Maternal and Paternal Preconception Endocrine Disrupting Chemicals Exposure and Birth Outcomes

Carmen Messerlian, PhD
Assistant Professor of Environmental Reproductive Epidemiology
Yu Zhang, PhD Student
<table>
<thead>
<tr>
<th>No.</th>
<th>Section</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>BACKGROUND (CM)</td>
<td>CM</td>
</tr>
<tr>
<td>02</td>
<td>STUDY DESIGN (CM)</td>
<td>CM</td>
</tr>
<tr>
<td>03</td>
<td>METHODS (YZ)</td>
<td>YZ</td>
</tr>
<tr>
<td>04</td>
<td>MIXTURES ANALYSIS (YZ)</td>
<td>YZ</td>
</tr>
<tr>
<td>05</td>
<td>PRETERM BIRTH AND BIRTHWEIGHT (YZ)</td>
<td>YZ</td>
</tr>
<tr>
<td>06</td>
<td>CONCLUSIONS (CM)</td>
<td>CM</td>
</tr>
</tbody>
</table>
Works to understand how the Environment impacts reproductive health from the very earliest stages of life – from the formation of gametes and embryos – to the birth of infants and throughout child health and development.

Our mission is to
Use cutting-edge evidence to inform clinical practice, translate science into policy action, and implement prevention strategies to improve the health of mothers, fathers, and their children.
01

BACKGROUND
BACKGROUND

Birth Outcomes
Prenatal period
Preconception period

Preconception Period
Oogenesis
Spermatogenesis
Uterine receptivity
Overall health

Pregnancy and Birth
Couple-based outcome
**BACKGROUND**

- **EDCs**
  Exogenous chemicals that interfere with any aspect of endocrine system or hormonal action

- **PHTHALATES**
  High Molecular Weight
  Medical devices, toys
  Low Molecular Weight
  Paints, adhesives
  Personal care products

- **BPA**
  Plastic bottles
  Food packaging
  Toys

- **MIXTURES**
  Beyond a single-chemical problem, real word exposure scenarios are much more complex
ENDOCRINE
Alters any aspect of endocrine function

EPIGENETIC
Alters epigenetic regulation
Genomic imprinting required for embryo-fetal development

IMMUNE
Impacts inflammation and immune function

METABOLIC
Impacts metabolic processes and regulation
HYPOTHESIS

Chemical mixtures impact reproduction before conception

PRECONCEPTION

Chemical mixtures impact reproduction before conception

DISRUPTED EPIGENETICS
Oocytes and spermatozoa
Uterine receptivity

DISRUPTED PREGNANCY
Fertilization, implantation, embryogenesis
Determine the extent to which maternal and paternal preconception urinary concentrations of phenol and phthalate mixtures were associated with birth outcomes.
02

STUDY DESIGN

PROSPECTIVE PRECONCEPTION COHORT
EARTH STUDY
STUDY DESIGN

Maternal Preconception Window

1 urine

Study Entry

Tx Cycle (n)

2 urines

Conception Cycle

2 urines

Pregnancy

6w 21w 34w

Birth

Maternal Prenatal Window

SAMPLE COLLECTION: URINE

Paternal Preconception Window

1 urine

Study Entry

Tx Cycle (n)

1 urine

Conception Cycle

1 urine

Pregnancy

Birth

HARVARD

T.H. CHAN

SCHOOL OF PUBLIC HEALTH

MGH

1811
03

METHODS

EXPOSURES. OUTCOMES
METHODS

EXPOSURES

Urinary Concentrations
11 phthalate metabolites
BPA
Parabens
Mixtures

OUTCOMES

Medical Records
Birthweight (g)
Gestational age accuracy
Preterm Birth (<37 weeks)
MIXTURE OF CHEMICALS
Individual preconception windows
Couples' joint window

PRINCIPAL COMPONENT ANALYSIS
PCA

BAYESIAN KERNAL MACHINE REGRESSION
BKMR
**PCA**
- Reduces individual biomarker concentrations into uncorrelated groups (factors) based on the correlation structure
- Useful for the real-life exposure patterns and potential shared sources
- Regression models were fit to examine the association between the PCA-derived groups and birth outcomes

**BKMR**
- Univariate associations, interactions, and cumulative effect of the mixture
- Hierarchical variable selection in BKMR compares the relative importance of groups (e.g., maternal group vs paternal)
- PCA-derived factors informed groups within in maternal and paternal BKMR models
- Permits examination of relative impact of maternal vs paternal mixture groups on outcomes
COVARIATES
Selected a priori with a casual diagram
Maternal covariates added to paternal models

MATERNAL AND PATERNAL
Age, BMI, education, smoking, race, fertility treatment

COUPLE MODEL
Adjusted for all maternal and paternal covariates
RESULTS
PRETERM BIRTH AND BIRTHWEIGHT
RESULTS

**FEMALE**
N=384
83% Nulliparous
~ 35 years of age

**MALE**
N=211
27% Male Factor
~ 36 years of age

**COUPLES**
N=203
White Educated Non-Smokers
PRETERM BIRTH

RESULTS
### PCA MODELS

Table 1. Risk Ratio of Preterm Birth for every unit increase in PCA Factor Score

<table>
<thead>
<tr>
<th>PCA-derived factors</th>
<th>Adjusted RR (95%CI) Preterm Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maternal</td>
</tr>
<tr>
<td>DEHP-BPA factor</td>
<td>1.36 (1.00, 1.84)</td>
</tr>
<tr>
<td>Paraben factor</td>
<td>0.93 (0.65, 1.32)</td>
</tr>
<tr>
<td>High molecular weight phthalate factor</td>
<td>0.88 (0.61, 1.26)</td>
</tr>
<tr>
<td>Low molecular weight phthalate factor</td>
<td>0.96 (0.65, 1.41)</td>
</tr>
</tbody>
</table>
This BKMR derived figure depicts the association between a given exposure concentration and preterm birth, holding all other individual biomarkers at their median concentration.
RESULTS – PRETERM BIRTH

This BKMR derived figure depicts the association between a given exposure concentration and preterm birth, holding all other individual biomarkers at their median concentration.
Increasing trend of preterm birth estimate across quantiles of maternal and couples' total preconception mixture concentrations
RESULTS

**BKMR – Posterior Inclusion Probability (PIP)**

Maternal preconception model: DEHP-BPA high PIP

Paternal preconception model: DEHP-BPA high PIP

Couple-based model: similar PIP for maternal and paternal groups

**BKMR - SUMMARY**

Maternal preconception **BPA** – associated with higher preterm birth risk, holding all other biomarker concentrations at their median

Paternal preconception **DEHP** metabolites – associated with higher preterm birth risk, holding all other biomarker concentrations at their median

Higher preterm birth across quantiles of maternal and **couples’ total mixture** concentrations
BIRTHWEIGHT

RESULTS
## PCA MODELS

Table 2. Change in Birthweight (g) for every unit increase in PCA Factor Score

<table>
<thead>
<tr>
<th>PCA-derived factors</th>
<th>Adjusted Change in Birthweight (gram)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maternal</td>
</tr>
<tr>
<td>DEHP-BPA factor</td>
<td>-1.99 (-55.51, 51.53)</td>
</tr>
<tr>
<td>Paraben factor</td>
<td>-18.60 (-72.58, 35.39)</td>
</tr>
<tr>
<td>High molecular weight phthalate factor</td>
<td>16.95 (-37.31, 71.22)</td>
</tr>
<tr>
<td>Low molecular weight phthalate factor</td>
<td>-51.45 (-105.09, 2.18)</td>
</tr>
</tbody>
</table>

Zhang et al., Under Review
This BKMR derived figure depicts the association between a given exposure concentration and birthweight, holding all other individual biomarkers at their median concentration.
This BKMR derived figure depicts the association between a given exposure concentration and birthweight, holding all other individual biomarkers at their median concentration.
Decreasing trend of birthweight across quantiles of maternal, paternal and couples’ total preconception mixture concentrations

Zhang et al., Under Review
Maternal preconception model: DEHP-BPA high PIP

Paternal preconception model: DEHP-BPA and low molecular weight phthalate - high PIP

Couple-based model: higher PIP for **paternal mixture group** than maternal mixture group

Maternal preconception **BPA** exposure associated with decreased birthweight, holding all other biomarker concentrations at their median

Paternal preconception **MBP** exposure associated with decreased birthweight, holding all other biomarker concentrations at their median

Lower **birthweight** across quantiles of **maternal, paternal** and **couples’ total** mixture concentrations
CONCLUSIONS

INTERPRETATION AND IMPLICATIONS
## CONCLUSIONS

### MODELS | WINDOW | BIOMARKER/FACTOR | FINDING
---|---|---|---
PCA | Maternal | DEHP-BPA | Preterm birth
PCA | Paternal | DEHP-BPA | Preterm birth
PCA | Paternal | Paraben | Preterm birth
BKMR | Maternal | BPA | Preterm birth
BKMR | Maternal | Total Mixture | Preterm birth
BKMR | Paternal | DEHP | Preterm birth
BKMR | Couples | Total Mixture | Preterm birth
CONCLUSIONS

PRETERM BIRTH RISK

Maternal: DEHP-BPA, BPA, and Total Mixture

Paternal: DEHP-BPA, Paraben, DEHP

Couples: Total Mixture
<table>
<thead>
<tr>
<th>MODELS</th>
<th>WINDOW</th>
<th>BIOMARKER/FACTOR</th>
<th>FINDING</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR</td>
<td>Paternal</td>
<td>DEHP-BPA</td>
<td>↓ Birthweight</td>
</tr>
<tr>
<td>PCR</td>
<td>Paternal</td>
<td>LMWP</td>
<td>↓ Birthweight</td>
</tr>
<tr>
<td>BKMR</td>
<td>Maternal</td>
<td>BPA</td>
<td>↓ Birthweight</td>
</tr>
<tr>
<td>BKMR</td>
<td>Paternal</td>
<td>MBP</td>
<td>↓ Birthweight</td>
</tr>
<tr>
<td>BKMR</td>
<td>Maternal</td>
<td>Total Mixture</td>
<td>↓ Birthweight</td>
</tr>
<tr>
<td>BKMR</td>
<td>Paternal</td>
<td>Total Mixture</td>
<td>↓ Birthweight</td>
</tr>
<tr>
<td>BKMR</td>
<td>Couples</td>
<td>Total Mixture</td>
<td>↓ Birthweight</td>
</tr>
</tbody>
</table>
CONCLUSIONS

BIRTHWEIGHT

Paternal: DEHP-BPA, LMWP, MBP, and Total Mixture

Maternal: BPA, and Total Mixture

Couples’ Total Mixture
CONCLUSIONS

IMPLICATIONS

Fathers and Mothers phthalate and phenol mixtures contributed equally to preterm birth risk

Couples’ total mixture associated with lower birthweight

Fathers’ phthalate and phenol exposure reduces birthweight more than mothers’

Couples’ preconception health is a modifiable exposure

Interventions at the couple level before pregnancy attempt may improve perinatal outcomes
ACKNOWLEDGEMENTS

Preconception PFAS Exposure and Reproduction (PREPARE) Study R01ES031657 (PI: Messerlian)

NIEHS Program Officers
Antonia Calafat
Centers for Disease Control and Prevention

Dr John Petrozza
Dr Irene Souter
Vincent Center for Reproductive Biology
Massachusetts General Hospital

Vicente Mustieles
Yang Sun
Yixin Wang
Stelios Vagios
Paige Williams
THANK YOU

Carmen Messerlian, PhD
cmesser@hsph.harvard.edu

Yu Zhang, PhD student
yuzhang@hsph.harvard.edu

HARVARD
T.H. CHAN
SCHOOL OF PUBLIC HEALTH

SEED
Scientific Early Life
Environmental Health &
Development Program