectives. 2013
EDCs affect the whole endocrine system

- EDCs initially associated with disrupted reproductive function and cancer
- More evidence that the whole endocrine system is susceptible

Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. 2009
Factors associated with EDC effects

• Genetic susceptibility
• Duration of exposure
• Latency period
• Clearance
• Mixture of EDCs
• Non-monotonic dose-response dynamics

Solorzano and McCartney. Reproduction. 2010
Mouritsen et al. International Journal of Andrology. 2010
Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. 2009
Dose response curves

http://epa.gov/ncct/edr/non-monotonic.html
Factors associated with EDC effects

- Genetic susceptibility
- Duration of exposure
- Latency period
- Clearance
- Mixture of EDCs
- Non-monotonic dose-response dynamics
- Age or developmental stage

Solorzano and McCartney. Reproduction. 2010
Mouritsen et al. International Journal of Andrology. 2010
Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. 2009
Critical Periods of Exposure

• “Developmental origins of adult disease”

• The thrifty-phenotype hypothesis
  – “in utero fetal nutritional status determines the risk for obesity and associated metabolic syndrome diseases” Grun and Blumberg 2006

• “DES sons and daughters”

Newbold. Hormones. 2010
EDCs are present in 100% of pregnant women
Children may be more vulnerable to effects of EDCs

1. Higher exposure to many fat-soluble contaminants in breast milk or formula
2. High hand-to-mouth behavior
3. Closer proximity to the ground
4. Higher body surface area relative to their body weight

What is the evidence regarding the effects of EDCs on obesity in children and adolescents?

Prevalence of obesity is increasing

- Caused by:
  - High energy intake
  - Low energy expenditure
  - Genetic predisposition

- Do these sufficiently explain the global obesity epidemic?

Increased prevalence of overweight adults parallels production of synthetic chemicals.
Obesogens

- Grun and Blumberg in 2006:
  “molecules that inappropriately regulate lipid metabolism and adipogenesis to promote obesity”

- Adipose tissue
  - Is an active organ
  - Acts as a reservoir for EDCs

<table>
<thead>
<tr>
<th>Known and Suspected Obesogens</th>
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</thead>
<tbody>
<tr>
<td><strong>Diet</strong></td>
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<tr>
<td>- Fructose</td>
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<td>- Genistein</td>
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<tr>
<td>- Monosodium Glutamate</td>
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<tr>
<td><strong>Smoking</strong></td>
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<tr>
<td>- Nicotine</td>
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<tr>
<td><strong>Pharmaceuticals</strong></td>
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<tr>
<td>- Diethylstilbestrol</td>
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<tr>
<td>- Estradiol</td>
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<tr>
<td><strong>Industrial Chemicals</strong></td>
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<tr>
<td>- Bisphenol A (BPA)</td>
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<td>- Organotins</td>
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<tr>
<td>- Perfluorooctanoic Acid (PFOA)</td>
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<tr>
<td>- Phthalates</td>
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<tr>
<td>- Polybrominated Diphenyl Ethers (PBDEs)</td>
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<tr>
<td>- Polychlorinated Biphenyl Ethers (PCBs)</td>
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<tr>
<td><strong>Organophosphate Pesticides</strong></td>
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<tr>
<td>- Chlorpyrifos</td>
</tr>
<tr>
<td>- Diazinon</td>
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<tr>
<td>- Parathion</td>
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<tr>
<td><strong>Other Environmental Pollutants</strong></td>
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<tr>
<td>- Benzo[a]pyrene</td>
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<td>- Fine Particulate Matter (PM$_{2.5}$)</td>
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<tr>
<td>- Lead</td>
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</table>
Phthalates

• Used to soften polyvinyl chloride (PVCs), add fragrance, or enhance pliability in plastics and other products
• Found in personal care products, scented products, medical equipment, building materials, enteric coatings, and art supplies
• Banned in toys since 1999 in EU and 2008 in US
• Linked to genital abnormalities in boys, reduced sperm counts, endometriosis, and metabolic disruption and obesity
<table>
<thead>
<tr>
<th>Study population</th>
<th>Exposure assessment</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>US, male participants from NHANES 1999–2002 aged &gt; 18 yr (n=1,443)</td>
<td>Cross-sectional study Urine – 6 phthalates (MBP, MEP, MEHP, MBzP, MEHHP, MEOHP)</td>
<td>Positive association between WC and MEP, MBzP, MEHHP, MEOHP</td>
<td>Stahlhut et al.(^{43})</td>
</tr>
<tr>
<td>US, participants from NHANES 1999–2002 aged 6–80 yr (n=6,369)</td>
<td>Cross-sectional study Urine – 6 phthalates (MBP, MEP, MEHP, MBzP, MEHHP, MEOHP)</td>
<td>Positive association between BMI/WC and MEP in males aged 20–59 yr Negative association between BMI and MEHP in females aged 12–59 yr</td>
<td>Hatch et al.(^{44})</td>
</tr>
<tr>
<td>US, participants from NHANES 2007–2010 aged &gt; 6 yr</td>
<td>Cross-sectional study Urine – 10 phthalates LMW phthalates (MBP, MEP, MiBP), HMW phthalates (MECPP, MEHHP, MEOHP, MEHP, MBzP, MCNP, MCOP)</td>
<td>Positive association between obesity risk and LMW metabolites in males aged 6–19 yr</td>
<td>Buser et al.(^{49})</td>
</tr>
<tr>
<td>Sweden, elderly aged 70 yr (n=1,016)</td>
<td>Prospective study Blood – 4 phthalates MEP, MEHP, MiBP, MMP</td>
<td>Positive association between MEP and WC/fat mass obtained 2 yr later among females</td>
<td>Lind et al.(^{47})</td>
</tr>
<tr>
<td>US, participants from NHANES 2003–2008 aged 6–19 yr (n=2,884)</td>
<td>Cross-sectional study Urine – 9 phthalates LMW phthalates (MBP, MEP, MiBP), HMW phthalates (MECPP, MCPP, MEHHP, MEOHP, MEHP, MBzP)</td>
<td>Positive association between obesity risk and sum of molar concentrations LMW phthalates among non-Hispanic blacks</td>
<td>Trasande et al.(^{45})</td>
</tr>
<tr>
<td>New York, children aged 6–8 yr Hispanic and Black</td>
<td>Prospective study Urine – 9 phthalates LMW phthalates (MBP, MEP, MiBP), HMW phthalates (MECPP, MCPP, MEHHP, MEOHP, MEHP, MBzP)</td>
<td>Positive association between LMW phthalates and BMI/WC obtained 1 yr later among overweight children No associations among normal weight subjects</td>
<td>Teitelbaum et al.(^{48})</td>
</tr>
</tbody>
</table>
Bisphenol A (BPA)

- Estrogen analog
- Much lower affinity to the estrogen receptor (1/1,000-10,000)
- Found in plastic products, lining of canned foods
- > 96% of all Americans have BPA in their bodies (source: CDC)
- Found in urine, blood, umbilical cord blood, and amniotic fluid
Perinatal BPA exposure causes weight gain in rats

Access to drinking water containing 1 mg/L BPA from day 6 of gestation through the end of lactation

Somm et al. Environ Health Perspect. 2009
Increased adipose tissue in female rats exposed perinatally to BPA

Somm et al. *Environ Health Perspect.* 2009
Studying effects of EDCs is challenging

• **Human studies**
  – Epidemiological and cross-sectional studies cannot establish causality
  – Exposure is not limited to one EDC
  – Methodological and logistic limitations

• **Animal studies**
  – Animal models are NOT humans
  – Different endocrine and reproductive systems
  – Exposure dose and mixture
What are the potential mechanisms of how EDCs lead to obesity?
EDCs bind directly to nuclear receptors

- **Nuclear receptors:**
  - Estrogen
  - Androgen
  - Thyroid
  - PPARy

- **EDCs may act as:**
  - Agonists
  - Antagonists
These obesogens act via the ER or TR

<table>
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<tr>
<th>Chemical</th>
<th>Commercial use</th>
<th>Relevant EDC action</th>
<th>Obesogenic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPA</td>
<td>Plastics</td>
<td>Binds ER, ERRy</td>
<td>Induces adipogenesis (C), obesity (A)</td>
</tr>
<tr>
<td>Hexachlorobenzene</td>
<td>Fungicide</td>
<td>Alters TH signaling</td>
<td>Gestational exposure levels influence BMI (H)</td>
</tr>
<tr>
<td>PBDEs</td>
<td>Fire retardants</td>
<td>Reduces thyroid function</td>
<td>Stimulate fat production (C)</td>
</tr>
<tr>
<td>DES</td>
<td>Pharmaceutical estrogen</td>
<td>Binds ER</td>
<td>Perinatal exposures cause obesity (A), BMI in young children (H)</td>
</tr>
<tr>
<td>Perfluoroalkyl sulfonate</td>
<td>Non-stick coatings</td>
<td>Binds ER</td>
<td>Perinatal exposures cause obesity, alter insulin and leptin levels (A)</td>
</tr>
<tr>
<td>DDE</td>
<td>DDT metabolite</td>
<td>Binds ER</td>
<td>Concentrations in mothers associated with weight and BMI in female offspring (H)</td>
</tr>
</tbody>
</table>

Adapted from Zoeller et al. WHO State of the Science of Endocrine Disrupting Chemicals. 2012
EDCs may lead to obesity via (PPARγ)

• PPARγ = Peroxisome Proliferator-Activating Receptor gamma
  – Nuclear receptor mainly expressed in adipose tissue
  – Regulates adipocyte differentiation
  – Promotes fat accumulation and storage in the adipose tissue
  – Represses lipolysis

Grun and Blumberg. Endocrinology. 2006
These obesogens act via PPARy

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<th>Relevant EDC action</th>
<th>Obesogenic activity</th>
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</thead>
<tbody>
<tr>
<td><strong>Tributyltin</strong> (TBT)</td>
<td>Pesticide, wood preservation</td>
<td>Binds PPARy</td>
<td>Changes identity of adipose precursors, increases triglycerides in adipose tissue (A)</td>
</tr>
<tr>
<td><strong>Phthalates</strong></td>
<td>Plasticizer</td>
<td>Binds PPARy</td>
<td>Induce adipocyte differentiation (C), men’s waist size (H)</td>
</tr>
<tr>
<td><strong>PFOA</strong> (Perfluorooctanoic acid)</td>
<td>Non-stick coatings</td>
<td>Weakly activates PPARy</td>
<td>Induce adipocyte differentiation (C)</td>
</tr>
<tr>
<td><strong>Flavanone</strong></td>
<td>Natural plant products used as flavourings</td>
<td>Binds PPARy</td>
<td>Induce adipocyte differentiation (C)</td>
</tr>
</tbody>
</table>

Adapted from Zoeller et al. WHO State of the Science of Endocrine Disrupting Chemicals. 2012
Other potential mechanisms

• *Indirect* actions on nuclear receptors?
• Alteration of neuronal synapse formation?
• Interaction with different target organs (pancreas, adipocytes, etc.)?
• Transgenerational effects via epigenetics?
• Simultaneous multiple mechanisms?
Key points

1. EDCs?  

   *Ubiquitous chemicals (synthetic or natural) that disrupt normal endocrine function*

2. Evidence for obesity?

   “The evidence on adverse effects on the reproductive system is strong; the evidence on other endocrine systems, including obesity and metabolism, is mounting.”  
   *Endocrine Society*

3. Mechanisms?

   *EDCs likely act via multiple mechanisms*
Acknowledgements

• Division of Endocrinology & Diabetes

• C.A.R.E Program
  – Micah Olson, MD
  – Oliver Oatman, MD
  – Reeti Chawla, MD
  – Synthia Puffenberger, PhD
  – Christine Roberts, PhD, MBA
  – Gabe Shaibi, PhD
  – Yessica Chavez
  – Debbie Whitewater
  – Paulette Savino, RD
  – April Callahan, RD
  – Candace Johnson, RD
100% For Children

Questions
Future Directions

• GOAL: reducing exposure for disease prevention

• Further research

• Increase awareness

• Regulation