Heightened susceptibility
A review of how pregnancy and chemical exposures influence maternal health

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Collaborative on Health and the Environment
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Presentation outline

• Background
• What we did
• What we found
• Conclusions
• Implications
Pregnancy: A unique period of rapid biological changes
Overview of physiological changes during pregnancy

• Placenta invades maternal tissues and blood vessels to redirect maternal blood flow to fetus
• Cardiovascular system increases cardiac output and heart/respiratory rates while decreasing blood pressure
• Metabolic system shifts from glucose to fat, increasing insulin resistance to pre-diabetic condition
• Reproductive system prepares for lactation as mammary glands differentiate and prepare for milk production
• Endocrine system drives physiological changes through tightly coordinated and complex series of molecular signaling pathways
Borderline disease state of pregnancy increases disease risk

Physiological changes during pregnancy require maternal adaptation to overcome
- >200% increased production of insulin
- Sustained vasodilation rather than vasoconstriction
- Exponential sustained rise in reproductive hormones

Figure 1: Biological changes to blood vessels, metabolism, and breast tissue during pregnancy can heighten susceptibility pregnancy-related health complications, such as preeclampsia and gestational diabetes, as well as future breast cancer risk. Image created by Swati Rayasam.

Maternal health complications and breast cancer

<table>
<thead>
<tr>
<th>Pregnancy-induced hypertensive disorders</th>
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<tbody>
<tr>
<td><strong>Pregnancy-induced hypertension</strong></td>
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<tr>
<td>New-onset high blood pressure &gt;= 20 weeks gestation</td>
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<tr>
<td><strong>Preeclampsia (PE)</strong></td>
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<td>Pregnancy-induced hypertension with &gt;= 1 systemic symptom (e.g., proteinuria)</td>
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<td><strong>HELLP syndrome</strong></td>
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<td>Hemolysis, elevated liver enzymes and low platelets</td>
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<td><strong>Eclampsia</strong></td>
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<td>Severe progression of PE that presents with additional stroke or seizure</td>
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<th>Gestational diabetes mellitus (GDM)</th>
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<td>Maternal insulin levels insufficient to meet increased metabolic demands of pregnancy</td>
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<th>Pregnancy-associated breast cancer (PABC)</th>
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<td>Breast cancer diagnosed during pregnancy or in the first postpartum year</td>
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**Maternal complications and breast cancer contribute to a significant proportion of women’s health issues**
### Concerning trends and statistics

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<th>Pregnancy-induced hypertensive disorders</th>
<th>Gestational diabetes mellitus (GDM)</th>
<th>Breast cancer</th>
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</thead>
<tbody>
<tr>
<td>• Leading cause of maternal morbidity/mortality worldwide</td>
<td>• Affects 14–18% of pregnant women worldwide</td>
<td>• Leading cause of cancer mortality among women worldwide</td>
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<tr>
<td>• 5–10% (~ 8 million) pregnancies</td>
<td>• 10–100% increased prevalence over past 20 years</td>
<td>• 14–20% increased incidence and mortality risk over last decade</td>
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<td>• 25% increase over past 20 years</td>
<td>• Additional increases expected due to recent diagnostic criteria changes and rising</td>
<td>• Pregnancy-associated breast cancer (PABC) contributes 10–20% of total incidence among younger women (&lt; 30 years old), with incidence rising alongside global trends in delayed childbearing</td>
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<tr>
<td>• 5-fold increased risk of severe PE among young U.S. women</td>
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- PE, GDM, and breast cancer share common pathophysiological elements and complex risk patterns
- Multifactorial diseases with unexplained complex etiologies
Pregnant women are ubiquitously exposed to environmental chemicals

Phthalates, phenols (e.g., BPA), per- and polyfluoroalkyl substances (PFASs), polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), pesticides (DDT/DDE), metals (e.g., lead, arsenic), etc.

**Aim 1**
Examine maternal-fetal PBDE levels and cross-tissue correlation among potentially vulnerable groups.

**Aim 2**
Investigate association of placental PBDE levels with biomarkers of placental development/disease.

**Biomarkers of Placental Development and Disease**
- Pregnancy Complications
- Adverse Birth Outcomes
- Chemical Exposure
  - Reproductive and developmental harm
  - Chronic high body burden levels
Heightened susceptibility to chemical exposures during pregnancy

- Dramatic changes to vascular physiology, metabolism, reproductive organs, endocrine activity, and the immune system can increase maternal susceptibility to chemical exposures and associated health risks
  - *Ex.* Lifetime lead accumulation released from bones over the course of pregnancy
- Yet, maternal health risks for most environmental chemicals not characterized
Structured search and narrative review of epidemiologic literature

<table>
<thead>
<tr>
<th>Category</th>
<th>Terms</th>
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### Overview of epidemiologic studies

<table>
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<tr>
<th>Health outcome</th>
<th>Number of studies</th>
<th>Sample size range</th>
<th>Study design</th>
</tr>
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<tbody>
<tr>
<td>PE including blood pressure and pregnancy-induced hypertension (PIH) as clinical PE indicators</td>
<td>37</td>
<td>58 to 295,374</td>
<td>Mostly case control studies due to small number of PE cases (~25–85)</td>
</tr>
<tr>
<td>GDM and/or gestational impaired glucose tolerance (IGT)</td>
<td>24</td>
<td>200 to &gt;81,000</td>
<td>Mostly cohort studies (15–406 cases)</td>
</tr>
<tr>
<td>Maternal breast cancer</td>
<td>3</td>
<td>224 to 483</td>
<td>Nested case-control (112–250 cases) with long-term follow-up period in cohort</td>
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- Total 64 epidemiologic studies since 2000
- Methodological considerations include multiple sources of epidemiological bias
PE and chemical exposures

37 studies

Persistent organic pollutants (8)

Pesticides (10)

Non-persistent chemicals (9)

Metals (13)

Modest increasing association between high PFAS exposure levels and PE

Mixed results found for DDT/DDE and PE (both increasing and inverse associations), and high exposure levels associated with increased risk in African but not U.S. populations

Some evidence of increasing association between BPA or phthalates and PE, but differences in sampling matrix, timing of measurement, confounding adjustment, study population, and correction for urine dilution makes comparability difficult

Divergent blood pressure associations with phthalates and phenols also found

Increased risk associated with lead, cadmium, and to a lesser extent mercury and arsenic (issues with study comparability)
GDM and chemical exposures

24 studies

Persistent organic pollutants (10)

Pesticides (6)

Non-persistent chemicals (5)

Metals (7)

Some evidence of increasing but non-linear dose response associations found for PCBs or PBDEs and GDM risk, but mixed results and limited comparability due to variable study locations, exposure levels, and timing of measurement (just before conception to soon after delivery).

PFAS associated with GDM and/or IGT in 3 studies across diverse locations.

Null associations largely found for non-persistent chemicals, although positive association identified with occupation as cosmetologist or manicurist.

Increased GDM or IGT risk associated with arsenic in water and non-urinary biomatrices (i.e., blood, meconium, and nails), with evidence of increasing dose-response relationship. First trimester identified as potential window of vulnerability in one prospective analysis.
BC and chemical exposures

3 studies

Persistent organic pollutants (2)

Pesticides (1)

Ratio of PCB congeners (deleterious/protective) associated with three-fold higher breast cancer risk, indicating deleterious association outweighed protective associations

Mixed results found for PFAS and breast cancer risk. However, PFOSA and PFHxS associated with more than 3-fold increase and decrease in maternal breast cancer risk, respectively, among younger Danish pregnant women (diagnosed < 40 years old) in one study

DDT/DDE associated with increased breast cancer risk in young women, suggesting importance of early life exposures (imprecise risk estimates)

Limited studies due to long-term follow-up required for breast cancer
Conclusions

• Sufficient evidence to justify concern about impact of chemical exposures on women’s health

• Substantial variation in study design, method of measurement, and analytical approach limit study comparability and interpretation of literature

• Efforts to incorporate deliberate biomarker selection, appropriate timing and method of measurement, consistent analysis of confounders, cumulative exposures, and non-linear associations
Research recommendations

- Leveraging existing studies to evaluate maternal outcomes
- Incorporating biomarkers to strengthen epidemiologic research
- Recognizing pregnancy as a critical period for women’s health

**Figure 1.** Vulnerable stages for adverse maternal health outcomes across the life course.

Varshavsky et al. 2019 Reproductive Toxicology
Consideration of pregnancy as a sensitive window of development for women in chemical risk assessment

Don’t put pregnancy in a corner: It’s about more than fetal health

Focus on study populations with greater vulnerability and underlying baseline disease risk
Thank you

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