Concept Clearance

Branch: Population Health Branch

Council Period: 201905

Concept Title: Pregnancy as a Vulnerable Time Period for Women's Health

Introduction

This concept aims to accelerate multidisciplinary research projects studying the effects of environmental chemicals on maternal physiology, and endocrine and metabolic functions during and shortly after pregnancy, as well as potential long-term health effects caused by environmental exposures. During pregnancy, childbirth, and the postpartum periods women undergo dramatic metabolic, hormonal, and physical changes. Many studies have linked maternal environmental exposures with increased susceptibility to adverse health effects in the offspring, such as increased risk of miscarriage, intrauterine growth restriction, low birth weight, preterm birth, birth defects, and motor and cognitive delays in offspring. However, few studies have focused on the impact of exposures during pregnancy on the short- and long-term health of the mother, regardless of her future reproductive plans.

Emerging research suggests that maternal gestational exposure to environmental toxicants poses risks to women's health after parturition as well as to fetal and child health and development. Rates of maternal mortality and morbidities such as pre-eclampsia, eclampsia, and gestational hypertension are on the rise in the US (CDC; GBD 2015 Maternal Mortality Collaborators, 2016). These conditions that arise during pregnancy are associated with an increased long-term risk of cardiovascular disease (CVD) which is also the leading cause of death for women in the US (Murphy et al. PMID: 29235985).

The increases in maternal mortality have been seen across most ethnic groups, but the largest increase has been in Non-Hispanic Black and American Indian women (Moaddab et al. 2018 Obstet Gynecol). Black women in the United States are 3-4 times more likely to die from pregnancy-related causes than white women and are disproportionately affected by adverse maternal health conditions such as preeclampsia which is linked to poor cardiovascular outcomes later in life. Little is understood about what is driving these increased risks, but higher environmental exposures and stressors could be contributing to this health disparity.

Epidemiologic studies have shown a probable link between C8 (PFOA) exposure and pregnancy-induced hypertension and preeclampsia. Others have reported that maternal arsenic exposure and impaired glucose tolerance during pregnancy. An agricultural health study reported that pesticide exposure was associated with self-reported gestational diabetes mellitus (Saldana). In studies of breast cancer there is an indication that women who took the endocrine disrupting chemical diethylstilbestrol (DES) during pregnancy have a modest increased and bisphenol A (BPA) may promote the growth of aggressive breast tumors in pregnant mothers possibly interfering with chemotherapy treatment.

Most *in utero* exposure studies in animals focus entirely on the health of the offspring, and only a few have reported exposure effects on maternal health making this a potential high impact field of study. NIEHS-supported research has shown that exposure to air pollution during gestation can have long-term cardiovascular effects on maternal physiology during and after pregnancy in a mouse model. This vulnerability is tied to the changes in metabolic demands, cardiovascular remodeling, and angiogenesis that take place during pregnancy. A study in mice showed that in utero exposures to tetrabromobisphenol A (TBBPA), a commonly used brominated flame retardant, reduces maternal immunosuppressive cells (Tregs), potentially leading to a compromised immune system. A European group reported that exposure to bisphenol (BPA) during pregnancy can disrupt glucose homeostasis in pregnant mice as well as in their male offspring.

NIEHS is interested in exploring this further through epidemiological and animal research to investigate the impacts of exposures during pregnancy, childbirth, and the postpartum period on the subsequent health of the mother. Indeed, we have identified very few NIEHS-funded grants focused on environmental influences on the health of the mother (e.g. only 5 epidemiological projects), however there are over 30 birth cohorts that collected baseline maternal health data (pregnancy to delivery) with banked samples and well-characterized exposure data that remains unanalyzed and could be followed-up to examine the health of the mothers. Similarly, in the animal-based *in utero* exposure studies we are missing the opportunity to follow up on both short- and long-term health of the dames.

The recent Trans-NIH Strategic Plan for Women's Health Research specifically calls for expanding "research on conditions and diseases that affect women, including reproductive stages, with a focus on maternal and gynecologic health."

Research Goals and Scope

We propose an FOA to better understand the effects of environmental exposures on maternal health and physiology during pregnancy and on the short- and long-term health of the mother.

The FOA aims to support epidemiological and mechanistic work on pregnancy as a critical window of susceptibility for the mother's health by stimulating research in existing birth cohorts with baseline maternal information and banked biospecimens, and in animal models that consider the mechanisms by which exposures during gestation alter physiology and metabolism after parturition.

We plan to work collaboratively with the Office of Research on Women's Health, the National Institute on Minority Health and Health Disparities, and the National Institute of Child Health and Human Development to integrate research needs with respect to better understanding the role of the environment on maternal health.

Currently, there are numerous epidemiological studies that established birth cohorts to consider the effects of prenatal exposures on the development of the offspring. We would encourage applicants to leverage these existing resources to focus on the mother's health during this critical window and after the birth of the child.

These studies will help us better understand how environmental exposures impact women during and after pregnancy and may identify drivers of the observed health disparities in maternal morbidity and mortality in the United States and potential modifiable factors for disease prevention.

Mechanism and Justification

We propose a to develop funding opportunities to spur animal-based mechanistic and epidemiological research to investigate exposures during pregnancy, childbirth, and the postpartum periods to determine the life-long effects of on a woman's health. These goals will be pursued through R01 grant mechanisms.

In addition to supporting the Trans-NIH Strategic Plan for Women's Health, this concept will support the NIEHS 2018-2023 Strategic Plan Theme 1, Goal 2 "Advancing Environmental Health Sciences, Individual Susceptibility" and Theme 2, Goal 4 "Promoting Translation – Data to Knowledge to Action, Environmental Health Disparities and Environmental Justice."