Pre-Conception Exposures and Children’s Health

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Disclaimers

- I have no financial conflicts of interest related to the material being presented
- I was financially compensated as an expert witness in a lawsuit related to secondhand tobacco smoke exposures
Do Dads Matter?

- I never thought of fatherhood as something that could affect a kid.

  – Homer Simpson
Beyond Prenatal: Preconception

New results challenge two paradigms:

1. Gestation, infancy, and childhood are most important periods of susceptibility
2. Fathers only influence child health by Mendelian inheritance
Paternal Fear Conditioning (Diaz and Ressler, Nat Neurosci, 2014)

- Paternal preconception fear of acetophenone passed on to F1 & F2 male offspring
  - Neuroanatomical changes
  - DNA hypomethylation in offspring sperm
Paternal stress and offspring health

(Rodgers et al., 2013 and 2015)

- Paternal preconception stress caused:
  - ↓ offspring HPA axis response
  - Changes in sperm miRNA
- Sperm miRNAs recapitulated phenotype
Paternal BPA and Rodent Neuro (Fan et al., PLoS ONE, 2018)

- Male rats exposed to BPA (50 µg/kg/d)
- Offspring anxiety (OFT and EPM) and corticosterone
- Exposed females displayed more signs of anxiety and had higher post-test corticosterone
Paternal/Maternal BPA & Rodent Neuro (Harris et al., Horm & Behav, 2018)

- Male mice exposed to BPA (dose not reported)
- No effect of paternal BPA on offspring EPM and vocalizations
- Exposed males weighed less than controls
- Species-specific effects?
Epidemiological Studies of Pre-Conception Environmental Exposures

- Most epi studies of preconception exposures limited to studies of childhood cancer & birth defects
- Mostly occupational exposures
  - Paternal benzene and childhood leukemia
  - Paternal pesticides and childhood leukemia

Transgenerational Effects of DES

- Grandchildren of grandmothers exposed to DES during pregnancy at increased risk of ADHD
  - OR: 1.4 (95% CI: 1.1, 1.7)
  - Strongest for 1\textsuperscript{st} trimester (OR: 1.6; 95% CI: 1.2, 2.3)
  - No sex-specific effects

- Other EDCs?

Kioumourtzoglou et al., JAMA Peds, 2018
Preconception Phthalates & Health

- Non-persistent, multifunctional class of chemicals
- Concern over toxicity
  - Anti-androgenic effects
  - Thyroid disruption
  - PPAR
- Sperm DNA methylation
  - Altered sperm DNA methylation in genes related to growth, development, and cell movement and structure

Wu et al., Human Repro, 2017
The PEACE Study

- Preconception cohort of subfertile couples attending MGH clinic (2004-present)
- Maternal preconception and prenatal exposure, paternal preconception
- Ongoing follow-up of children at age 6-10 years (550+ eligible)
- Neurodevelopment, asthma/allergy, pubertal development, body composition, & cardiometabolic risk
The PEACE Study

Enrollment & Fertility Tx

Paternal/Maternal Pre-Conception:
- Blood, urine, and hair
- Sperm (subset)
- Follicular Fluid (IVF)
- Exposure history
- Diet (FFQ)
- SES

Pregnancy

Maternal/Infant Pregnancy:
- Blood, urine, and hair
- Exposure history
- Labor & Delivery

6-10 Years

Children:
- Blood, urine, and hair
- IQ
- Behavior
- Executive function
- Body composition
- Metabolism
- Eating behaviors
Maternal Preconception Urinary Phthalate Concentrations and Child Externalizing Behaviors (n=148)

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EMM p-value <= 0.05

Messerlian et al., Environ Res, 2017
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EMM p-value = $<0.10$

Messerlian et al., Environ Res, 2017

**Child Sex**
Pre-Conception Exposures and Birth Weight

- Messerlian, et al., Environ Int, 2017
  - Paternal DEHP associated with lower BW in 195 father-infant
  - Association stronger among babies conceived via IVF (p<0.05)
    - 90 gram decrease in BW with increasing DEHP (95% CI: -165, -15)
  - Association stronger after adjustment for maternal prenatal levels

- Mustieles et al., Human Reproduction, 2018
  - Maternal preconception BPA associated with reduced BW
    - 119 gram decrease in BW with increasing BPA (95% CI: -212, -27)
  - Association remained after adjusting for prenatal exposure
Preconception Triclosan and Thyroid

- EARTH Study
- Preconception urinary triclosan associated with decreased fT3 in women
  - N=317

\[ \beta: -0.06; 95\% \text{ CI: } -0.11, -0.01 \]

Skarha et al., Environ Int, Under Review
Challenges to Epidemiological Studies of Preconception Exposures

Challenges

- Enrolling couples at risk of becoming pregnant
  - ~10% of US women become pregnant each year and ~63% are intended pregnancies
- Potential for loss to follow-up and censoring
  - Conceiving, live-birth, and continued follow-up
- Generalizability

Solutions

- Fertility clinic enrollment, targeted internet advertising, and brute-force
  - LIFE, EARTH, and PRESTO Studies
- Large sample sizes or retrospective assessment
- Scientific validity

Braun, Messerlian, and Hauser; Curr Epidem Rep; 2016
Concluding Remarks

- Potential for preconception environmental exposures to affect children’s health
- Fathers matter
- Public health implications
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