

## 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.<sup>1</sup> Preeclampsia occurs in about 3% of pregnancies,<sup>2</sup> and is associated with an approximate 2-fold increased risk of CVD and cerebrovascular disease.<sup>3</sup> Some risk factors associated with preeclampsia are shared with those for CVD and cognitive decline, including hypertension, metabolic syndrome, and insulin resistance.<sup>4-7</sup>

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).<sup>8-10</sup> In addition, reported changes in cognition associate with the severity of preeclampsia<sup>11</sup> or posttraumatic stress symptoms of preeclampsia.<sup>12</sup> 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.<sup>13</sup> In contrast, others have found slower motor speed,<sup>8</sup> poorer attention,<sup>12</sup> or poorer learning and memory<sup>11</sup> 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.<sup>14</sup> In brief, Hospital Adaptation of the *International Classification of Diseases* codes and the population-based Rochester Epidemiology Project medical records linkage system<sup>15</sup> 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	<p>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.</p> <p>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.</p>
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	<p>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.</p> <p>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.</p>
Visuospatial processing	<p>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.</p> <p>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.</p>
Learning and memory	<p>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.</p> <p>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.</p> <p>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.</p>

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(continued)

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

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