Human Evidence: Environment and Gestational Diabetes

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Outline

I. Brief background

II. Bisphenol-A and GDM

III. Phthalates and Blood Glucose

IV. Air Pollution and GDM
Exposure to Environmental Chemicals

• Exposure to environmental chemicals and metals are ubiquitous
  • Air, water, soil, food, consumer products

• US pregnant women exposed
  • 43 chemicals (NHANES, 2003-2004)
Public Health Importance

Environmental chemical exposure during pregnancy may exacerbate progression of gestational diabetes mellitus (GDM) and may contribute to developing type II diabetes mellitus after pregnancy.


Type 2 Diabetes

- Two defects are required for progression of type 2 diabetes
  - Defect in insulin secretion (pancreatic b-cell dysfunction)
  - Defect in insulin action (insulin resistance)
BPA and GDM (2013)

Is bisphenol-A exposure during pregnancy associated with blood glucose levels or diagnosis of gestational diabetes?


Journal of Toxicology and Environmental Health, Part A, 76(14), 865-873
Specific Aim

Examine the association between maternal urinary BPA, blood glucose and diagnosis of GDM
Study Population

• GDM Cases (n=65) and controls (n=244) recruited from University of Oklahoma Medical Center Women’s & High Risk Pregnancy Clinics between August 2009 and May 2010
Eligibility Criteria

- Lived in 9 counties served by clinic (Oklahoma, Kingfisher, Logan, Lincoln, Pottawatomie, Cleveland, Canadian, McClain and Grady)

- ≥18 years of age

- No pre-existing type 1 or 2 diabetes

- Spoke English or Spanish
Pilot Study

• Training Grant Obtained for BPA Analyses

• Analyze Banked Samples for 22 GDM Cases and 72 Controls
Outcome Assessment

• Blood Glucose Levels
  • 1 hour 50 gram oral glucose challenge test

• Clinical Diagnosis of GDM (Carpenter et.al. 1982)
  • Initial screening value $\geq 135$ mg/dl
  • 3 hour 100 gram oral glucose tolerance test values exceeded thresholds $\geq 2$ time points
Exposure Assessment

• Spot urine sample collected at enrollment

• Total BPA (free + conjugates)

• Corrected for urinary dilution using specific gravity (SG)
BPA Exposure

• Tertiles
  • Tertile 1 (Referent): ≤0.99 μg/L
  • Tertile 2: >0.99 to <2.16 μg/L
  • Tertile 3: ≥2.16 μg/L
Covariates

- Enrollment Questionnaire
  - Age
  - Race/Ethnicity
  - Educational Level
  - Annual Household Income
  - Parity
  - Previous DX of GDM
  - Family HX type 2 DM
  - Self-reported pre-pregnancy BMI
  - Gestational age at enrollment
  - Active maternal smoking (urinary cotinine ≥15 ng/ml)
Statistical Methods

• Logistic Regression
  • Model odds of higher BPA exposure among GDM cases compared to odds of higher BPA exposure among controls

• Cases
  • No Family HX of type 2 DM (n=4)
  • Previous GDM DX (n=8)
  • Active smoker (n=0)
Statistical Methods

- Linear Regression
  - Model log blood glucose levels by categories of total urinary BPA concentrations
  - Limited to controls (n=72)
Summary of Results

• This study was unable to demonstrate an association between total urinary BPA concentrations and blood glucose levels or diagnosis of GDM in a low income and racially diverse obstetric population
Phthalates and Blood Glucose (2015)

• Urinary Phthalate Metabolite Concentrations and Blood Glucose Levels During Pregnancy

• Robledo, C. A., Peck, J. D., Stoner, J., Calafat, A. M., Carabin, H., Cowan, L., & Goodman, J. R.

• International Journal of Hygiene and Environmental Health, 218(3), 324-330
Study Population

- Pregnant women (n=110) recruited during first prenatal visit at OU Medical Center Women’s Clinic between February and June 2008

- Eligibility Criteria
  - \( \leq 22 \) weeks gestation
  - \( \geq 18 \) years of age
  - Spoke either English or Spanish
Study Population

- Ineligible
  - Medically threatened pregnancy
  - Multiple Gestation
  - History of Diabetes (type 1, 2 or GDM)
  - Preeclampsia
  - Preterm rupture of membranes
  - Preterm labor
- Restricted population to those with results for 1 hour 50 gram oral glucose tolerance test (n=72)
Outcome Assessment

- Blood glucose levels (n=72)
  - 1 hour 50 gram tolerance test

- Abnormal glucose test (n=15)
  - ≥ 135 mg/dl
Exposure Assessment

• Urine specimen collected at enrollment

• Centers for Disease Control, Division of Laboratory Sciences, National Center for Environmental Health

• Concentration of nine phthalate metabolites measured in urine
Covariates

- Maternal age
- Race/Ethnicity
- Annual Household Income
- Educational Level
- Pre-Pregnancy BMI
- Parity
- Gestational age at enrollment
- Gestational age at screening
- Active smoker (self reported or urinary cotinine >15 ng/ml)
Measured Phthalate Di-esters and Their Metabolites

*Molecular weight <250 Daltons is low and ≥250 Daltons is high.
Phththalate Exposure

- Tertiles

- Sum Variables
  - Parent Compound
    - DEHP
    - DBP
  - Molecular weight
    - Low (<250 Da)
    - High (≥250 Da)
Statistical Methods

- Descriptive statistics were calculated for all categorical and continuous sample characteristics (n=72)

- Geometric mean concentrations, 95% CI and distribution percentiles of unadjusted phthalate concentrations were calculated
Statistical Methods

• Linear Regression
  • Used to assess association between tertiles of exposure and blood glucose levels (mg/dL)

• Modified Poisson Regression with robust error variance
  • Multivariate adjusted risk ratios (RR) and 95% CI to ascertain whether urinary concentrations of phthalate metabolites associated with risk of having an abnormal glucose level at time of GDM screen

• Models were adjusted for urinary dilution by including urinary creatinine in model as independent factor
Statistical Methods

• Linear Regression
  • Interaction
    • Two-way interaction terms between covariates and examining parameter estimates for statistical significance (p<0.05)
  • Confounding
    • Examined by comparing estimates of model parameters (β) for each exposure of interest with individual covariates in model
    • Covariates retained in final model if controlling for covariate produced >10% change
Statistical Methods

• Poisson models for abnormal glucose (n=15)
  • 10 Events per variable rule
  • Confounding and Interaction not assessed
Summary

• When compared to women in the lowest tertile of phthalate exposure, pregnant women with urinary concentrations in the highest tertile had mean blood glucose levels that were 18 mg/dl lower.

• No associations were observed between phthalate metabolite urinary concentrations and the risk of an abnormal glucose level at GDM screen.
Strengths & Limitations

• Small sample size
  • Statistical power
  • Assessment of interaction and confounding

• Misclassification of Exposure
  • Half Life
  • Spot urine specimen

• Timing of Exposure Assessment
  • BPA (Cases 30 weeks, Controls 28 weeks)
    • About 4 weeks after screen
  • Phthalates (13 weeks)
    • About 15 weeks prior to screen
Strengths & Limitations

• First studies to examine associations between blood glucose levels, diagnosis of GDM and abnormal glucose levels (≥135 mg/dl) at GDM screen with phthalate and BPA exposure in pregnant women
Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus


Environmental research, 137, 316-322
Air Pollution and Inflammation

Air Pollution

- Danger Signals
- TLRs/NLRs
- Oxidative Stress (NADPH)
- Systemic Inflammation

Unhealthy Diet

- Gluconeogenesis ↑
- Lipid Deposition ↑
- Glucose Uptake ↓
- Insulin Resistance

Adapted from Liu et al. 2012
Air Pollution and Maternal Child Health

- Adversely impacts birth outcomes (Shah and Balkhair, 2011; Sram et.al. 2005)

- Air pollution in non-pregnant women linked to:
  - **Hypertension** (Basile and Block, 2012; Coogan 2012)
  - **Type 2 diabetes**
    - Prevalence (Brook et.al. 2008; Pearson et.al. 2010)
    - Incidence (Kramer et.al. 2010)
    - Mortality (Jarett et.al. 2005; Raaschou-Nielsen et.al. 2012)
Link with Pregnancy

- Gestational diabetes mellitus (GDM)
  - Precursor to type 2 diabetes in women
  - Insulin-resistant state

- During pregnancy
  - Nitrogen dioxides (NO\textsubscript{X}) associated with
    - GDM prevalence  (Malmqvist et.al. 2013)
    - Abnormal glucose tolerance  (Fleisch et.al., 2014)
Hypothesis

Pregnant women exposed to higher concentrations of criteria air pollutants are more likely to be diagnosed with GDM
GDM (Outcome)

- **Consortium of Safe Labor** (n=208,618) (PI: Grewal & Laughon)
  - Singleton deliveries
  - No pregestational diabetes

- GDM diagnosis (n=11,334)
  - EMR+Discharge ICD-9 Codes

- Covariates
  - Site, maternal race/ethnicity, maternal age, SES factors (i.e. health insurance), parity, pre-pregnancy BMI
Air Pollution (Exposure)

- **Air Quality and Reproductive Health Study**
  (PI: Mendola)

- Modified Community Multi-scale Air Quality Model (CMAQ)
  - Predicts ambient pollutant levels

- 15 Hospital Referral Regions (19 Hospitals)
  - 36 km domain
Criteria Air Pollutants (Exposure)

- Mean hourly exposure estimates

  - Ozone [O3] parts per billion (ppb)
  - Carbon Monoxide [CO] ppb
  - Nitrogen Oxides [NO, NO2, NOx] ppb
  - Sulfur Dioxide [SO2] ppb
  - Particulate Matter [PM10]
    - 2.5 to 10 mg/m3
  - Fine Particulate Matter [PM2.5]
    - <2.5 mg/m3
Standard Exposure Windows

• Preconception Period (91 days prior to LMP)

• First Trimester (LMP to 13 weeks 6 days)

• Weekly Averages (Gestational weeks 1-28)
Statistical Analyses

- Binary regression models with the log link function

- Estimate RRs of GDM
  - per 1-unit increase in PM and SO2
  - per each 10-ppb increase in NOX, O3 and CO

- Adjusted for study site, maternal age and race
Sensitivity Analyses

- Examined consistency of the association between air pollution and GDM in models
  - Adjusted for other pollutants
  - Stratified by body mass index
Adjusted RR and 95% CI sfor association between GDM and each 1-unit increase in air pollutant levels among CSL singleton pregnancies (n=219, 952), 2002-2008

<table>
<thead>
<tr>
<th>Criteria Air Pollutant</th>
<th>Preconception</th>
<th>First Trimester</th>
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<tbody>
<tr>
<td>PM$_{2.5}$ (mg/m$^3$)</td>
<td>0.995 [0.987,1.003]</td>
<td>0.989 [0.978,1.000]</td>
</tr>
<tr>
<td>PM$_{10}$ (mg/m$^3$)</td>
<td>0.999 [0.994,1.004]</td>
<td>1.005 [0.999,1.009]</td>
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<tr>
<td>NO$_X$ (ppb)</td>
<td>1.014 [1.007,1.022]</td>
<td>1.009 [1.002,1.016]</td>
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<tr>
<td>SO$_2$ (ppb)</td>
<td>1.015 [1.004,1.026]</td>
<td>0.999 [0.987,1.013]</td>
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<tr>
<td>CO (ppb)</td>
<td>1.000 [0.999,1.001]</td>
<td>0.999 [0.999,1.001]</td>
</tr>
<tr>
<td>O$_3$ (ppb)</td>
<td>0.972 [0.959,0.986]</td>
<td>0.999 [0.987,1.013]</td>
</tr>
</tbody>
</table>
Adjusted RRs and their 95% CI for the association between GDM and a 1-ppb increase in SO2 from 3 months prior to conception through gestational week 28*

* P represents risk for the average 3 months prior to conception. All estimates adjusted for maternal age, race and site.
Summary

• We demonstrate in a large retrospective cohort of pregnancies that the risk of GDM

  • Increased with NO\textsubscript{X} and SO\textsubscript{2} exposures at preconception and through the first seven weeks of pregnancy

  • Decreased with ozone exposures at preconception but increase later in pregnancy

  • Not associated with particulate matter or carbon monoxide exposures at preconception or during pregnancy
Conclusions

• Preconception and early pregnancy are critical windows for the effects of air pollution on GDM

• Emissions from traffic and fossil fuel combustion may largely account for observed associations between air pollution and GDM