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Impaired Fetal Growth Mediates the Association Between Hypertensive Disorders of Pregnancy and Neurodevelopment in Extremely Preterm Infants

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Abstract

Objective: To evaluate the association between hypertensive disorders of pregnancy (HDP) and neurodevelopmental outcomes in extremely preterm (EPT) infants and determine whether fetal growth mediates this relationship.

Study Design: Retrospective multicenter cohort study of infants born at 22 $^{0}/_{7}$–26 $^{6}/_{7}$ weeks' gestation within the NICHD Neonatal Research Network (2012–2019). HDP was defined as maternal hypertension before/during pregnancy. Primary outcome was Bayley-3 cognitive composite score at 22–26 months corrected age; secondary outcomes included language, motor, and composite death/neurodevelopmental impairment (NDI). Multivariable regression adjusted for maternal, perinatal, and socioeconomic confounders. Mediation analyses evaluated mediating role of birth weight Z-scores and gestational age.

Results: Among 4,712 infants, 1,178 (25%) were HDP-exposed. HDP exposure was associated with lower cognitive, language, and motor scores, and higher odds of death/NDI. Birth weight Z-scores mediated ~65% of this relationship.

Conclusions: HDP exposure was associated with adverse neurodevelopment in EPT infants, largely mediated through impaired fetal growth.

Introduction:

Hypertensive disorders of pregnancy (HDP), including gestational and chronic hypertension, affect 25–50% of extremely preterm (EPT) deliveries,[1,2] with increasing rates in the United States.[3] Both forms can progress to severe conditions such as pre-eclampsia and eclampsia, negatively impacting maternal health[1] and contributing to adverse neonatal outcomes such as premature birth,[4] intrauterine growth restriction,[5,6] and long-term metabolic problems.[7,8]

HDP represents a spectrum of placental vascular disorders characterized by abnormal spiral artery remodeling, impaired uteroplacental perfusion, oxidative stress, endothelial dysfunction, and chronic fetal hypoxemia.[9] Preclinical studies suggest that intrauterine HDP exposure can hinder fetal brain development,[10–14] through placental insufficiency,[15] triggering an inflammatory cascade and nutrient deficiency that impairs fetal growth, disrupts fetal programming,[10–12] leading to epigenetic changes that affect brain development and cause white matter[16,17] and cerebrovascular injury.[18] Together, these mechanisms may contribute to impaired neurodevelopment resulting in cognitive, language, and motor delays, as evident in term infants.[19–21]

Human studies in term-born infants consistently report impaired neurodevelopment associated with HDP exposure.[21–24] However, findings in EPT infants are inconsistent. While some studies suggest poor outcomes,[22,25–28] many indicate better neurodevelopment in the exposed, suggesting a potential

neuroprotective effect of HDP.[29–33] Yet, many of these studies inappropriately controlled for intermediate factors such as fetal growth restriction and prematurity that lie in the causal pathway between maternal hypertension and later outcomes.[29,33–36] These intermediate variables partly account for the total effect, and their adjustment in analyses results in overadjustment that negates the total effect.[37,38]

An additional challenge in evaluating the association between HDP and neurodevelopment among EPT infants is the etiologic heterogeneity of EPT birth. HDP-associated EPT deliveries are frequently medically indicated, whereas unexposed EPT births more commonly result from spontaneous preterm labor, preterm rupture of membranes, or intrauterine inflammation, leading to a substantially higher prevalence of histologic chorioamnionitis in the unexposed group.[26,28,39] Because chorioamnionitis is independently associated with adverse neurodevelopmental outcomes,[39,40] a higher prevalence of chorioamnionitis in the unexposed group may contribute to worse neurodevelopmental outcomes in that group and potentially create or exaggerate an apparent neuroprotective association with HDP.[30,41,42] Accounting for chorioamnionitis is therefore important when estimating the association between HDP and neurodevelopment, particularly when interpreting previously reported associations suggesting better neurodevelopment among HDP-exposed EPT infants.[33,43]

The objective of our study was to evaluate the association between maternal HDP and neurodevelopment of EPT infants. We propose that birth weight is a key mediator in the causal pathway between HDP and infant neurodevelopmental outcomes, rather than a confounder. Additionally, factors such as chorioamnionitis and socioeconomic status,[44] which influence both exposure and outcomes, should be included as confounders.

Methodology:

Study Participants

We included EPT infants born at 22 0/7–26 6/7 weeks gestation between 7/1/2012 and 12/31/2019 who attended the NICHD Neonatal Research Network's 22–26-month follow-up visit. We excluded infants with major congenital anomalies that affected the central nervous system, congenital heart disorders, and chromosomal abnormalities. The Follow-up study was approved by the Institutional Review Board at each participating center.

Variable Definition

Trained research staff collected maternal and infant data during the birth hospitalization. We defined HDP exposure as maternal diagnosis of hypertension present before or during pregnancy, per obstetricians' clinical guidelines.[45] Antenatal corticosteroid and magnesium therapy were defined as receipt of any dose before delivery.[45] Histologic chorioamnionitis was defined as placental inflammatory infiltration on pathological examination by pathologists.[46] Maternal race and ethnicity were self-identified by the mother. Socioeconomic status was assessed using mother's health insurance status.

Neurodevelopmental Evaluation: We assessed neurodevelopment at 22–26 months corrected age (CA) using the 3rd edition of the Bayley Scales of Infant and Toddler Development (Bayley-3),[47] administered by certified examiners following reliability standards established by the NICHD NRN.[48] The Bayley-3 is a widely used standardized tool designed to assess development in children.[47] The primary outcome was the Bayley-3 cognitive composite score because experimental and human studies suggest that placental insufficiency, fetal hypoxia, inflammation, and impaired white matter maturation associated with HDP may particularly affect higher-order cortical development and later cognitive functioning.[10,11,26,28] Additionally, cognitive performance at 2 years CA is strongly associated with later educational and functional outcomes in EPT infants.[49] Secondary outcomes included language (a combination of expressive and receptive language scores), motor (including both fine and gross motor skills) composite scores, and a composite measure of neurodevelopmental impairment (NDI) and death. Deaths were included if they occurred during the hospitalization or before 2 years follow-up. NDI was defined as 1 or more of the following according to the latest NRN definition: Bayley-3 Cognitive Composite Score < 85, Bayley-3 Motor Composite Score < 85, cerebral palsy with Gross Motor Function Level ≥ 2,[50] bilateral blindness, or hearing impairment with or without amplification.[51] Analyses of Bayley-3 scores were restricted to surviving infants with available cognitive assessments at 22–26 months CA. Analyses evaluating the composite outcome of death/NDI included the entire eligible live-born cohort to minimize survivor bias and competing risk bias.

Statistical Analysis

Baseline patient characteristics were compared between HDP-exposed versus unexposed infants using t-tests or Wilcoxon rank sum tests for continuous variables and Chi-square for categorical variables.

Associations between HDP exposure and Bayley-3 scores or NDI/death were analyzed, adjusting for *a priori* covariates: histologic chorioamnionitis, antenatal steroids, antenatal magnesium sulfate, infant sex, multiple gestation, birth hospital, maternal age, maternal race, and mother's health insurance status. We used maternal health insurance as a proxy for socioeconomic status due to minimal missing data, whereas maternal education and household income did not differ significantly between groups. The β estimates and their 95% confidence intervals were obtained using generalized linear regression for continuous outcomes. Odds ratios are presented for the categorical binary outcome of NDI/death using logistic regression. Because mortality represents a competing outcome among EPT infants, separate analyses were performed for neurodevelopmental outcomes among survivors and for the composite outcome of death or NDI in the full eligible cohort. This approach was used to reduce survivor bias and better capture the overall burden associated with HDP exposure.

Confounders were selected *a priori* based on biologic plausibility and causal inference principles informed by directed acyclic graph methodology. Variables occurring downstream of HDP exposure, including gestational age, birth weight, interventricular hemorrhage (IVH), sepsis, severe bronchopulmonary dysplasia (BPD), necrotizing enterocolitis, and other neonatal morbidities, were considered potential mediators rather than confounders as they may lie in the pathway between HDP

and infant neurodevelopment, and therefore were excluded in adjusted models (Fig. 1) to avoid overadjustment bias.[37] Importantly, although histologic chorioamnionitis is unlikely to influence the occurrence of HDP and therefore may not represent a conventional confounder, it was intentionally included as an a priori covariate because of its marked imbalance between groups and its established association with neurodevelopmental outcomes in EPT infants.[39] Antenatal corticosteroid and magnesium sulfate exposures were included as prespecified covariates because their administration may differ according to the obstetric circumstances leading to EPT delivery and both have established associations with neonatal and neurodevelopmental outcomes. Antenatal magnesium sulfate was additionally considered relevant because it may be administered either for fetal neuroprotection or in the management of severe hypertensive disease. Gestational diabetes mellitus (GDM) was not included in the adjusted models because data were available only from 2016 onward, resulting in substantial missingness. Additionally, routine GDM screening typically occurs at 24–28 weeks' gestation, potentially limiting ascertainment among EPT pregnancies.

We specifically evaluated the mediating roles of gestational age and fetal growth restriction on the association between HDP and neurodevelopment using mediation analyses with the SAS 9.4 CAUSALMED procedure. Separate models assessed the indirect effects of HDP through gestational age at birth and birth weight Fenton Z-scores[52] while distinguishing these from direct effects of HDP on Bayley-3 outcomes. Outcome and mediator models were adjusted for a priori confounders, and 95% confidence intervals were estimated using 1000 bootstrap iterations. Further, given the heterogeneity of HDP, we conducted a sensitivity analysis restricted to pregnancies complicated by pre-existing maternal hypertension. Additional methodological details are provided in Supplement 1.

Results:

Of 8574 EPT infants born at NRN centers between 07/1/2012 and 12/31/2019, 331 met exclusion criteria, 19 were ineligible for follow-up (not born at NRN hospitals or not enrolled in NRN study), and 2590 died before the 22-26 months assessment. Among surviving eligible infants, 909 lacked Bayley-3 cognitive data, including 668 lost to follow-up. Ultimately, 4712 infants with complete Bayley-3 cognitive outcomes were included, of whom 1178 (25%) were HDP-exposed and 3534 were unexposed (Figure 2).

Infants with and without HDP exposure differed in maternal age, race, antenatal magnesium exposure, histologic chorioamnionitis, GDM, primary language, outborn status (defined as if the infant was born at an outside hospital other than the study center and needed transfer), multiple gestation, gestational age, birth weight, infant sex, IVH, and severe BPD (Table 1). Infants with and without follow-up differed in maternal age, race, education, birth hospital, gestational age, and birth weight (Table 2). Neurodevelopmental outcomes were significantly worse among HDP-exposed infants than unexposed infants (Table 3).

In both unadjusted and adjusted models, HDP exposure was associated with lower Bayley-3 cognitive, language, and motor composite scores (Table 4). After adjustment, HDP-exposed infants scored 2.44

points lower on the cognitive (95% CI: -3.57 to -1.32, p < 0.01), 2.80 points lower on the language (95% CI: -4.13 to -1.46, p < 0.01), and 2.91 points lower on the motor (95% CI: -4.18 to -1.64, p < 0.01) composites. The odds of NDI/death were 1.23 times higher in the HDP-exposed group (Table 4).

Mediation analysis demonstrated that the association between HDP and cognitive outcomes was largely mediated through impaired fetal growth, as measured by birth weight Fenton Z-scores. The direct effect of HDP was not significant, whereas the indirect effect through birth weight Z-score was highly significant (p<0.01), accounting for 64.6% of the total effect. Similar findings were observed for language and motor outcomes (Figure 3, Table 5).

We also evaluated gestational age as a potential mediator of the association between HDP and Bayley-3 outcomes (Supplementary Table 1). Mediation analysis demonstrated a suppression effect, with direct and indirect effects in opposite directions, likely reflecting methodological artifact rather than a true biologic effect. This finding may relate to the restricted cohort of live-born EPT infants, where unexposed infants were born at earlier gestational ages (i.e., 24 weeks) than HDP-exposed infants (i.e., 25 weeks). Because longer gestation is neuroprotective in EPT infants, gestational age could not be fully evaluated as a mediator across the full spectrum of HDP-exposed pregnancies. These findings should therefore be interpreted cautiously.

In a sensitivity analysis restricted to infants exposed to pre-existing/chronic maternal hypertension, the results remained similar (Supplement Table 2).

Comment:

In our multisite prospective study involving 4712 EPT infants born at < 27 weeks gestation, HDP exposure was significantly associated with worse cognitive, motor, and language outcomes at two years CA. This relationship was largely mediated by HDP's impact on in-utero growth, accounting for approximately 65% of the total effect, supporting a potential role of placental dysfunction and impaired fetal growth in neurodevelopmental vulnerability.

Our study showed that HDP exposure was associated with a 2- to 3-point reduction in Bayley-3 scores (~ 20% SD), which, while modest, could be clinically relevant. Although the effect size is relatively small at the individual level, even subtle early developmental differences can accumulate over time, especially in the absence of interventions, potentially impacting school readiness, executive functioning, and future academic success, particularly among EPT infants already at high neurodevelopmental risk. Identifying these differences early enables tailored interventions, such as early speech therapy, occupational therapy, or enriched learning environments, that can enhance long-term educational, behavioral, and health outcomes.

The mechanisms linking maternal-placental health and fetal neurodevelopment remain incompletely understood. HDP may impair placental perfusion, causing hypoxia, ischemia, inflammation, and nutrient restriction,[53] which may disrupt fetal neurogenesis, contributing to cortical gliosis, white matter lesions,

decreased Purkinje fibers, increased apoptosis of pre-oligodendrocytes, and hypomyelination, observed in animal models, ultimately culminating in adverse neurodevelopmental outcomes.[10–14]

However, evidence on HDP's impact on preterm infants' neurodevelopment is inconsistent, with studies reporting no association,[34,54] adverse outcomes,[22,25–28] or even apparent neuroprotection.[29–33] This variability may reflect inappropriate comparison groups, particularly those consisting of other high-risk preterm infants with significant comorbidities, such as chorioamnionitis, a leading cause of preterm births.[30,41,42] Acute chorioamnionitis is associated with impaired brain development[39] and long-term neurodevelopmental deficits in preterm infants.[40] In our cohort, histologic chorioamnionitis was more than twice as common among unexposed infants (68% vs 29%), suggesting inadequate adjustment for chorioamnionitis in prior studies may have biased findings toward a perceived neuroprotective effect of HDP. Studies adequately controlling for chorioamnionitis, including ours, consistently report associations between HDP exposure, abnormal brain maturation, and neurodevelopmental delay.[26,28]

Inconsistent findings may also reflect overadjustment in prior studies, particularly for gestational age and markers of fetal growth restriction such as birth weight or small-for-gestational-age status.[29,33–35] These covariates function as mediators rather than confounders, as they lie on the causal pathway between maternal HDP and infant neurodevelopment (Fig. 1).[37] Adjusting for these mediators in multivariable models can obscure the true impact of HDP by artificially diminishing group differences and thus masking HDP's role as a neurodevelopmental risk factor.[38] Nakamura et al. reported that adjustment for birth weight substantially reduced the observed association between HDP and neurodevelopmental outcomes at 3 years of age.[29]

We conducted mediation analyses to better delineate the mechanisms through which HDP impacts neurodevelopment. Mediation analyses allow us to separate HDP's direct effects on the developing brain, such as those stemming from placental ischemia, hypoxia, and inflammation, from its indirect effects, which occur through pathways involving nutrient restriction and impaired fetal growth. We demonstrated that impaired fetal growth, attributable to HDP exposure, mediated approximately 65% of the total effect on cognitive, motor, and language outcomes at two years CA, underscoring that intrauterine growth restriction is a critical intermediary through which HDP exerts its influence on early brain development, emphasizing that growth restriction is a mediator rather than a confounder. Similarly, our prior work demonstrated that birth weight Z-score mediated approximately 22% of the association between HDP and structural brain abnormalities on term-equivalent MRI in preterm infants.[28] Together, these findings highlight that mediation analysis is instrumental in distinguishing between HDP's direct neurotoxic effects and its secondary impact via impaired fetal growth. By clarifying these distinct pathways, our results add important insight into HDP's multifaceted impact on neurodevelopment in EPT infants.

Interestingly, HDP-exposed infants had lower rates of severe IVH despite worse neurodevelopmental outcomes, suggesting mechanisms beyond overt hemorrhagic injury contribute to impaired brain

development following HDP exposure. Experimental and neuroimaging studies implicate chronic placental insufficiency, fetal hypoxia, inflammation, impaired cerebral perfusion, and disrupted white matter maturation as potential pathways even without severe IVH.[26] Similarly, our prior work demonstrated that term-equivalent

MRI abnormalities partially mediated the association between HDP exposure and adverse neurodevelopment at 2 years CA.[28] Together, these findings support that HDP-related neurodevelopmental vulnerability may arise from disrupted fetal brain maturation secondary to HDP-associated placenta dysfunction.

We also examined the potential mediating role of gestational age between HDP exposure and neurodevelopmental outcomes. Gestational age operated as a suppressor rather than a mediator, reducing the total effect by 22% (Supplementary Table 1).[55] This likely reflects a methodological artifact rather than a true causal relationship, as there is no evidence suggesting HDP is associated with increased gestational age and is primarily driven by the younger gestational age of unexposed infants (mean of 24 weeks) compared with HDP-exposed infants (mean of 25 weeks; see Table 1). Further, because our cohort was restricted to live-born EPT infants, gestational age could not be fully evaluated as a mediator; therefore, these findings should be interpreted with caution.

Strengths and Limitations:

Our study examined the neurodevelopmental effects of HDP in over 4700 EPT infants born before 27 weeks' gestation, allowing a comprehensive analysis with robust statistical power to detect meaningful associations. We rigorously controlled for significant confounders, particularly histologic chorioamnionitis, an important condition associated with adverse neurodevelopmental outcomes in preterm infants and a potential bias if left uncontrolled. Placental pathology was available for 95% of the cohort. We employed advanced statistical methods, specifically mediation analysis, which allowed us to differentiate the direct impact of HDP on neurodevelopment from its indirect effects via in utero growth restriction and prematurity. This approach helps clarify the causal pathway and the specific mechanisms through which HDP affects preterm infant development.

However, the retrospective design introduces potential selection bias and residual confounding, despite adjusting for known confounders. The NRN database lacked information on HDP timing, severity, and subtype, precluding assessment of differential effects of HDP phenotype. Approximately 16% of infants were lost to follow-up, potentially introducing attrition bias despite adjustment for baseline antenatal differences. Survivor bias is another consideration, as severe HDP may increase fetal and neonatal mortality, potentially underestimating adverse effects among survivors. Although we evaluated the composite outcome of death or NDI, stillbirths and fetal deaths were unavailable. Future studies using fetus-at-risk or competing-risk approaches are needed to better characterize the total impact of HDP on offspring outcomes. Further, adjustment for histologic chorioamnionitis cannot fully account for the distinct obstetric pathways leading to EPT birth among HDP-exposed and unexposed pregnancies, and

residual confounding related to these underlying phenotypes remains possible. Finally, while our findings provide valuable insights, the study's generalizability may be limited to EPT infants, and results may not apply to infants born closer to term.

Conclusion:

Our findings underscore that HDP is an independent risk factor for adverse neurodevelopmental outcomes in EPT infants, affecting cognitive, language, and motor skills at two years CA. Much of this effect is mediated by HDP's impact on fetal growth, highlighting intrauterine growth restriction as a significant pathway through which HDP influences early brain development. While the study addresses a major gap in understanding HDP's role in preterm infant neurodevelopment, future research should investigate specific HDP subtypes and their severity, consider additional confounders, and aim for prospective, longitudinal studies to further elucidate HDP's mechanisms. Comprehensive prenatal care aimed at managing HDP and mitigating its effects could potentially improve neurodevelopmental outcomes for at-risk infants. Furthermore, infants exposed to HDP should receive consistent follow-up in NICU high-risk clinics, with early intervention strategies to support long-term development.

Abbreviations

EPT
extremely preterm
HDP
hypertensive disorders of pregnancy
SD
standard deviation
IQR
interquartile range

Declarations

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Tables

Tables 1-5 are available in the Supplementary Files section.

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