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

The Environment and Diabetes

Thayer, K. A., Heindel, J. J., Bucher, J. R., & Gallo, M. A. (2012). Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review. *Environ Health Perspect*, *120*(6), 779-789.

Kuo, C. C., Moon, K., Thayer, K. A., & Navas-Acien, A. (2013). Environmental chemicals and type 2 diabetes: an updated systematic review of the epidemiologic evidence. *Current diabetes reports*, *13*(6), 831-849.

Taylor, K. W., Novak, R. F., Anderson, H. A., Birnbaum, L. S., Blystone, C., DeVito, M., ... & Lind, L. (2013). Evaluation of the association between persistent organic pollutants (POPs) and diabetes in epidemiological studies: a national toxicology program workshop review. *Environmental health perspectives*, *121*(7), 774-783.

Everett, C. J., & Matheson, E. M. (2010). Biomarkers of pesticide exposure and diabetes in the 1999–2004 National Health and Nutrition Examination Survey. *Environment international*, *36*(4), 398-401.

Howard, S. G., Heindel, J. J., Thayer, K. A., & Porta, M. (2011). Environmental pollutants and beta cell function: relevance for type 1 and gestational diabetes. *Diabetologia*, *54*(12), 3168-3169.

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?

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

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 ≥135 mg/dl
  - 3 hour 100 gram oral glucose tolerance test values exceeded thresholds ≥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
  - ≤22 weeks gestation
  - ≥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

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

Phthalate 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 were18 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

Air Pollution and GDM (2015)

Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus

Robledo, C. A., Mendola, P., Yeung, E., Männistö, T., Sundaram, R., Liu, D., ... & Grantz, K. L. (2015)

Environmental research, 137, 316-322

Air Pollution and Inflammation

Air Pollution + **Unhealthy Diet**

↓

Danger Signals

↓

TLRs/NLRs

↓

Oxidative Stress (NADPH)

↓

Systemic Inflammation

Gluconeogenesis ↑
Lipid Deposition ↑
Glucose Uptake ↓

↓

Insulin Resistance

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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_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)

- **C**onsortium of **S**afe **L**abor (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)

- **A**ir **Q**uality and **R**eproductive **H**ealth 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

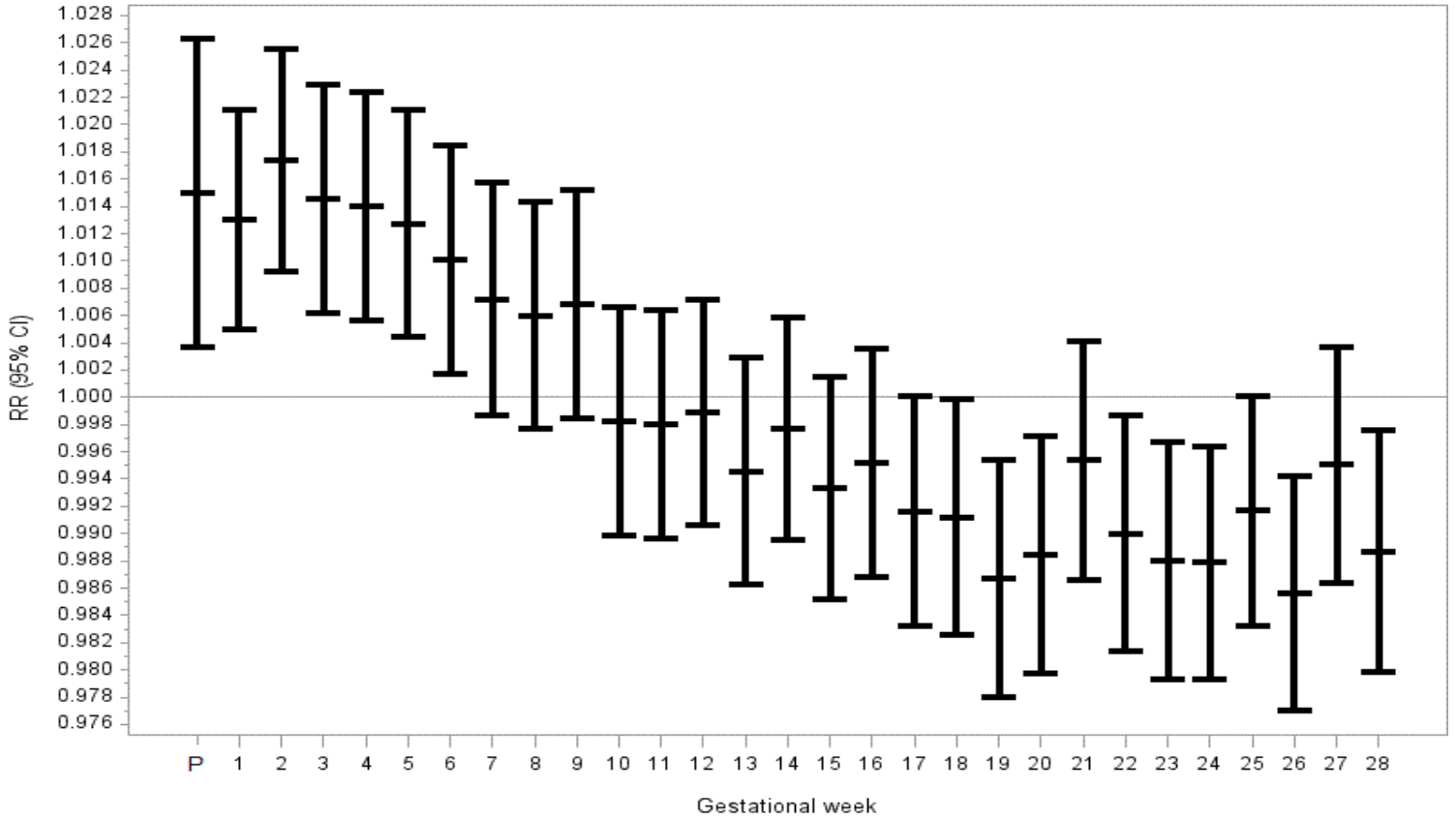
Sensitivity Analyses

- 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

	Preconception	First Trimester
Criteria Air Pollutant		
$PM_{2.5}$ (mg/m^3)	0.995 [0.987,1.003]	0.989 [0.978,1.000]
PM_{10} (mg/m^3)	0.999 [0.994,1.004]	1.005 [0.999,1.009]
NO_X (ppb)	1.014 [1.007,1.022]	1.009 [1.002,1.016]
SO_2 (ppb)	1.015 [1.004,1.026]	0.999 [0.987,1.013]
CO (ppb)	1.000 [0.999,1.001]	0.999 [0.999,1.001]
O_3 (ppb)	0.972 [0.959,0.986]	0.999 [0.987,1.013]

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_X and SO_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