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Obstetrics, Gynecology
& Reproductive Sciences

Heightened susceptibility

A review of how pregnancy and chemical exposures influence maternal health

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Generation Chemical Webinar
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Presentation outline

- Background
- What we did
- What we found
- Conclusions
- Implications

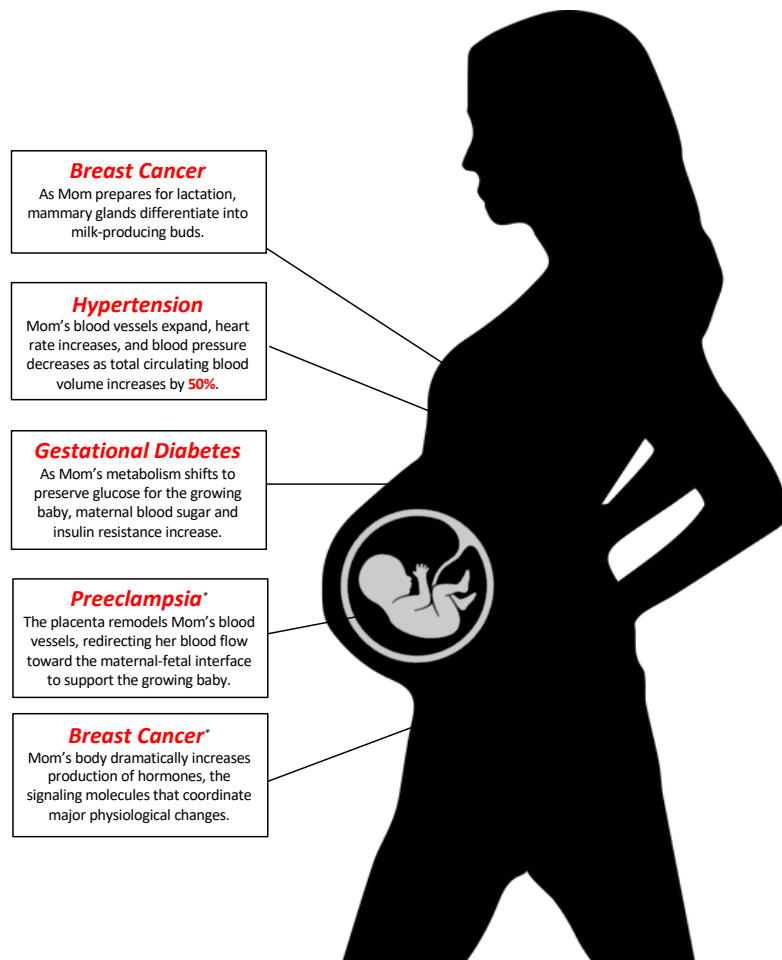
Pregnancy: A unique period of rapid biological changes



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

Pregnancy-induced hypertensive disorders



Pregnancy-induced hypertension

New-onset high blood pressure \geq 20 weeks gestation

Preeclampsia (PE)

Pregnancy-induced hypertension with \geq 1 systemic symptom (e.g., proteinuria)

HELLP syndrome

Hemolysis, elevated liver enzymes and low platelets

Eclampsia

Severe progression of PE that presents with additional stroke or seizure

Gestational diabetes mellitus (GDM)

Maternal insulin levels insufficient to meet increased metabolic demands of pregnancy

Pregnancy-associated breast cancer (PABC)

Breast cancer diagnosed during pregnancy or in the first postpartum year

Maternal complications and breast cancer contribute to a significant proportion of women's health issues

Concerning trends and statistics

Pregnancy-induced hypertensive disorders

- Leading cause of maternal morbidity/mortality worldwide
- 5–10% (~ 8 million) pregnancies
- 25% increase over past 20 years
- 5-fold increased risk of severe PE among young U.S. women

Gestational diabetes mellitus (GDM)

- Affects 14–18% of pregnant women worldwide
- 10–100% increased prevalence over past 20 years
- Additional increases expected due to recent diagnostic criteria changes and rising

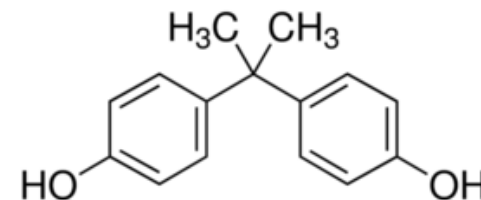
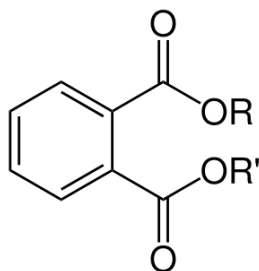
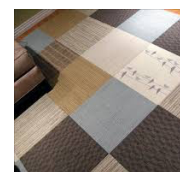
Breast cancer

- Leading cause of cancer mortality among women worldwide
- 14–20% increased incidence and mortality risk over last decade
- Pregnancy-associated breast cancer (PABC) contributes 10–20% of total incidence among younger women (< 30 years old), with incidence rising alongside global trends in delayed childbearing

- 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.



Chronic high body burden levels

Reproductive and developmental^B harm

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

Chemical exposure *during pregnancy* and PE, GDM, or breast cancer *during or after pregnancy*

Varshavsky et al. 2019
Reproductive Toxicology

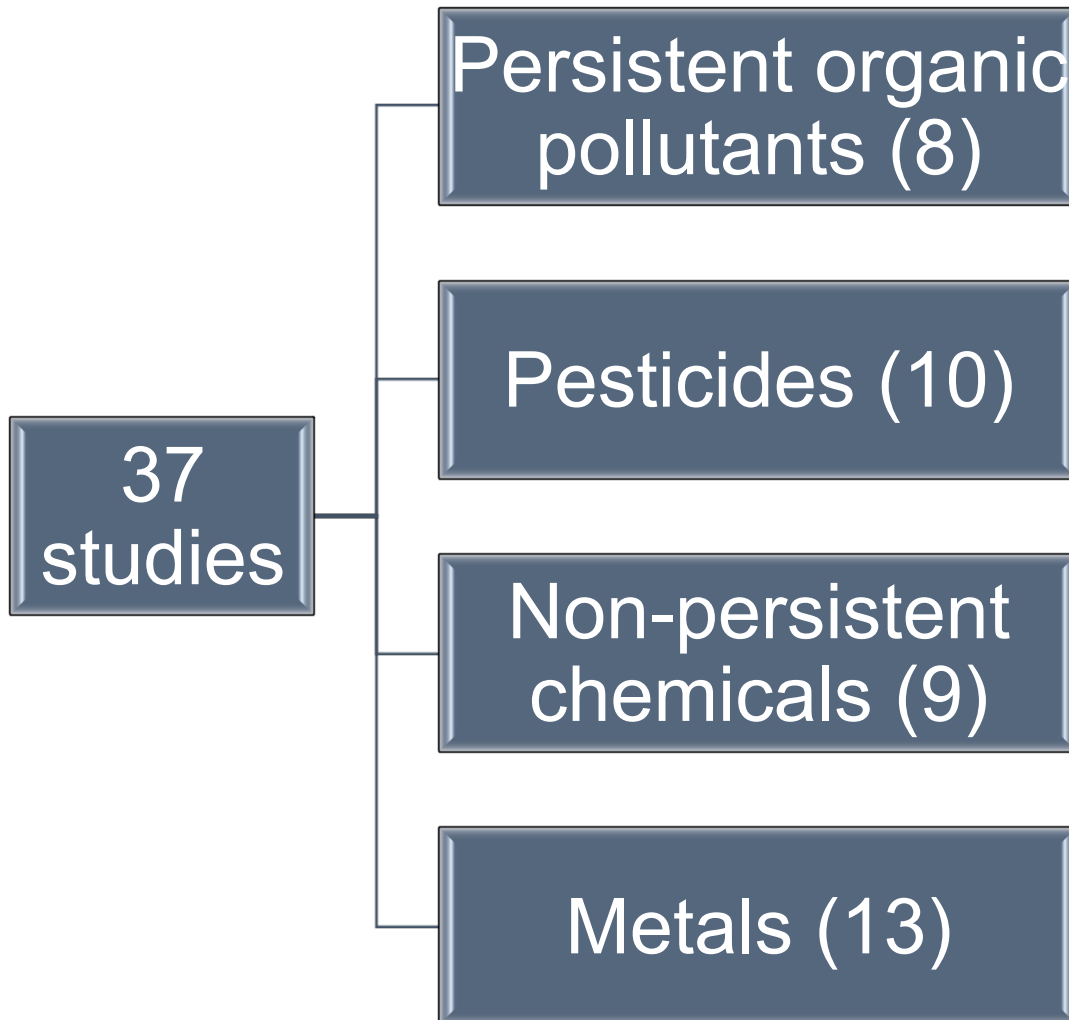
Category	Terms
(1) During pregnancy	(pregnancy[MeSH Terms] OR pregnant women[MeSH Terms] OR pregnancy[tiab] OR pregnant[tiab] OR mothers[MeSH Terms] OR prenatal[Title] OR maternal risk[tiab])
(2) Maternal Exposure	(chemical[tiab] OR endocrine disruptors[MeSH Terms] OR endocrine disruptors[tiab] OR environmental pollutants[MeSH Terms] OR environmental pollution[MeSH Terms] OR environmental exposure[mh] OR exposure[tiab] OR maternal exposure[mh])
(3) Maternal Outcome	(breast neoplasms[MeSH Terms] OR mammary glands, human[MeSH Terms] OR mammary gland[tiab] OR breast cancer[tiab] OR mammary cancer[tiab] OR breast density[MeSH Terms] OR breast density[tiab] OR mammographic density[tiab] OR "breast tissue"[tiab] OR "maternal complications"[tiab] OR "pregnancy complications"[tiab] OR placenta diseases[MeSH Terms] OR "placental weight"[Title] OR diabetes, gestational[MeSH Terms] OR blood pressure[MeSH Terms] OR hypertension[MeSH] OR pre-eclampsia[MeSH Terms] OR (Labor, Obstetric[mh] AND timing[tiab])) OR ("maternal breast cancer")
(4) #1 AND #2 AND #3	

Overview of epidemiologic studies

Health outcome	Number of studies	Sample size range	Study design
PE including blood pressure and pregnancy-induced hypertension (PIH) as clinical PE indicators	37	58 to 295,374	Mostly case control studies due to small number of PE cases (~25–85)
GDM and/or gestational impaired glucose tolerance (IGT)	24	200 to >81,000	Mostly cohort studies (15–406 cases)
Maternal breast cancer	3	224 to 483	Nested case-control (112–250 cases) with long-term follow-up period in cohort

- Total 64 epidemiologic studies since 2000
- Methodological considerations include multiple sources of epidemiological bias

PE and chemical exposures



Modest increasing association between high PFAS exposure levels and PE

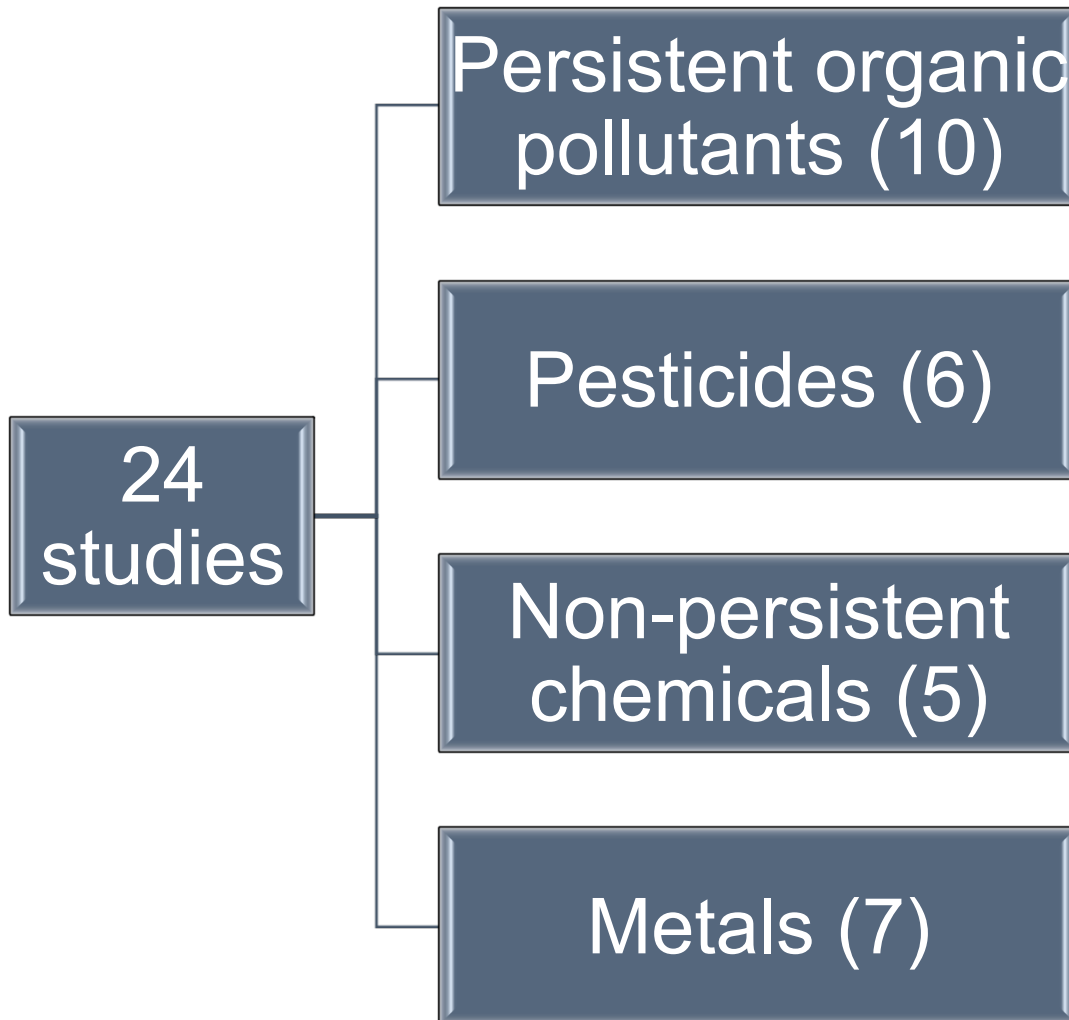
Mixed results found for DDT/DDE and PE (both increasing and inverse associations), and high exposure levels associated with increased risk in African but not U.S. populations

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



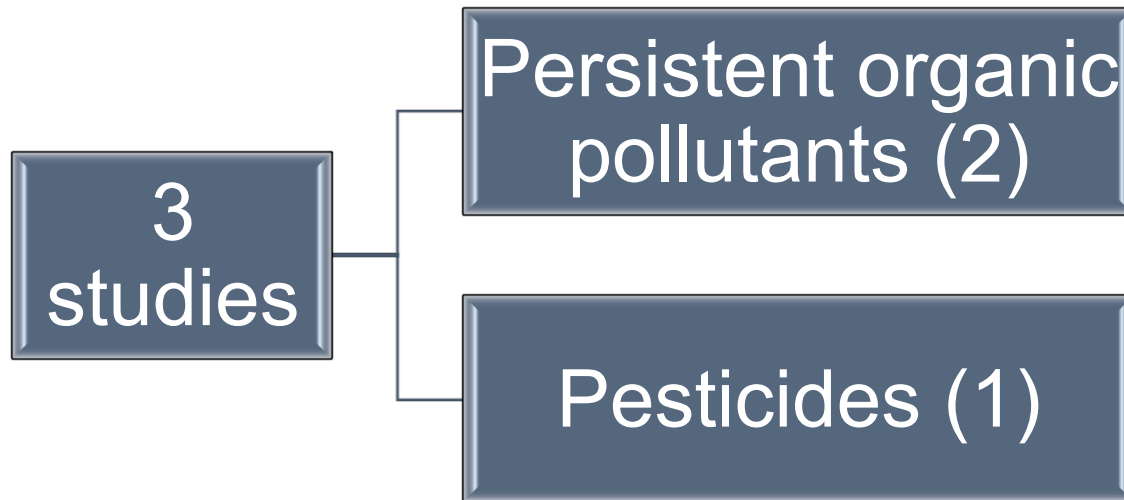
Some evidence of increasing but non-linear dose response associations found for PCBs or PBDEs and GDM risk, but mixed results and limited comparability due to variable study locations, exposure levels, and timing of measurement (just before conception to soon after delivery)

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



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

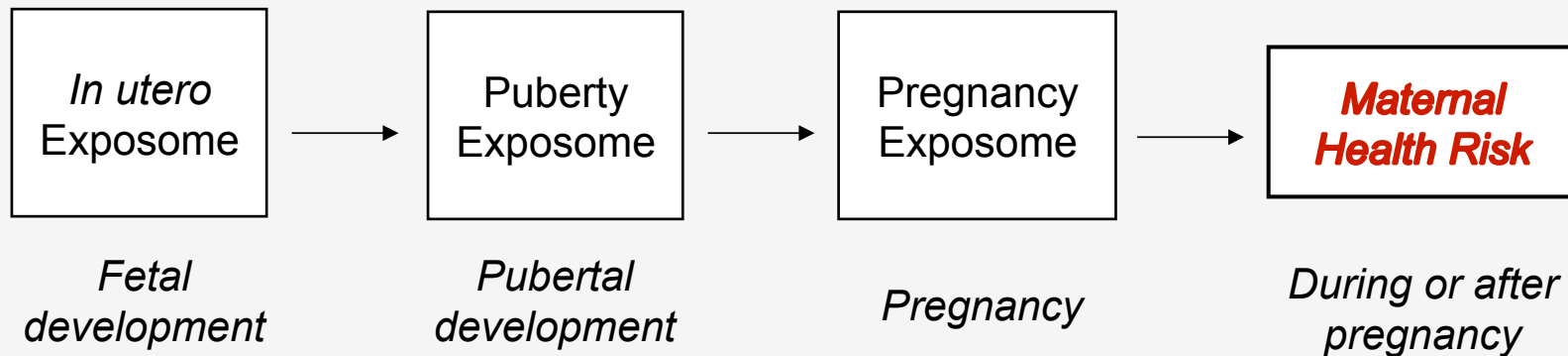
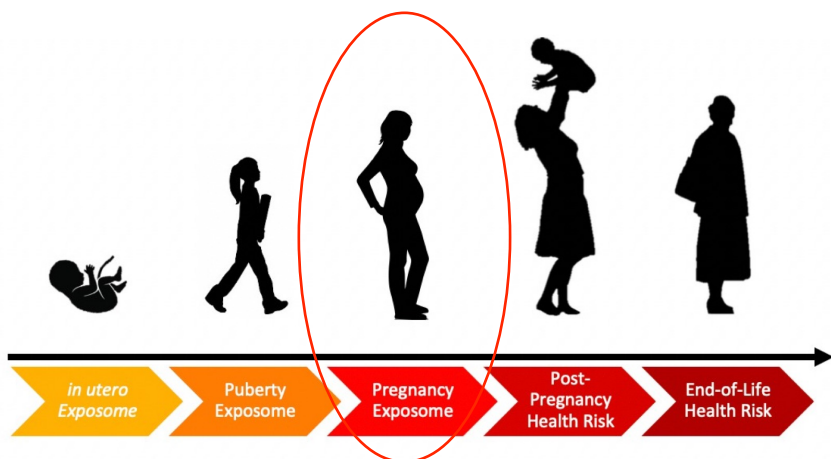


Figure 1. Vulnerable stages for adverse maternal health outcomes across the life course.

Varshavsky et al. 2019 *Reproductive Toxicology*

Implications

Lifespan susceptibility to chemical exposures and associated health risks



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



JUNE 25, 2019 – JULIA VARSHAVSKY

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

Thank you

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PRHE blog: Varshavsky, J. 2019. *Don't put pregnancy in a corner: it's about more than fetal health*. Program on Reproductive Health and the Environment. <https://prheucsf.blog/2019/06/25/dont-put-pregnancy-in-a-corner-its-about-more-than-fetal-health/>.



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