

A PHENOME-WIDE ASSOCIATION STUDY OF MATERNAL HYPERTENSION AND STRUCTURAL BIRTH DEFECTS

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Keywords: epidemiology; primary prevention; congenital anomalies; hypertension; maternal and child health

Background: Maternal hypertension has been associated with congenital heart disease. However, there remain questions about the broader range of birth defects associated with hypertension and whether there are differences in risk among offspring of women with pre-gestational vs. gestational diagnosis. We evaluated these associations using data from one of the world's largest population-based active birth defects surveillance systems and a novel statistical approach.

Materials/Methods: We performed a phenome-wide association study (PheWAS) to evaluate risk of a broad range of birth defects among offspring of women with hypertension, overall and stratified by pre-gestational versus gestational diagnosis, among all livebirths (N >6,500,000) and birth defects cases regardless of pregnancy outcome (N >290,000) in Texas during 2005-2015. We computed prevalence ratios (PR) for 130 birth defects with >10 cases diagnosed among exposed offspring, adjusting for maternal age, race/ethnicity, education level, number of livebirths, and BMI. Data were randomly divided into discovery (60%) and replication (40%) partitions. Bonferroni adjustment was performed in the discovery partition based on the number of phenotypes evaluated ($p < 3.8E-4$). Birth defects associated with maternal hypertension at this threshold in discovery were re-tested in replication, and those associated with maternal hypertension at $p < 0.05$ were considered statistically significant. To maximize precision, PRs and 95% confidence intervals (CIs) for replicated birth defects were then calculated among the pooled dataset.

Results: Maternal hypertension was associated with increased prevalence of any birth defect (PR 1.32, 95% CI 1.30-1.34), non-isolated birth defects (PR 1.38, 95% CI 1.35-1.40), and 27 specific birth defects, including novel (e.g., microcephaly) and previously reported phenotypes (e.g., hypospadias, ventricular septal defects). Pre-gestational compared to gestational hypertension was a stronger risk factor for any birth defect (PR 1.38, 95% CI 1.34-1.43 vs. 1.28, 95% CI 1.26-1.30), non-isolated birth defects (PR 1.47, 95% CI 1.41-1.54 vs. 1.35, 95% CI 1.32-1.38), and several specific birth defects (Figure 1).

Conclusions: Our findings suggest that maternal hypertension is associated with a broad range of structural birth defects across organ systems. A number of structural birth defects were differentially associated with pre-gestational and gestational hypertension.

Images / Graph / Table

