OBSTETRICS

Preeclampsia and cognitive impairment later in life

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BACKGROUND: Hypertension is a risk factor for cerebrovascular disease and cognitive impairment. Women with hypertensive episodes during pregnancy report variable neurocognitive changes within the first decade following the affected pregnancy. However, long-term follow-up of these women into their postmenopausal years has not been conducted.

OBJECTIVE: The aim of this study was to examine whether women with a history of preeclampsia were at increased risk of cognitive decline 35-40 years after the affected pregnancy.

STUDY DESIGN: Women were identified and recruited through the medical linkage, population-based Rochester Epidemiologic Project. Forty women with a history of preeclampsia were age- and parity-matched to 40 women with a history of normotensive pregnancy. All women underwent comprehensive neuropsychological assessment and completed self-report inventories measuring mood, ie, depression, anxiety, and other symptoms related to emotional state. Scores were compared between groups. In addition, individual cognitive scores were examined by neuropsychologists and a neurologist blinded to pregnancy status, and a clinical consensus diagnosis of normal, mild cognitive impairment, or dementia for each participant was conferred.

RESULTS: Age at time of consent did not differ between preeclampsia (59.2 [range 50.9-71.5] years) and normotensive (59.6 [range 52.1-72.2] years) groups, nor did time from index pregnancy (34.9 [range 32.0-47.2] vs 34.5 [range 32.0-46.4] years, respectively). There were no statistically significant differences in raw scores on tests of cognition and mood between women with histories of preeclampsia compared to women with histories of normotensive pregnancy. However, a consensus diagnosis of mild cognitive impairment or dementia trended toward greater frequency in women with histories of preeclampsia compared to those with normotensive pregnancies (20% vs 8%, $P = .10$) and affected more domains among the preeclampsia group ($P = .03$), most strongly related to executive dysfunction ($d = 1.96$) and verbal list learning impairment ($d = 1.93$).

CONCLUSION: These findings suggest a trend for women with a history of preeclampsia to exhibit more cognitive impairment later in life than those with a history of normotensive pregnancy. Furthermore, the pattern of cognitive changes is consistent with that observed with vascular disease/white matter pathology.

Key words: cardiovascular disease, cerebrovascular disease, cognition, dementia, hypertensive pregnancy, mild cognitive impairment, preeclampsia

Introduction

Hypertensive disorders of pregnancy, including preeclampsia, confer increased risk of cardiovascular disease (CVD) morbidity and mortality.[1] Preeclampsia occurs in about 3% of pregnancies,[2] and is associated with an approximate 2-fold increased risk of CVD and cerebrovascular disease.[3] Some risk factors associated with preeclampsia are shared with those for CVD and cognitive decline, including hypertension, metabolic syndrome, and insulin resistance.[4-7]

Women with a history of hypertensive pregnancy more frequently report subjective cognitive symptoms and endorse more physical and psychological symptoms that negatively impact physical, social, and emotional well-being and quality of life than women with a history of normotensive pregnancy (hNTP).[8-10] In addition, reported changes in cognition associate with the severity of preeclampsia[11] or posttraumatic stress symptoms of preeclampsia.[12] However, studies examining the impact of hypertensive pregnancy on cognitive performance report mixed results. For example, no differences in sustained attention or executive functioning were reported in women in their late 30s to early 40s, up to a decade following an index pregnancy of preeclampsia or eclampsia, compared to age-matched women with normotensive pregnancies.[13] In contrast, others have found slower motor speed,[8] poorer attention,[12] or poorer learning and memory[11] in women with a history of hypertensive pregnancy. Long-term follow-up of these women into their postmenopausal years has not been conducted. Therefore, in the current study, cognition and mood were evaluated in women approximately 35 years after preeclamptic or normotensive pregnancy. We hypothesized that women with a history of preeclampsia (hPE) would be more likely than women with a hNTP to have cognitive impairment and that the pattern would resemble changes characteristic of vascular/white matter disease.

Materials and Methods

Participants

Recruitment details have been previously reported.[14] In brief, Hospital Adaptation of the *International Classification of Diseases* codes and the population-based Rochester Epidemiology Project medical records linkage system[15] were used to identify 40 women with hPE and 40 women with hNTP. Sample size was based on power calculation to detect

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TABLE 1
Measures of cognition and mood

Attention	Wechsler Adult Intelligence Scale-III digit span measures auditory attention and working memory capacity. This test involves repetition of oral sequences of numbers of increasing length exactly as they are presented in forward condition and then in reverse in backward condition. Digit span forward measures simple auditory attention capacity and digit span backward measures working memory capacity. Score is total number of forward and backward sequences repeated correctly. Trail Making Test A measures visual attention and processing speed. It is paper-and-pencil test requiring rapid connection of consecutively numbered circles. Score is time (in seconds) to complete trial, with higher score reflecting poorer performance.
Working memory	Wechsler Adult Intelligence Scale-III letter-number sequencing measures auditory working memory. Letters and numbers of increasing length are orally presented in random order. Mental manipulation is required to rearrange numbers and letters and then repeat in ascending order. Score is total number of correct sequences.
Psychomotor processing	Wechsler Adult Intelligence Scale-III digit symbol coding measures visual scanning, motor persistence, sustained attention, response speed, and visuomotor coordination. It involves quickly transcribing symbols into blank spaces below numbers that correspond to symbol-number pairs presented in key above. Score is total number of symbols correctly transcribed within specified amount of time.
Executive functioning	Trail Making Test B measures visuomotor speed, divided attention, and cognitive flexibility. It increases demands of Trail Making Test A by requiring rapid connection of not only consecutively numbered circles but also lettered circles and alternating between them. Score is time (in seconds) to complete trial, with higher score reflecting poorer performance.
Language	Phonemic (C, F, L) and semantic (animals, fruits, vegetables) verbal fluency measure ability to produce fluent speech. It has also been used to assess ability to think flexibly and gauge how efficiently one uses search and retrieval strategies to organize thoughts. Objective is to rapidly generate as many words as possible within certain amount of time that begin with specified letters and belong to specified categories. Scores are total number of words generated for 3 letters and 3 categories. Boston Naming Test measures ease and accuracy of word retrieval and how intact semantic networks are. It also gives some indication of vocabulary level. This test requires providing name for common objects presented in black and white drawings. Score is total number of objects correctly named.
Visuospatial processing	Wechsler Adult Intelligence Scale-III picture completion measures ability to measure attention to visual detail. Pictures of common objects and scenes with detail missing from them are presented, and examinee is asked to identify what is missing. Score is total number of correct responses. Wechsler Adult Intelligence Scale-III block design measures visual problem-solving and understanding of part-to-whole relationships. It involves manual manipulation of 3-dimensional blocks to match 2-dimensional line drawings. Score is total number of correct designs.
Learning and memory	Auditory Verbal Learning Test measures learning efficiency, immediate memory span, sensitivity to interference with learning and recall, and rates of forgetting and retention. List of unrelated words is serially presented. Object is to learn as many words as possible over repeated trials, recall them after being presented distractor list, and recall them again after 30-min delay. Several scores are derived: learning score is sum of number of words recalled immediately on each trial, delay score is number of words recalled after long delay, and percent retention score is number of words on delayed recall trial divided by number of words recalled on last learning trial. Wechsler Memory Scale-Revised logical memory I and II measure learning, recall, and retention of logically organized verbal information. Paragraph-length prose passages are read out loud to examinee, who is to recall as much information from stories as possible immediately following presentation and again after 25- to 35-min delay. Logical memory I score is total number of story details recalled immediately following presentation, logical memory II is total number of story details recalled after longer delay, and percent retention is number of story details on delayed recall divided by immediate recall. Wechsler Memory Scale-Revised visual reproduction I and II measure visual learning, memory, and retention of geometric designs. Cards with line drawings are presented for brief amount of time, taken away, and then examinee is asked to reproduce designs as accurately as possible. After 25- to 35-min delay, examinee is asked to again reproduce as many of designs as possible, but this time without being shown cards. Visual reproduction I score is total number of design details recalled immediately following presentation, visual reproduction II is total number of design details recalled after longer delay, and percent retention is number of design details on delayed recall divided by immediate recall.

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differences in cardiovascular parameters. To be eligible for the study, a woman had to be a resident of Olmsted County, Minnesota, when delivering a baby from a pregnancy lasting >20 weeks (live birth or stillbirth) from Jan. 1, 1976, and Dec. 31, 1982; had to have had a documented clinical visit within the last 2 years to confirm that women did not have

TABLE 1
Measures of cognition and mood *(continued)*

Mood state	Beck Depression Inventory-II is 21-item self-report scale measuring range of affective, cognitive, and physiologic symptoms of depression (eg, sense of failure, loss of interest, indecisiveness, appetite, libido). Each item contains 4 statements of graded severity expressing how person might feel or think about aspect of depression under consideration, with scores ranging from 0 for absence of problems in that area to 3 for most severe level of that problem. Score is sum of all statements endorsed, with higher score representing greater severity. Beck Anxiety Inventory is 21-item self-report scale measuring range of subjective, physiologic, autonomic, and panic-related symptoms of anxiety (eg, unable to relax, hands trembling, heart pounding or racing, fear of worst happening). Each item contains 4 statements of graded severity expressing how person might feel or think about aspect of depression under consideration, with scores ranging from 0 for absence of problems in that area to 3 for most severe level of that problem. Score is sum of all statements endorsed, with higher score representing greater severity. Profile of Mood States is 65-item self-report measure of 6 mood states: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. It contains adjectives that describe how person may be feeling (eg, unhappy, relaxed, exhausted, rebellious, efficient), and individuals are asked to rate how much during past week they have had that feeling. Scores range from 0–4, with 0 being not at all and 4 being extremely. Subscale score is derived for each of 6 mood states, with higher score representing greater difficulty in all but vigor-activity state, where higher score is better.

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a cardiovascular or other neurological event that could potentially confound results; and had to live within 120 miles of Olmsted County to be available for in-person visits.

The medical records of all women were fully abstracted for demographic and clinical information. A potential exposure was confirmed as preeclampsia if a woman had at least 1 preeclamptic pregnancy from 1976 through 1982 that met the standard definition: (1) ≥2 blood pressure readings of a systolic blood pressure (SBP) >140 mm Hg or a diastolic blood pressure (DBP) >90 mm Hg at least 4 hours apart >20 weeks' gestation; and (2) new-onset proteinuria, as defined by a urine dipstick 1+, or proteinuria ≥0.300 g/24 h, or a protein/creatinine ratio equivalent to ≥0.300 g/24 h. Emergency room visits were not included. Women were sequentially contacted and recruited. Each of the 40 women with hPE was age- and parity-matched to a woman with hNTP. All women were postmenopausal and index pregnancies were first pregnancies. Eligible women were sent a letter describing the study, given contact information, and if no response within 2 weeks, contacted by telephone. Of the 77 women with confirmed hPE, 25 (32%) refused and 7 (9%) did not respond. Five (6%) were found to be ineligible after further screening. For women with hNTP, 104 women were contacted, 18 (17%) refused, 41 (39%) did not respond, and 5 (5%) wanted to participate but another matched control had already agreed.

As the primary focus of this study was to understand the potential mechanisms that place women with hPE at risk for subclinical CVD and cognitive decline, women were excluded with a medical-record confirmed clinical diagnosis of myocardial infarction, congestive heart failure, stroke, dementia, cancer (excluding nonmelanoma skin cancer), autoimmune disease (eg, multiple sclerosis, lupus), and neurological conditions (eg, epilepsy). All protocols were approved by Mayo Clinic and Olmsted Medical Center Institutional Review Boards (PR10-005198-05) and all participants gave written informed consent.

Clinical assessment of cardiovascular risk

Demographic and clinical data obtained from medical records and patient interviews at the time of the in-clinic assessment included age, body mass index (BMI), SBP, DBP, antihypertensive and lipid-lowering medications, and chart-abstracted and physician-confirmed diagnoses of hypertension, hyperlipidemia, and diabetes mellitus. The diagnosis of hypertension was confirmed if a prior diagnosis and/or use of prescription antihypertensive medication was confirmed upon medical record review, or if SBP ≥140 mm Hg or DBP ≥90 mm Hg was documented in the medical records on 2 separate occasions. The diagnosis of dyslipidemia was confirmed if ≥1 of the following criteria were met: use of lipid-lowering drugs or laboratory measurements revealing a total cholesterol ≥200 mg/dL, triglycerides ≥150 mg/dL, or high-density lipoprotein ≤50 mg/dL. Diabetes mellitus was diagnosed by hemoglobin A1c ≥6.5%, fasting glucose >126 mg/dL, or a physician diagnosis in the past, with or without current glucose-lowering agents. Coronary artery calcification (CAC) is a measurement of the amount of calcium in the walls of the arteries that supply the heart muscle and is recorded in Agatston units (AU). The higher the number, the greater the amount of plaque. CAC was evaluated by computed tomography and was previously reported.[14]

Cognitive assessment

Women underwent comprehensive cognitive testing administered by an experienced psychometrist under the supervision of a neuropsychologist. The 2.5-hour battery included standardized and validated tests of attention, working memory, psychomotor processing speed, executive functioning, language, perceptual processing, learning, and memory administered in a fixed order. Women also completed self-report

TABLE 2
Demographics and clinical characteristics by hypertensive pregnancy status

Variable	Normotensive, n = 40	Preeclampsia, n = 40	*P* value
Age at study consent, y	59.6 (56.2, 62.5)	59.2 (56.3, 62.5)	.814
Age at first live birth, y	24.0 (22.3, 26.3)	24.5 (21.7, 25.8)	.931
Time since first live birth/index pregnancy, y	34.5 (33.6, 36.7)	34.9 (32.9, 36.7)	.564
Parity	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	.967
Education			.219
≤High school	3 (8%)	6 (15%)	
Some college/technical/vocational	21 (53%)	22 (55%)	
≥College graduate	16 (40%)	12 (30%)	
BMI, kg/m^2	25.3 (23.1, 32.0)	29.8 (25.9, 33.7)	.023
Diastolic blood pressure, mm Hg	75.2 (69.7, 84.0)	79.7 (69.3, 83.3)	.368
Systolic blood pressure, mm Hg	128.7 (116.5, 145.7)	131.7 (119.7, 140.2)	.613
LDL cholesterol, mg/dL	123.0 (99.7, 136.4)	106.1 (87.9, 124.3)	.087
HDL cholesterol, mg/dL	64.0 (50.5, 76.5)	54.5 (41.0, 69.5)	.054
Triglycerides, mg/dL	97.5 (72.0, 123.5)	108.0 (85.0, 163.0)	.078
Fasting glucose, mg/dL	95.5 (91.0, 101.5)	98.0 (91.5, 109.5)	.151
Diabetes	2 (5%)	4 (10%)	.414
Albumin/creatinine ratio, mg/mmol	2.0 (0.00, 6.1)	2.4 (0.00, 5.1)	.992
Past or current hormone therapy	17 (43%)	17 (43%)	1.000
Ongoing hormone therapy	8 (20%)	6 (15%)	.556
17β-Estradiol, pg/mL	3.5 (2.1, 9.5)	5.4 (2.4, 7.8)	.495
Estrone, pg/mL	22.0 (14.0, 32.0)	26.0 (14.5, 32.5)	.956
Coronary artery calcification, AU	0.0 (0.0, 0.3)	0.0 (0.0, 28.0)	.007
ApoE-4 polymorphism	9 (23%)	11 (28%)	.606
Hypertension	8 (20%)	24 (60%)	<.001
Medication with potential cognitive side effects	16 (40%)	29 (73%)	.003
Obstructive sleep apnea	7 (18%)	12 (30%)	.189
Family history of dementia	13 (33%)	12 (30%)	.809

Continuous variables are reported as median (25th, 75th percentiles) whereas discrete variables are presented as count (%).

ApoE-4, apolipoprotein E-4; *AU*, Agatston unit; *BMI*, body mass index; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein.

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mood questionnaires 1 week prior to or at the same time as cognitive testing. (See Table 1 for complete description of cognitive and mood measures.)

Clinical assessment of cognitive impairment

Three experienced neuropsychologists and a behavioral neurologist blinded to pregnancy status independently examined age-corrected scaled scores for each of the 80 women and assigned ratings of normal, single-domain mild cognitive impairment (MCI), multiple-domain MCI, or dementia. A consensus diagnosis was determined based on agreement of at least 3 raters.

Most diagnostic criteria require objective evidence of mild impairment (typically 1-1.5 SD below the normative mean and a decline from baseline functioning) in ≥1 cognitive domains. For this study, incorporating published guidelines and criteria,[16-18] MCI was defined as mild impairment on ≥2 measures within a single domain, or mild impairment on ≥1 measures within at least 2 domains. A diagnosis of dementia was considered if there were cognitive deficits ≥2 SD below the mean in ≥2 domains. Education was used to estimate baseline functioning.

Statistical analyses

Demographic, clinical, and cognitive test data were summarized with descriptive statistics, including percentages for discrete variables and quartiles (median,

TABLE 3
Cognitive and mood comparisons (raw scores) by hypertensive pregnancy status

Cognitive domain	Variable	Normotensive n = 40	Preeclampsia n = 40	*P* value	Cohen *d*
Attention	Trail Making Test A, time/sec[a]	24.0 (20.0, 28.0)	25.5 (20.5, 31.0)	.643	0.39
	Digit span	16.0 (13.5, 18.0)	15.5 (13.5, 18.0)	.887	0.12
Working memory	Letter-number sequencing	10.0 (9.0, 11.0)	9.0 (8.0, 11.0)	.778	0.07
Psychomotor speed	Digit symbol coding	60.5 (55.0, 66.5)	59.0 (52.0, 64.0)	.778	0.29
Executive functioning	Trail Making Test B, time/sec[a]	56.5 (51.5, 66.0)	64.0 (50.5, 77.5)	.643	0.37
Language	Letter fluency	39.0 (32.5, 46.0)	41.0 (35.5, 45.5)	.887	0.00
	Category fluency	52.0 (46.5, 60.5)	50.5 (42.5, 61.0)	.778	0.21
	Boston Naming Test	57.0 (55.5, 59.0)	57.0 (55.0, 58.5)	.778	0.24
Visuospatial	Picture completion	15.0 (14.0, 16.0)	15.0 (14.0, 16.0)	.981	0.07
	Block design	27.0 (24.0, 35.5)	27.5 (22.0, 32.0)	.778	0.21
Learning/immediate memory	AVLT trials 1–5	52.5 (46.0, 59.0)	50.0 (47.0, 55.5)	.738	0.30
	Logical memory I	27.0 (23.0, 30.0)	24.0 (20.0, 28.0)	.333	0.52
	Visual reproduction I	32.0 (29.0, 36.0)	34.0 (31.0, 35.5)	.778	0.13
Delayed memory	AVLT delay	10.5 (9.0, 12.5)	10.5 (8.0, 12.0)	.778	0.22
	AVLT percent retention	83.0 (64.0, 100.0)	84.0 (68.0, 93.0)	.915	0.11
	Logical memory II	23.0 (19.0, 26.5)	19.0 (14.5, 23.0)	.161	0.65
	Logical memory percent retention	87.5 (76.5, 94.0)	79.0 (66.0, 88.5)	.309	0.48
	Visual reproduction II	26.5 (24.0, 32.0)	30.0 (27.0, 33.0)	.778	0.04
	Visual reproduction percent retention	83.5 (75.5, 97.0)	92.0 (79.0, 96.5)	.778	0.03
Mood	Beck Depression Inventory[a]	2.0 (0.0, 5.5)	4.0 (1.0, 7.5)	.643	0.14
	Beck Anxiety Inventory[a]	1.5 (0.0, 4.0)	3.0 (1.0, 6.0)	.580	0.07
	POMS anger[a]	0.0 (0.0, 1.0)	0.0 (0.0, 2.5)	.643	0.23
	POMS confusion[a]	5.0 (4.0, 7.0)	5.0 (4.0, 7.5)	.887	0.02
	POMS depression[a]	1.0 (0.0, 2.5)	1.0 (0.0, 5.0)	.778	0.02
	POMS fatigue[a]	1.0 (0.0, 4.0)	2.5 (0.0, 4.5)	.643	0.36
	POMS tension[a]	2.0 (1.0, 4.5)	2.0 (1.0, 4.5)	.981	0.09
	POMS vigor	18.5 (13.5, 23.5)	16.5 (11.0, 21.5)	.643	0.32

Scores are presented as median (25th, 75th percentiles). No significant differences were found after correction for multiple comparisons.

AVLT, Auditory Verbal Learning Test; *POMS*, Profile of Mood States.

[a] Higher score is worse—scores are total raw scores.

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25th and 75th percentiles) for continuous variables. Bivariate comparisons between groups with hPE or hNTP were performed using the χ^2 test or Wilcoxon rank sum test, or with a Cochran-Armitage trend test for ordinal measures of cognitive impairment. To correct for multiple comparisons among all cognitive tests that were included, *P* values were adjusted according to the method described by Benjamini and Hochberg.[19] The magnitude of effect on measures of cognitive functioning was estimated with Cohen *d* standardized effect size.[20] Convention suggests .2 is a small effect size, .5 moderate, and .8 large. All data were recorded and managed in a secure database (Medidata Rave, Medidata Solutions Inc, New York, NY), and were analyzed using statistical software (SAS, Version 9.4; SAS Institute Inc, Cary, NC).

Results

Demographics and current clinical characteristics by pregnancy status are presented in Table 2. Compared to women with hNTP, women with hPE had higher BMI (29.8 kg/m^2 [interquartile range {IQR} 25.9-33.7] vs 25.3

TABLE 4
Consensus-based assessment of cognitive status

Variable	Normotensive n = 40 N (%)	Preeclampsia n = 40 N (%)	*P* value
Cognitive impairment			.03[a]
None	37 (93)	32 (80)	
MCI single domain	2 (5)	0 (0)	
MCI multiple domains	1 (3)	7 (18)	
Dementia	0 (0)	1 (3)	
No. of domains affected			.03[a]
0	37 (93)	32 (80)	
1	2 (5)	0 (0)	
2	1 (3)	5 (13)	
3	0 (0)	1 (3)	
4	0 (0)	2 (5)	
MCI/dementia			.10
No	37 (93)	32 (80)	
Yes	3 (8)	8 (20)	

MCI, mild cognitive impairment.

[a] Measure of impairment analyzed as ordinal variable with Cochran-Armitage trend test.

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kg/m^2 [IQR 23.1-32.0], $P = .004$), had more CAC (0.0 AU [IQR 0.0-28.0] vs 0.0 AU [IQR 0.0-0.3], $P = .007$), and were more frequently diagnosed with hypertension (60% vs 20%, $P < .001$). More women with hPE than with hNTP were taking medications that could potentially affect cognition (73% vs 40%, $P = .003$). In the hNTP group, none of the women with MCI were taking them. In the hPE group, 3 of the women with MCI were taking them but not the 1 with dementia.

After correction for multiple comparisons, there were no significant differences in women with hNTP or hPE on any measure of cognition or mood. Test scores for each cognitive and mood variable are presented in Table 3. Cohen *d* for magnitude of effect between scores from women with hNTP or hPE indicated moderate effect sizes for logical memory I ($d = 0.52$) and logical memory II ($d = 0.65$), with lower scores in the hPE group. When examining clinical consensus diagnosis, in which impairment was rated on a scale from none to dementia and secondly as a count (observed range 0-4) of affected domains (Table 4), there was a more widespread pattern of cognitive impairment in women with hPE compared to women with hNTP ($P = .03$). Using a binary measure in which all classifications of cognitive impairment are grouped together, there was a modest yet nonsignificant difference ($P = .10$) in the frequency of cognitive impairment among women with hPE (n = 8; 20%) compared to women with hNTP (n = 3; 8%). Further, 2 of the 3 women with hNTP had single-domain (memory) and 1 had multidomain MCI, while all of the 8 women with hPE and cognitive impairment had multiple domains affected, including 7 with MCI and 1 with dementia. None of the women with cognitive impairment reported depression or anxiety sufficient to explain cognitive scores (ie, none reported depression and 1 with hPE reported marginal mild anxiety). Comparing women with hPE with cognitive impairment to hPE without, the largest effect sizes were observed for Trail Making Test B—a test of cognitive speed and flexibility used to assess executive functioning ($d = 1.96$), followed by verbal learning ($d = 1.93$), visual memory ($d = 1.87$), and auditory attention ($d = 1.69$) (Table 5).

In women with hPE, the amount of CAC was greater in those who had cognitive impairment vs those who did not (67.5 AU [IQR 6.0-180.0] vs 0.0 AU [IQR 0.0-25.0], $P = .043$). There was no significant difference in carriers of apolipoprotein E-4 polymorphism between hPE women with and without cognitive impairment nor was there any difference in use of hormone replacement therapy, BMI, frequency of hypertension, or use of medications with cognitive side effects (Table 6).

Comment

The first major finding from this study was a trend toward cognitive impairment being more frequently clinically diagnosed in women with hPE than in women with hNTP. Second, women with hPE showed a more diffuse range (ie, multiple domains) of cognitive impairment, most prominently affecting abilities commonly ascribed to frontal subcortical brain processing, such as executive functioning, verbal learning, and attention.

Previous studies show that women with hPE exhibit variable neurocognitive changes in the first decade following the index pregnancy.[8,13] Results of the current study extend the literature by providing long-term objective and clinical assessment of women with hPE 35 years after the affected pregnancy and are consistent with prior studies showing no differences in scores on objective cognitive measures between women with and without hPE. However, using a clinical approach where women were diagnosed with MCI or dementia according to standard criteria, more women with hPE than hNTP met such criteria. Differences in outcomes based on individual clinical characterization and effect sizes vs statistical group comparisons that obscure important individual differences may help explain disparate results in the literature, for example, frequent subjective cognitive symptoms

TABLE 5
Cognitive and mood comparisons (raw scores) by cognitive status in women with preeclampsia

Cognitive domain	Variable	No impairment n = 32	Impairment n = 8	*P* value	Cohen *d*
Attention	Trail Making Test A, time/sec[a]	25.0 (20.5, 31.0)	27.0 (21.0, 43.0)	.753	0.45
	Digit span	17.0 (14.0, 19.0)	11.0 (11.0, 14.0)	.016	1.69
Working memory	Letter-number sequencing	10.0 (8.5, 11.0)	8.0 (6.5, 8.5)	.018	1.32
Psychomotor speed	Digit symbol coding	59.0 (55.0, 65.5)	54.5 (34.0, 64.0)	.487	0.83
Executive functioning	Trail Making Test B, time/sec[a]	59.5 (48.5, 72.0)	101.0 (70.0, 157.0)	.018	1.96
Language	Letter fluency	42.0 (36.5, 47.5)	32.5 (23.0, 40.5)	.034	1.25
	Category fluency	54.5 (48.0, 62.5)	40.5 (31.0, 44.5)	.018	1.40
	Boston Naming Test	57.0 (55.0, 59.0)	54.5 (52.0, 58.0)	.243	0.72
Visuospatial	Picture completion	15.0 (14.0, 16.0)	14.0 (12.0, 15.0)	.178	0.85
	Block design	28.0 (25.0, 32.0)	22.5 (16.0, 26.0)	.108	0.95
Learning/immediate memory	AVLT trials 1—5	53.0 (47.0, 56.0)	41.5 (29.5, 47.0)	.016	1.93
	Logical memory I	25.0 (22.5, 29.0)	18.5 (16.5, 23.0)	.019	1.40
	Visual reproduction I	34.5 (32.0, 36.0)	31.5 (28.5, 34.0)	.134	0.69
Delayed memory	AVLT delay	11.0 (9.0, 12.0)	7.0 (4.0, 9.0)	.018	1.44
	AVLT percent retention	87.5 (69.0, 93.0)	76.5 (46.0, 85.0)	.228	0.81
	Logical memory II	20.0 (15.0, 24.5)	15.5 (10.0, 19.5)	.116	0.92
	Logical memory percent retention	79.0 (69.0, 88.5)	78.0 (55.0, 89.0)	.897	0.26
	Visual reproduction II	30.0 (28.0, 33.5)	16.0 (11.5, 27.0)	.026	1.87
	Visual reproduction percent retention	93.0 (81.5, 96.5)	64.5 (33.5, 91.0)	.134	1.72
Mood	Beck Depression Inventory[a]	4.0 (1.0, 6.5)	3.5 (1.0, 9.0)	.933	0.08
	Beck Anxiety Inventory[a]	3.0 (1.0, 6.0)	3.5 (0.5, 6.0)	.922	0.15
	POMS anger[a]	0.0 (0.0, 2.5)	0.5 (0.0, 4.0)	.854	0.02
	POMS confusion[a]	5.0 (3.5, 7.5)	7.0 (5.0, 7.5)	.409	0.39
	POMS depression[a]	1.0 (0.0, 5.0)	0.0 (0.0, 4.5)	.659	0.14
	POMS fatigue[a]	2.0 (0.0, 4.5)	3.0 (0.0, 8.0)	.895	0.33
	POMS tension[a]	2.0 (1.0, 4.5)	1.5 (0.5, 4.5)	.640	0.13
	POMS vigor	16.0 (11.0, 21.5)	18.0 (13.5, 20.5)	.753	0.19

Scores are presented as median (25th, 75th percentiles).

AVLT, Auditory Verbal Learning Test; *POMS*, Profile of Mood States.

[a] Higher score is worse—scores are total raw scores. Significant group differences are corrected for multiple comparisons.

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reported by women with hPE yet no objective psychometric evidence.

Factors known to increase brain vulnerability and associate with CVD and cognitive dysfunction include hypertension,[4,5,21] diabetes,[22] dyslipidemia,[23] obesity and BMI,[24,25] carotid intima-media thickness,[26] CAC,[27,28] and genetic polymorphisms (eg, apolipoprotein E-4).[29,30] Many of these factors also share association with hypertensive pregnancy disorders.[1,31-35] Our study is consistent with the literature in that women with hPE had higher BMI, had higher CAC, and were more frequently hypertensive than women with hNTP. In the women with hPE, those with cognitive impairment had more CAC than those without cognitive impairment.

In preeclampsia, pathophysiological mechanisms associated with vascular disease may exist before, and persist long after, the affected pregnancy.[36-39] It is unclear whether hypertensive pregnancies induce vascular changes or whether they further stimulate a cascade of already evolving changes. Vascular pathology is present in 29-41% of dementia cases that come to autopsy.[40-42] Microvascular and macrovascular changes that disrupt blood flow integrity can cause structural and functional brain changes,[43] which can lead to vascular

TABLE 6
Demographics and clinical characteristics of women with history of preeclampsia by cognitive status

Variable	No impairment, n = 32	Impairment, n = 8	*P* value
Age at study consent, y	58.3 (55.6, 61.2)	63.2 (59.3, 65.4)	.063
Age at first live birth, y	24.4 (21.7, 25.2)	26.4 (22.1, 29.9)	.166
Time since first live birth/index pregnancy, y	34.9 (32.9, 36.7)	35.2 (32.7, 37.0)	.892
Parity	3.0 (2.0, 3.5)	2.0 (2.0, 2.5)	.055
Education			.053
≤High school	3 (9%)	3 (38%)	
Some college/technical/vocational	18 (56%)	4 (50%)	
≥College graduate	11 (34%)	1 (13%)	
BMI, kg/m^2	29.4 (25.7, 33.3)	32.5 (27.8, 34.1)	.398
Diastolic blood pressure, mm Hg	78.7 (71.0, 82.2)	83.0 (66.5, 94.8)	.407
Systolic blood pressure, mm Hg	130.8 (119.7, 139.2)	136.5 (124.3, 144.7)	.398
LDL cholesterol, mg/dL	106.1 (90.7, 124.3)	93.1 (70.6, 131.1)	.447
HDL cholesterol, mg/dL	49.0 (37.5, 68.5)	60.0 (48.5, 84.5)	.171
Triglycerides, mg/dL	116.0 (91.0, 178.0)	97.5 (77.0, 114.5)	.223
Fasting glucose, mg/dL	101.0 (91.5, 112.0)	97.5 (90.0, 98.5)	.457
Diabetes	3 (9%)	1 (13%)	1.000
Albumin/creatinine ratio, mg/mmol	2.6 (0.0, 5.1)	2.3 (0.0, 7.2)	.901
Past or current hormone therapy	13 (41%)	4 (50%)	.631
Ongoing hormone therapy	5 (16%)	1 (13%)	1.000
17β-Estradiol, pg/mL	5.5 (2.4, 8.0)	4/0 (2.5, 6.4)	.447
Estrone, pg/mL	26.5 (15.0, 34.0)	22.5 (8.0, 29.5)	.302
Coronary artery calcification, AU	0.0 (0.0, 25.0)	67.5 (6.0, 180.0)	.043
ApoE-4 polymorphism	8 (25%)	3 (38%)	.479
Hypertension	18 (56%)	6 (75%)	.333
Medication with potential cognitive side effects	25 (78%)	4 (50%)	.111
Obstructive sleep apnea	8 (25%)	4 (50%)	.168
Family history of dementia	8 (25%)	4 (50%)	.168

Continuous variables are reported as median (25th, 75th percentiles) whereas discrete variables are presented as count (percentage).

ApoE-4, apolipoprotein E-4; *AU*, Agatston unit; *BMI*, body mass index; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein.

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cognitive impairment directly[44] or indirectly by disrupting white matter pathways.[45-47] White matter hyperintensities on imaging associate with decreased performance on tests of executive functioning and psychomotor speed and processing with a fair amount of consistency, and more variably to diminished learning, episodic memory, and visual memory and organization.[48,49] Although most of these studies have focused on persons age >65 years, findings were similar in a large cohort where the average age was 61 (range 34-88) years.[48] This suggests that vascular changes associated with cognitive changes may not be purely age-related and lend support to changes observed in the current sample of younger women (age 59 [range 52-72] years).

The association of white matter hyperintensities and decreased cognitive performance on tasks of executive functioning and psychomotor processing[48] raises speculation that compromised white matter tracts result in the disruption of cortical-subcortical pathways that subserve these functions.[47] Indeed, in women with hPE examined in their late 30s, approximately 5 years from index pregnancy, white matter lesions were greater compared to women with hNTP.[50] In further support that hypertensive pregnancy is an independent predictor of change in cognition and brain structure, women with a history of

hypertensive pregnancy disorders have been shown to have smaller brain volumes than women with normotensive pregnancies decades later, even after adjusting for traditional cardiovascular risk factors,[51] in addition to increased risk of CAC.[14] A recent study found no relationship between white matter hyperintensities, objective cognitive performance, or subjective cognitive symptoms in formerly preeclamptic women 40 years of age 6 years after pregnancy,[52] and we postulate that these women have not yet reached an age threshold that challenges cognitive reserve.

The fact that 25% of women with normal cognition and 38% with impaired cognition in our preeclampsia group were found to have an apolipoprotein E-4 polymorphism suggests that this gene may not independently increase risk of cognitive decline, but rather, interact with other underlying disease pathology, including cerebrovascular disease.[53] Hormone replacement therapy, too, has been linked to negative cognitive function, and in particular, conjugated equine estrogen.[54] In our study, we do not have information on type of hormone treatments, but current hormone levels (17β-estradiol and estrone) were measured in all women and did not differ between groups (Tables 2 and 6).

A goal of the study was to assess the subclinical effect of hPE on cognitive functioning. A strength of our study is our extensive medical record data that allowed us to closely match women with and without hPE and to exclude women with potential neurologic confounding comorbidities.

Limitations of this study include the small sample size and potential response and selection biases. If women with hPE experience more cognitive decline and are more self-aware of cognitive inefficiencies, it may be that some were less likely to participate for fear of confirming their subjective experience of cognitive loss. In addition, a reported history of dementia was exclusionary. If this study captured a "more normal than not" sample, it might explain the lack of significant cognitive differences in comparisons of test scores between women with and without hPE. Results may also be biased toward less physically healthy women since women per inclusion criteria who did not have a documented clinical visit within the last 2 years, perhaps because they were healthier, were not contacted. Lastly, this study reflects Olmsted County, Minnesota, which is primarily white, non-Hispanic, and fairly highly educated. Higher levels of education and cognitive reserve[55-57] have been associated with reduced risk of cognitive decline and dementia. Both groups were comparably educated, which could limit our ability to detect subtle cognitive changes. Women with hPE and cognitive impairment were less highly educated than those without cognitive impairment, although the sample size is too small for this to be a meaningful finding. In addition, 23 of the 40 hNTP and 26 of the 40 hPE women reported ethnicity, and all identified as white/Caucasian. Therefore, these findings may not generalize to women with lower education or of other races and ethnicities.

In summary, women with hPE more frequently have a higher BMI, hypertension, and metabolic dysregulation, exacerbating an increased risk of cardiovascular morbidity and mortality over the life course. CVD is associated with cognitive decline and dementia. Results of this study suggest a trend for women with hPE to exhibit more cognitive impairment 35 years later than women with similar demographics but who experienced a normotensive pregnancy. The mechanisms underlying this difference are unclear, but could reflect common mechanisms contributing to CAC and brain changes, such as white matter lesions. White matter lesions are common even in the early years following index pregnancy, and the pattern of cognitive impairment observed in this study appears to reflect disruption in frontal subcortical white matter tracts, although a larger sample size will be needed to delineate this more clearly. The broader implications are that many cardiovascular risk factors are modifiable, and lifestyle interventions, particularly in women with hPE, may help prevent cognitive impairment. Obstetricians/gynecologists are often the only care provider women see regularly throughout their menopausal years, and as such are in a unique position to integrate pregnancy history into risk assessment for future neurologic morbidity, recognize often missed cognitive impairment, and initiate individualized prevention and treatment plans. ■

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