Air Pollution Exposure for Reproduction and Pregnancy: Critical Windows and Implications for Population Health

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Ambient Air Pollution and Health

• WHO: 4.2 million premature deaths each year (contributed to 7.6% of deaths in 2016)
  • 58% due to ischemic heart disease and stroke
  • 18% to COPD
  • 18% to acute lower respiratory infections
  • 6% to lung cancer

• Relationship of air pollution with other health outcomes less clear

• Events during reproduction and pregnancy may be particularly susceptible
Air Pollution During Reproduction and Pregnancy

**Paternal**
- Semen quality
- DNA integrity
- Epigenetics/gene expression

- Oocyte quality
- Endometrial function
- Hormones

- Invasion of trophoblast cells
- Vascularization

**Maternal Adaptation to Pregnancy**
- Increased blood volume/cardiac output
- Increased blood glucose

**Preconception**

**Embryogenesis**

**Implantation + Placentation**

**Early pregnancy**

**Late pregnancy**
Population Health Impact of Pregnancy Complications

• Pregnancy complications are common and have major impacts on population health:

<table>
<thead>
<tr>
<th>Reproductive Outcomes</th>
<th>Complications of Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility</td>
<td>Preterm birth ~10% pregnancies</td>
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<tr>
<td>1 in 8 couples</td>
<td>Gestational diabetes 2-10% pregnancies</td>
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<tr>
<td>Pregnancy loss</td>
<td>Hypertensive disorders of pregnancy 5-8% pregnancies</td>
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<td>20-30% pregnancies</td>
<td>Low birthweight/growth restriction ~8% pregnancies</td>
</tr>
</tbody>
</table>
Our Work in the Epidemiology Branch, NICHD
Epidemiology Branch, Division of Intramural Population Health Research, NICHD

- Reproductive, perinatal and pediatric epidemiology
- Investigator-initiated prospective cohort studies and clinical trials:
  - High-risk, high-reward research
  - Studies with broad public health impact unlikely to be conducted in extramural research programs
- Focus on modifiable risk factors: environmental exposures, behavioral factors, low-cost medications/supplements
- Postdoctoral, predoctoral and post-baccalaureate training/mentoring
Our Current Air Pollution Research

<table>
<thead>
<tr>
<th>Preconception</th>
<th>LIFE Study</th>
<th>Outcome: Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paternal and Maternal</td>
<td>N=501 couples attempting pregnancy</td>
<td></td>
</tr>
<tr>
<td>Embryogenesis, Implantation and Placentation</td>
<td>Regions: Michigan and Texas</td>
<td></td>
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<tr>
<td>Early pregnancy</td>
<td>Years: 2005-2009</td>
<td></td>
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<tr>
<td>Late pregnancy</td>
<td>Consecutive Pregnancies Study</td>
<td></td>
</tr>
<tr>
<td>Maternal Adaptation to Pregnancy</td>
<td>N=50,005 women with 2+ deliveries</td>
<td></td>
</tr>
<tr>
<td>Region: Utah</td>
<td>Years: 2002-2010</td>
<td></td>
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</tbody>
</table>
LIFE Study – Estimation of Air Pollution

• Modified CMAQ models (developed 2011-2013)
  • Qi Ying, Associate Professor, Environmental and Water Resources Division, Zachry Department of Civil Engineering, Texas A&M University

• Modeled air pollution estimates (4x4 km grid cells) linked to participants’ residential address

• Model results fused with monitor data to improve performance
LIFE Study – Air Pollution Estimates

• Air pollutant species assessed:
  • Particulate matter (PM$_{10}$, PM$_{2.5}$), O$_3$, CO, NO$_x$/NO$_2$, SO$_2$

• Moderate levels of daily air pollution exposure:
  • O$_3$: Median 26.8 (IQR 19.8, 34.2) ppb
  • NO$_x$: Median 9.2 (IQR 5.1, 15.6) ppb
  • PM$_{2.5}$: Median 10.9 (IQR 8.0, 14.9) $\mu$g/m$^3$

• Risk models are based on interquartile range (IQR) change in air pollution exposure
LIFE Study: Probability of Pregnancy

Menstrual Cycle

- Ovulation
- Recruited Follicle
- Maturing Follicle
- Ovulation
- Corpus Luteum
- Degenerate C. Luteum

Detectable hCG

Ovulation

Implantation

Growth of endometrium

Next menstrual cycle or pregnancy

Ovulation and Implantation

https://commons.wikimedia.org/wiki/File:Human_Fertilization.png
Air Pollution Exposure Windows

Menstrual Cycle

• Acute daily windows of exposure:
  • Daily ambient air pollution exposure from 5 days before to 10 days following ovulation

Daily Average: -5 to 10 days surrounding ovulation

https://commons.wikimedia.org/wiki/File:Human_Fertilization.png
Main Findings: Air Pollution and Fecundability

Acute daily air pollution exposure and fecundability

Our Current Air Pollution Research

Preconception
Paternal and Maternal

Early pregnancy
Embryogenesis, Implantation and Placentation

Late pregnancy
Maternal Adaptation to Pregnancy

LIFE Study
N=501 couples attempting pregnancy
Regions: Michigan and Texas
Years: 2005-2009

Consecutive Pregnancies Study
N=50,005 women with 2+ deliveries
Region: Utah
Years: 2002-2010

Outcomes:
Growth restriction
Preeclampsia
Consecutive Pregnancy Study – Estimation of Air Pollution

- Modified CMAQ models (developed 2011-2013)
  - Qi Ying, Associate Professor, Environmental and Water Resources Division, Zachry Department of Civil Engineering, Texas A&M University

- Modeled air pollution estimates (12x12 km grid cells) across hospital referral region
- Model results fused with monitor data
- Estimates weighted for population density
Consecutive Pregnancies Study – Air Pollution Estimates

• Air pollutant species assessed:
  • Particulate matter (PM$_{10}$, PM$_{2.5}$), O$_3$, CO, NO$_x$, SO$_2$

• Moderate levels of first trimester air pollution exposure:
  • O$_3$: Median 42.5 (IQR 39.4, 44.5) ppb
  • NO$_x$: Median 16.6 (IQR 13.5, 20.9) ppb
  • PM$_{2.5}$: Median 7.5 (IQR 6.5, 9.8) μg/m3

• Risk models are based on interquartile range (IQR) change in air pollution exposure
Air Pollution and Fetal Growth Restriction

- Fetal growth restriction associated with significant adverse outcomes for offspring:
  - Stillbirth and neonatal morbidity and mortality
  - Developmental outcomes in childhood
  - Chronic disease risk in adulthood

- Affected 1.5% of pregnancies in the Consecutive Pregnancies Study
Exposure in 3rd trimester associated with higher risk of being <10th percentile birthweight

Exposure throughout gestation associated with diagnosed fetal growth restriction

Air Pollution and Hypertensive Disorders of Pregnancy

• Hypertensive disorders of pregnancy:
  • *Gestational hypertension*: Newly elevated blood pressure after 20 weeks’ gestation
  • *Preeclampsia*: Newly elevated blood pressure with additional organ dysfunction

• Gestational hypertension affected 4.0% and preeclampsia 3.2% of pregnancies in the Consecutive Pregnancies Study
Exposure in 2nd trimester associated with higher risk of gestational hypertension.

Exposure in the 1st trimester associated with lower risk of preeclampsia.

Challenges and Implications of Population Health Research in Air Quality
Strengths and Limitations Ambient Exposure

**Strengths**
- Reduces certain types of bias (e.g. individual behavior)
- Rich data on change in air pollution over time allows for examination of most relevant windows of exposure
- Practicality – cost and participant burden
- Translation of findings to policy

**Limitations**
- Misclassification of personal exposure will most likely lead to underestimation
- Can introduce spatial biases (e.g. neighborhood socioeconomic status)
Spatial and Temporal Resolution

• Ideally want high spatial and temporal resolution:
  • **Spatial resolution**: Approximation of personal exposure
  • **Temporal resolution**: Estimation of biologically relevant windows
  • Poor choice of resolution will increase misclassification

• Additional question of *where* an individual is mostly likely to be exposed and at what buffer: residence, workplace, etc.
Air Pollution Exposure as a Mixture

• Strong correlations and interdependency between air pollution species creates difficulty separating out effects:
  • Recent development of new mixture modeling techniques
  • Application of methods limited by availability of data on relevant co-pollutants and differences in their precision

• Additionally, statistical power often limited to evaluate non-linear, threshold and interaction effects
Policy Implications of Future Work

• Improve our understanding of critical exposure windows
  • Chronic and acute effects of air pollution

• Identify shared mechanistic pathways
  • Potential broad effects on reproduction and pregnancy

• Identify thresholds of risk for ambient air pollution in relation to reproductive and early childhood health to inform regulation
  • Majority of participants in our studies exposed to air pollution levels well below regulatory standards
## LIFE Study – Air Pollution Levels

Distribution of the daily mean of criteria pollutants 5 days before ovulation

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Min</th>
<th>25&lt;sup&gt;th&lt;/sup&gt;</th>
<th>Median</th>
<th>75&lt;sup&gt;th&lt;/sup&gt;</th>
<th>Max</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
<td>0.5</td>
<td>1.1</td>
<td>2.0</td>
<td>11.8</td>
<td>1.5</td>
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<tr>
<td>O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3.3</td>
<td>19.8</td>
<td>26.8</td>
<td>34.2</td>
<td>66.1</td>
<td>14.4</td>
</tr>
<tr>
<td>NO&lt;sub&gt;x&lt;/sub&gt;</td>
<td>0.2</td>
<td>5.1</td>
<td>9.2</td>
<td>15.6</td>
<td>171.0</td>
<td>10.5</td>
</tr>
<tr>
<td>NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.1</td>
<td>3.7</td>
<td>6.6</td>
<td>10.4</td>
<td>47.5</td>
<td>6.7</td>
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<tr>
<td>CO</td>
<td>52</td>
<td>157</td>
<td>219</td>
<td>291</td>
<td>1250</td>
<td>134</td>
</tr>
<tr>
<td>PM&lt;sub&gt;10&lt;/sub&gt;</td>
<td>0.3</td>
<td>12.8</td>
<td>21.4</td>
<td>29.3</td>
<td>64.5</td>
<td>16.5</td>
</tr>
<tr>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>0.6</td>
<td>8.0</td>
<td>10.9</td>
<td>14.9</td>
<td>32.0</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Gaseous pollutants in ppb and PM in μg/m<sup>3</sup>
Consecutive Pregnancies Study

• Correlation of air pollutants (Spearman rank)

Table A.2. Correlation of air pollutants during the first trimester, first pregnancy only (n=50,005)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>SO(_2)</th>
<th>O(_3)</th>
<th>NO(_X)</th>
<th>NO(_2)</th>
<th>CO</th>
<th>PM(_{2.5})</th>
<th>PM(_{10})</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO(_2)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O(_3)</td>
<td>-0.10</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO(_X)</td>
<td>0.21</td>
<td>-0.46</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO(_2)</td>
<td>0.43</td>
<td>-0.44</td>
<td>0.94</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>0.23</td>
<td>-0.36</td>
<td>0.92</td>
<td>0.87</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM(_{2.5})</td>
<td>0.33</td>
<td>-0.36</td>
<td>0.80</td>
<td>0.84</td>
<td>0.64</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PM(_{10})</td>
<td>0.67</td>
<td>-0.06</td>
<td>0.32</td>
<td>0.48</td>
<td>0.38</td>
<td>0.50</td>
<td>1</td>
</tr>
</tbody>
</table>

SO\(_2\), sulfur dioxide; O\(_3\), ozone; NO\(_X\), nitrogen oxides; NO\(_2\), nitrogen dioxide; CO, carbon monoxide; PM\(_{2.5}\), fine particulate matter <2.5 microns; PM\(_{10}\), particulate matter <10 microns

\(^a\)Spearman correlation coefficients
Air Pollution and Other Reproductive Outcomes

**Semen quality**: No clear associations, apart from a suggested relationship with sperm head defects

**Pregnancy loss**: Exposure in the first half of pregnancy associated with higher risk of loss:
- Ozone: Hazard Ratio= 1.13 (95% CI 1.08, 1.18)
- PM$_{2.5}$: Hazard Ratio= 1.13 (95% CI 1.03, 1.24)

Air Pollution and Health During Pregnancy

• Meta-analysis of existing studies suggests ozone and particulate matter may increase risk of preterm birth:
  • 10 ppb increase in O$_3$ – 3% increased risk (95% CI 1-4%)
  • 10 µg/m$^3$ increase in PM$_{10}$ – 9% increased risk (95% CI 3-16%)
  • 10 µg/m$^3$ increase in PM$_{2.5}$ – 24% increased risk (95% CI 8-41%)

• Suggested associations with lower term birthweight, but less clear
Next Steps: Air Pollution and Reproductive Health

Grant Submission: Air pollution and reproductive health

• Examine air pollution and reproductive outcomes in clinical trials
  • 1,228 women attempting pregnancy randomized to low-dose aspirin or placebo
  • 2,370 couples receiving infertility treatment with male partner randomized to zinc + folic acid or placebo
  • Evaluate biologic mechanisms (biomarkers of inflammation and oxidative stress) and leverage randomization to aspirin

• Air Pollution and Infertility Treatment Outcomes in Maryland
  • Air pollution and temperature exposure with outcomes of infertility treatment (*in vitro* fertilization and intrauterine insemination/ovulation induction)
Longitudinal Investigation of Fertility and the Environment (LIFE) Study

Prospective study of pregnancy and pregnancy loss

  - Followed until a positive pregnancy test or 12 months attempting pregnancy
  - Pregnant women followed through pregnancy

- Couple-based approach

Preconception
  - Paternal and Maternal

Early pregnancy
  - Embryogenesis, Implantation and Placentation

Late pregnancy
  - Maternal Adaptation to Pregnancy
Consecutive Pregnancies Study

Retrospective review of medical records
- 50,005 women with two or more singleton pregnancies (2002-2010)
  - 20 sites in Utah’s Intermountain Healthcare System
  - Data abstracted from delivery hospitalization records and ICD9 codes
Systemic Health Effects of Air Pollution

Air pollution associated with significant *morbidity/mortality*:

- Systemic increases in inflammation + oxidative stress
- Translocation of particles and gases

Effects on *pregnancy* less clear

- Whole- and late-pregnancy exposure with preterm birth and low-birthweight