

Neurology Journal Club: Hypertensive Disorders of Pregnancy and Cognitive Impairment

A Prospective Cohort Study

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Abstract

Women with gestational hypertension and preeclampsia, termed hypertensive disorders of pregnancy (HDP), are at risk of developing cardiovascular disease and potentially cognitive impairment years after pregnancy. In their study, Adank et al. hypothesized that patients with HDP might have worse cognitive performance compared with women with previous normotensive pregnancies and sought to evaluate long-term cognitive performance in these 2 populations. In this Journal Club article, we aim to review key study findings and discuss potential shortcomings and future directions.

Background

Cardiovascular disease has long been implicated as a contributor to cognitive decline.¹ However, little is known about hypertensive disorders during pregnancy and their long-term association with cognitive impairment. Women with gestational hypertension and preeclampsia, termed hypertensive disorders of pregnancy (HDP), are at risk of developing cardiovascular disease and potentially cognitive impairment years after pregnancy.²⁻⁴ Adank et al.⁵ hypothesized that patients with HDP might have worse cognitive performance compared with women with previous normotensive pregnancies and sought to evaluate long-term cognitive performance in these 2 populations.

Methods

This was an observational prospective cohort study, which is an appropriate design as experimental studies are not feasible in pregnant populations. The population comes from a database of an ongoing, prospective, population-based, birth cohort study, named the Generation R study. A subset of patients within the Generation R study were followed to conduct extensive measures on brain health, including neuroimaging and cognitive testing since 2017, as part of the ORACLE substudy. From these 2 databases, all pregnant women in Rotterdam, Netherlands, who delivered infants between April 2002 and January 2006 were invited to participate in this study.

Patients were categorized into whether they had HDP. HDP was defined using the 2001 International Society for the Study of Hypertension in Pregnancy criteria.⁶ Moreover, gestational hypertension was defined as development of a systolic blood pressure (SBP) of 140 mm Hg and/or diastolic blood pressure (DBP) of 90 mm Hg or more without proteinuria after 20 weeks of gestation in a previously normotensive female, whereas preeclampsia was defined as new-onset hypertension with an SBP of 140 mm Hg and/or a DBP of 90 mm Hg or more with proteinuria (300 mg/d) at or after 20 weeks of gestational age.

Baseline characteristics, including ethnicity, educational level, prepregnancy body mass index (BMI), and depressive symptoms, were compared between groups. Ethnicity was defined as European and non-European, and level of education was categorized as low, average, and high. Depressive symptoms were evaluated as well using the Center for Epidemiological Studies–Depression scale.

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The primary outcome was the results of a battery of cognitive tests. These were conducted by trained examiners and included 15-word learning test (15-WLT), Stroop task, letter-digit substitution task, verbal fluency test, Purdue pegboard, and design organization test. The 15-WLT evaluates verbal learning, retrieval from verbal learning, and recognition of verbal learning. The Stroop task tests speed of reading and speed of color naming, with interference of automated processing and attention. The letter digit substitution task tests processing speed and executive function. The verbal fluency test examines long-term memory. The Purdue pegboard test examines dexterity and fine motor skill. Finally, the desk organization test examines visuospatial ability. These adequately test all the cognitive domains. The study consisted of a primary analysis that investigated the association between all patients with HDP and cognitive results and a secondary analysis that was limited to only patients with gestational hypertension.

Traditional statistical methods were used to compare groups in univariate analysis. G-factor scores (global cognition) derived from specified tasks from all of cognitive function tests were calculated. The G-factor was defined as the first unrotated component of a principal component analysis (PCA) that incorporates tasks from all available cognitive function tests. For missing values of the covariates, multiple imputations were performed. A prespecified multivariate analysis investigating the association between HDP and cognitive test scores was performed, adjusting for ethnicity, prepregnancy BMI, and educational level.

Results

A total of 596 individuals were included in the study, of which 115 (19.3%) had HDP and 481 (80.7%) had a normotensive pregnancy. Of the 115 patients with HDP, 80 (69.6%) had gestational hypertension and 35 (30.4%) had preeclampsia (Figure).

Women with HDP tended to be of non-European descent and had lower educational attainment, higher prepregnancy BMI ($p < 0.001$), and elevated BP parameters earlier in pregnancy as expected. Of note, the children of patients with HDP had lower birth weight and younger gestational age at birth on average.

In follow-up (median 15.4 years, IQR 6.2–13.9 years), those with HDP continued to have higher BMI and BP parameters and were more likely to use antihypertensive medication than women with normotensive pregnancies. Patients with HDP were 3 times more likely to have depressive symptoms.

Women with HDP performed worse on cognitive tests than their normal counterparts. HDP was associated with G-factor, recognition, immediate and delayed recall subtasks for the 15-WLT, Stroop color naming subtask, letter digit substitution task, verbal fluency test, and design organization test (all statistically significant).

Adjusting for ethnicity, educational level, and prepregnancy BMI, HDP remained significantly associated with poor cognitive performance (immediate recall: SD score -0.25 , 95% CI $[-0.44$ to $0.06]$ and delayed recall: SD score -0.30 , 95% CI $[-0.50$ to $0.10]$). Similar results were observed when the analysis was limited to women with gestational hypertension only (immediate recall: -0.25 , 95% CI $[-0.47$ to $-0.02]$, $p < 0.03$, delayed recall: -0.35 , 95% CI $[-0.59$ to $-0.11]$, $p < 0.004$, and recognition: -0.32 , 95% CI $[-0.57$ to $0.07]$, $p < 0.01$).

Overall, this study gives insight into the characteristics and cognitive status of patients with and without HDP 15 years following a pregnancy. The authors show that women with HDP had significantly reduced cognitive function/reserve compared with those without HDP. This was true in both the overall cohort and gestational hypertension subgroup. It is important to stress that with an observational cohort study, these are associations and HDP is a marker of increased risk, rather of causation.

Interpretation

The cohort study design and the sample size provide adequate power to answer the authors' question. They provide a robust statistical analysis adjusting for known confounders. Despite low proportions of missing data, they used a multiple imputations statistical technique to minimize bias. In addition, to account for the variability across the battery of cognitive tests, the authors used PCA to derive G-factor scores. PCA is mathematical technique used to reduce the number of features in large data sets, while retaining most of the variation.⁷ This is accomplished by identifying directions/principal components where the variation in the data is maximal. However, given these are mathematical constructs, it is hard to interpret their meaning. In contrast with previous studies of preeclampsia only, the present analysis included gestational hypertension and had both a large sample size and a long follow-up period (~ 15 years).^{3,4,8}

The study had several limitations. First, the study population was derived from another ongoing study and recruited by invitation. Data on the number of eligible patients, extended invitations, and the characteristics of those who did not participate are not available. Clear inclusion and exclusion criteria were not defined, and thus, one cannot exclude selection bias. Second, the analysis did not adjust for depression present in 20% of the HDP group, which could have confounded the results. In fact, it is well established that depression can affect cognition and needs to be screened for in patients with cognitive complaints.⁹ Third, other influential factors, such as the existence of preenrollment cognitive impairment, structural brain abnormalities, CNS disorders, thyroid disease, and alcohol use, as well as comorbidities developed between the index pregnancy and follow-up, were not available/included in this analysis. Furthermore, neuroimaging collected in the ORACLE study was not presented. CNS structural abnormalities could have been seen on MRI, and additional MR biomarkers such as cortical thinning, whole brain/hippocampus volumes, and possibly fMRI or amyloid or tau PET could have provided further insights. Fourth, it would have been interesting to have baseline cognitive testing, as well as serial measurements during the follow-

Figure Visual Summary of Study Design and Main Findings

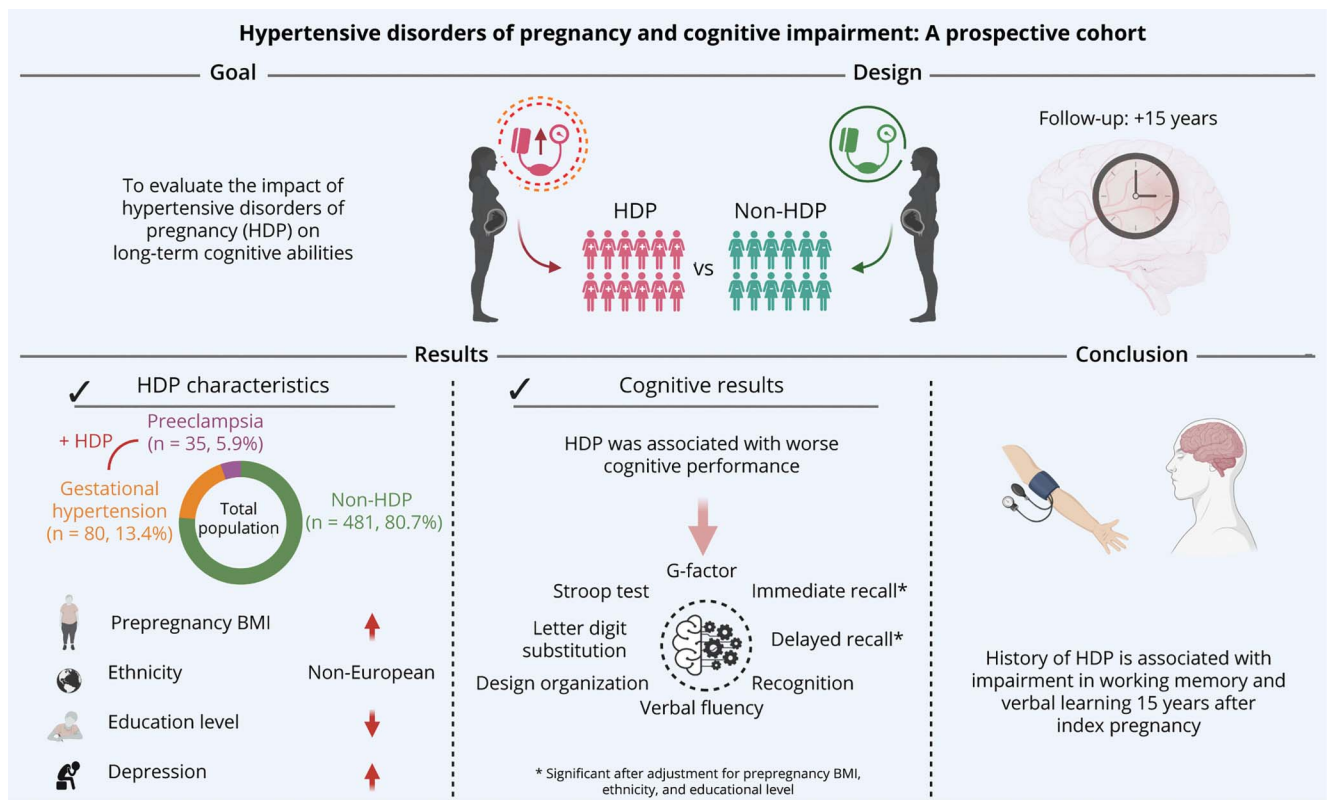


Illustration created using BioRender.com.

up period, to investigate whether there was worsening of performance over time. Moreover, the timing selected by the authors for cognitive assessment appears arbitrary and may not accurately reflect cognitive impairment. Fifteen years from age at pregnancy would still be relatively young, and patients may still have compensatory mechanisms. A lengthened follow-up with another cognitive reassessment would advocate for a stronger association between HDP and cognitive impairment. Finally, there is little known about the patients' ethnicities and educational level, such as first language or a defined educational level, or their socioeconomic status, a potential confounder.

Although the study does not offer strong evidence that would change current practice, it offers important insights into the natural history of HDP and might encourage more active cognitive surveillance in this patient population. Future studies with longer cognitive follow-up and research into neuroimaging biomarkers might help uncover potential therapeutic targets and help guide clinical care.

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Disclosure

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Name	Location	Contribution
Johanna Yun, MD	Emory University School of Medicine, Georgia	Manuscript preparation and critical revision of the manuscript
Mehdi Bouslama, MD	Emory University School of Medicine, Georgia	Manuscript preparation and critical revision of the manuscript

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