

Hypertensive Disorders of Pregnancy and Environmental Exposures: Disease as a Toxicology Focus

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Overview

Hypertensive disorders of pregnancy (HDP) complicate approximately 10% of pregnancies and are one of the leading causes of maternal and fetal morbidity and mortality worldwide. The American College of Obstetricians and Gynecologists classifies HDP into four categories: (1) gestational hypertension, (2) preeclampsia/eclampsia, (3) chronic hypertension, and (4) chronic hypertension with superimposed preeclampsia. These disorders are characterized typically by differences in the timing of onset of symptoms and can range in severity from hypertension alone (e.g., gestational hypertension) to multiorgan dysfunction and seizures (e.g., eclampsia). Preeclampsia, for example, is responsible for 50,000-60,000 maternal deaths worldwide each year and is associated with multiple maternal complications including renal and liver dysfunction, edema, stroke, and placental separation or blockage of the blood supply. Although viewed as a condition specific to the pregnancy and (in some cases) postpartum periods, HDP can have long-term effects on the mother's health and the health of her offspring.

Women who experience hypertension in pregnancy are not only at risk of complications during pregnancy, they are at an increased risk for developing cardiovascular disease, stroke, and type 2 diabetes later in life. Cardiovascular disease, specifically, is the leading cause of mortality worldwide and disproportionately affects minority women. That minority women, particularly African American women, are at a higher risk for developing HDP and that they also have the highest incidence of cardiovascular disease later in life is a potential relationship that needs to be explored to better characterize risk in susceptible populations. Understanding and reducing factors that contribute to maternal mortality is a significant public health concern and is considered a high priority by the National Institutes of Health.

Recent Efforts and Next Steps

In December 2019, NTP published a [systematic review](#)¹ that evaluated the evidence for associations between exposure to traffic-related air pollution (TRAP) and HDP. This systematic review was conducted due to the relationship between maternal blood pressure status during pregnancy and adverse maternal and early childhood health outcomes, as well as the increasing evidence that TRAP is significantly associated with hypertension during pregnancy. The evidence was evaluated using the [OHAT Approach for Systematic Review and Evidence Integration](#)² and hazard conclusions were developed based on a 4-point scale: known,

¹ https://ntp.niehs.nih.gov/ntp/ohat/trap/mgraph/trap_final_508.pdf

² <https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/handbook/index.html>

presumed, suspected, and not classifiable. NTP concluded that exposure to TRAP is *presumed to be a hazard to pregnant women*. This conclusion was based solely on human evidence because there were no animal studies that evaluated the impact of TRAP exposure on blood pressure parameters during pregnancy. The review also noted that very few mechanistic studies have evaluated the impact of environmental exposures on hypertension during pregnancy.

Although there are risk factors that increase the probability of developing HDP (e.g., obesity, diabetes), most cases occur in healthy women with no other obvious risks. Thus, environment may play an important role in the development and exacerbation of these diseases, yet the mechanisms by which environmental chemicals may act on relevant pathways represent a significant research/knowledge gap. As part of the DNTP Cardiovascular Health Effects Innovation program, we are developing a scoping review that will identify biomarkers that can be used to evaluate, diagnose, or predict hypertension in pregnancy in animal models. Scoping reviews are literature evaluations that summarize available evidence on broad research topics to present the current state of the science, generally without synthesis because of the broad topics addressed. These reviews categorize and present evidence by key concepts such as types of studies, exposures, or health outcomes and may include an interactive evidence map to assist readers in identifying patterns in the evidence and gaps in the research. The planned scoping review will be used to inform research that investigates the impact of environmental exposures on those biomarkers (using a variety of capabilities) as a predictive tool for hypertensive disorders of pregnancy and will ultimately serve to better inform this aspect of cardiovascular disease risk in women.

Challenges

Much of the effort in the HDP field has been in the area of prediction. The American College of Obstetricians and Gynecologists recognizes that biomarkers for the prediction of HDP are integral to disease stratification and targeted therapy. Some animal models of hypertension in pregnancy are available and have been used to assess aspects of these diseases; however, the etiologies of HDP and how mechanisms in these models may differ from that in humans are not well understood. Therefore, given the importance of biomarkers in the prediction of these diseases, an important consideration is whether these biomarkers translate across species and if new or existing animal models (and potentially *in vitro* systems, systems biology approaches, others) can be used to further elucidate mechanisms and predict diseases, especially mechanisms that may be affected by environmental exposures.