Neurocognitive Outcomes Are Not Improved by 17β-Estradiol in Postmenopausal Women Undergoing Cardiac Surgery

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Background and Purpose—Neurocognitive dysfunction is an important source of patient morbidity and mortality after cardiac surgery that may disproportionately affect postmenopausal women. 17β-Estradiol limits the extent of ischemic neuronal injury in a variety of experimental models. The purpose of this study was to evaluate whether perioperative administration of 17β-estradiol to postmenopausal women reduces the frequency of neurocognitive dysfunction after cardiac surgery.

Methods—One hundred seventy-four postmenopausal women not on estrogen replacement therapy who were undergoing cardiac surgery. In single-center and multicenter studies, we found a significantly higher frequency of perioperative neurological complications and higher stroke-related mortality for women compared with men.

Results—There were no differences in the frequency of neurocognitive dysfunction (primary outcome) between patients randomized to perioperative 17β-estradiol (n=86) and those randomized to placebo (n=88) 4 to 6 weeks after surgery (17β-estradiol, 22.4% versus placebo, 21.4%, P=0.45). The mean scores on tests of psychomotor speed were worse in women in the 17β-estradiol group than in the placebo group at the 4- to 6-week (P=0.005) postoperative testing sessions.

Conclusions—Perioperative treatment with 17β-estradiol did not result in improved neurocognitive outcomes in postmenopausal women undergoing cardiac surgery. (Stroke. 2007;38:000-000.)

Key Words: cardiac surgery ■ cognitive impairment ■ estrogen ■ neuroprotective agents

Despite having a lower lifetime risk for stroke, women who have stroke experience worse functional outcomes and have higher stroke-related mortality compared with men. The health impact of stroke increases markedly for women after menopause, resulting in equalization of stroke rates between the sexes. Worse stroke outcome is a particular concern for the increasing number of elderly women undergoing cardiac surgery. In single-center and multicenter studies, we found a significantly higher frequency of perioperative neurological complications and higher stroke-related operative mortality for women compared with men.

Our findings of higher stroke rates for women than men after cardiac surgery could not be explained by known stroke risk factors. Because the majority of women undergoing cardiac surgery are postmenopausal, we hypothesized that this higher risk might be linked to their hypoestrogenic state. This premise is supported by laboratory experiments that have consistently shown the salutary effects of estrogen for limiting ischemic neuronal injury. Despite these data, studies in community-dwelling subjects have found no benefit of long-term postmenopausal estrogen replacement therapy for the primary or secondary prevention of stroke. There is a paucity of clinical data, however, on the potential neuroprotective effects of short-term estrogen replacement, a scenario that more closely assimilates the laboratory experiments establishing such benefit. Furthermore, in contrast to long-term hormone replacement studies wherein treatment compliance ranged from 46% to 70%, estrogen replacement can be guaranteed in the perioperative setting and given before cerebral injury, perhaps providing a more reliable means for testing its neuroprotective efficacy.

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Clinical trial registration information is available at http://clinicaltrials.gov/show/NCT00123539.

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The purpose of this trial was to test the hypothesis that, compared with placebo, perioperative administration of 17β-estradiol to postmenopausal women reduces the risk of the most common neurological complication of cardiac surgery, neurocognitive dysfunction. The present report is based on data made available after the second scheduled interim analysis of this trial by the independent study data and safety monitoring committee. This committee recommended that enrollment be halted in the trial because of a low likelihood of finding differences in the primary outcome between the 2 treatment arms and of safety concerns.

Patients and Methods

Eligible patients were women ≥55 years of age undergoing coronary artery bypass graft and/or cardiac valve replacement surgery at 3 BJC Health Care System hospitals in St. Louis, Mo. All study procedures were approved by the human studies committee of each enrolling site and were performed after receiving written, informed consent. Exclusion criteria were as follows: (1) off-pump surgery; (2) elevated values on liver function tests or creatinine levels (>2 mg/dL); (3) emergency or reoperative surgery; (4) planned use of antifibrinolytic therapy; (5) history of venous thromboembolism; (6) vaginal bleeding; (7) history of breast cancer or endometrial cancer in the absence of hysterectomy; or (8) estrogen use within 6 months before surgery.

Perioperative 17β-Estradiol or Placebo Treatment

Patients were prospectively randomized by a computer-generated list to receive either 17β-estradiol or placebo in a double-blinded manner. Two identical 25-cm² transdermal patches containing 17β-estradiol (Climara, Berlex Laboratories, Wayne, NJ) or placebo (blank patches) were applied to the left scapular area the day before surgery and left in place until the fifth postoperative day. Each active transdermal patch contains 7.6 mg of 17β-estradiol and is designed to deliver 0.075 to 0.1 mg of 17β-estradiol per day. On the day of surgery, 30 minutes before cardiopulmonary bypass (CPB), a double-blinded intravenous infusion of 17β-estradiol or placebo was started and continued until the conclusion of surgery. The active drug was prepared to a final 17β-estradiol concentration of 20 ng/mL. (Dr Hogue was issued US Food and Drug Administration IND # 58,173.) The placebo was the carrier for 17β-estradiol (0.66% ethanol in 5% dextrose) prepared in an equal volume. The rate of 17β-estradiol infusion was 0.08 ng·kg⁻¹·min⁻¹; the placebo was given at the same rate. Our dosing scheme aimed to achieve 17β-estradiol blood levels at the high end of those targeted for postmenopausal estrogen replacement (90 to 120 pg/mL) and those providing neuroprotection in animal stroke models (60 to 180 pg/mL). Plasma 17β-estradiol concentrations were measured before treatment, before and at the conclusion of CPB, and on the morning of postoperative days 1 and 5. Blood was collected into glass tubes containing EDTA, and then the serum was stored at −80°C until the time of the assay. Measurement of 17β-estradiol concentrations was performed with a microparticle enzyme immunoassay technique (IMx, Abbott Laboratories, Abbott Park, Ill; assay sensitivity was 25 pg/mL).

Neurocognitive and Neurological Testing

The patients underwent psychometric testing 1 to 2 days before surgery, 4 to 6 weeks after surgery, and 6 months after surgery. The chosen tests (see supplemental Table I, available online at http://stroke.ahajournals.org) assessed a broad array of cognitive domains in accordance with consensus conference recommendations, including memory, complex attention, executive function, psychomotor processing, fine motor speed, and visuospatial processing.19–26 The patient’s mood state was assessed by the Beck Anxiety Inventory and the Beck Depression Inventory.²⁷–²⁸ Patients were evaluated on the National Institutes of Health Stroke Scale (NIHSS) before and after surgery by trained research personnel.²⁹

Perioperative Care and Monitoring

Details of the patients’ care during and after surgery have been previously reported.³⁰ Anesthetic drugs were given in doses permissive of early postoperative tracheal extubation. Nonpulsatile CPB with a membrane oxygenator and a 40-μm in-line arterial filter was used, and body temperature was maintained between 32°C and 34°C until separation from CPB. Mean arterial blood pressure was kept between 50 and 80 mm Hg during CPB with the use of vasoactive drugs. Epiacard ultrasonography was performed before aortic manipulations to assess for atherosclerosis of the ascending aorta, as previously described.²³ The patients were visited daily by members of the investigative team, and clinical complications were documented. The patients had ECG monitoring until hospital discharge for arrhythmia monitoring. Twelve-lead ECGs were obtained before surgery and on the first 4 postoperative days. Serum troponin I concentrations were measured before surgery, on arrival in the intensive care unit after surgery, and for the first 4 postoperative days with an enzyme immunoassay (normal levels <0.1 ng/mL).

Cardiovascular Complications

Atrial fibrillation was defined as an irregularly irregular cardiac rhythm in the absence of P-waves lasting ≥1 minute regardless of treatment. Two physicians blinded to treatment and patient outcomes independently reviewed 12-lead ECGs and the troponin I results. A Q-wave myocardial infarction (MI) was defined as the presence of a new Q-wave >1/3 the height of the ECG R-wave on the 12-lead ECG and a rise in troponin I concentrations ≥6 ng/mL from preoperative levels. A non-Q wave MI was diagnosed when there was an increase in the troponin I concentrations >13 ng/mL from preoperative baseline in the absence of a new Q-wave.³¹ The diagnosis of MI was made by consensus, and a third cardiologist was consulted when there was disagreement. Low cardiac output syndrome was defined as a cardiac index <2.0 L·min⁻¹·m⁻² for >8 hours regardless of treatment.

Neurological Complications

Consultation with a neurologist was obtained when there was a clinical diagnosis of stroke or when there was a postsurgical increase of ≥1 point from baseline on the NIHSS. All suspected cases of stroke were independently reviewed by 2 neurologists blinded to study treatment. A stroke was defined as a persistent (>24 hours) impairment in motor or sensory function or coma that was not explained by another diagnosis such as central nervous system-depressing drugs, hypoxia, or electrolyte or metabolic causes. The diagnosis of stroke was made by consensus.

Statistical Analysis

The planned study enrollment was 334 patients, and it assumed a 10% dropout rate at the 4- to 6-week postoperative testing session (primary end point). Power calculations were based on a 2-sided test of the equality of proportions at the 0.05 level of significance, with adjustment by the O’Brien-Fleming stopping rule.³² Power calculations assumed that 35% of control patients and 20% of 17β-estradiol patients would have neurocognitive deficits 4 to 6 weeks after surgery. A principal-components analysis demonstrated that the cognitive measures were not significantly intercorrelated, thus achieving our aim of developing a psychometric battery that assessed a broad array of cognitive domains. Cognitive decline was thus defined as a decrease from baseline by >1 SD on 2 or more of the psychometric tests. This definition is associated with fewer false-positive results than alternative definitions.³³ The primary study outcome was cognitive decline 4 to 6 weeks after surgery. Patients who experienced a perioperative stroke and died before postoperative psychometric testing were classified as having neurocognitive dysfunction. All statistical tests were 2 sided; data for continuous variables are presented as mean ± SD. Baseline comparisons were performed with t tests, the χ² test, or Fisher’s exact test (when cell counts were too low). When the assumptions of these tests were violated, Wilcoxon’s
test was used. A mixed-model repeated-measures ANOVA and ANCOVA were used to compare changes over time in continuous measures, with regression residuals being used to assess the fit of the model. Logistic regression provided covariate-adjusted, between-group comparisons of dichotomous measures, and the Hosmer-Lemeshow goodness-of-fit test was used to establish a good fit for the model. Covariates included in the regression models were those that differed across groups at baseline. All analyses were performed with SAS. When missing psychometric data were caused by the patient’s inability to perform the test, the value assigned was the worst value for that cognitive measure for all subjects at that time point. Because missing data in these instances were nonrandom, standard imputation methods would not be appropriate and would be far less precise than the assigned values that were based on the known inability of subjects to perform the required tasks.

### Results

One hundred eighty-six patients were enrolled in the trial. Twelve women were dropped from further study owing to a change in surgical plan (n=3), withdrawal of consent (n=4), previously undisclosed history of breast cancer (n=1), and...
decline occurred at a similar frequency between the treatment groups 4 to 6 weeks after surgery or 6 months after surgery.

Testing results for each psychomeric measure are listed in Table 4. The multiple-regression models in the Table were adjusted for chronic obstructive pulmonary disease and left ventricular function because there were baseline between-group differences for those variables. We did not adjust for the need for an intra-aortic balloon pump because of its low rate of use and because no placebo group subjects needed this support. Results were the same when analyses were repeated with intra-aortic balloon pump users excluded. The average scores on the Trails A test at the 4- to 6-week and the 6-month postoperative testing sessions were worse (higher score means worse performance for a timed test) in 17β-estradiol–treated patients compared with the placebo group. Improvement in test scores in the placebo group with subsequent testing likely contributed to this difference. Beck Anxiety Inventory score was higher in the 17β-estradiol group than in the placebo group at the 4- to 6-week (9.33±7.33 versus 6.76±5.18, \( P=0.02 \)) and at the 6-month (8.86±6.79 versus 6.52±5.24, \( P=0.04 \)) testing periods after surgery. Nonetheless, there were no differences between treatment groups in changes in the Beck Depression Inventory or Beck Anxiety Inventory results across the 3 time periods.

**Discussion**

Our findings are that, compared with placebo, treatment with 17β-estradiol beginning the day before cardiac surgery and continuing for the first 5 postoperative days does not reduce the frequency of neurocognitive dysfunction 4 to 6 weeks or 6 months after surgery in postmenopausal women. Scores for tests of psychomotor speed (Trails A) were in fact higher after surgery for the 17β-estradiol group compared with the placebo group. Women receiving 17β-estradiol were more likely than placebo-treated patients to have an increase from baseline in the NIHSS after surgery, a difference that was not statistically significant after adjustment for preoperative medical conditions.

Brain injury from cardiac surgery has a range of manifestations, including stroke, encephalopathy, and/or neurocognitive dysfunction. Although stroke is more often recognized clinically, affecting 1% to 3% of patients, neurocognitive dysfunction is more common, occurring in >30% of patients.

### Table 2. Perioperative Complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects n=174</th>
<th>Placebo Group n=88</th>
<th>17β-Estradiol Group n=86</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>42.2%</td>
<td>40.9%</td>
<td>43.5%</td>
<td>0.73</td>
</tr>
<tr>
<td>Low cardiac output syndrome</td>
<td>3.5%</td>
<td>2.3%</td>
<td>4.7%</td>
<td>0.44</td>
</tr>
<tr>
<td>Postoperative MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non–Q wave</td>
<td>11.8%</td>
<td>19.1%</td>
<td>5.5%</td>
<td>0.08</td>
</tr>
<tr>
<td>Q-wave</td>
<td>7.8%</td>
<td>4.3%</td>
<td>10.9%</td>
<td></td>
</tr>
<tr>
<td>NIHSS score on postoperative day 5</td>
<td>2.26±6.9</td>
<td>0.65±2.1</td>
<td>3.82±9.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Days in the intensive care unit</td>
<td>3.54±6.8</td>
<td>2.75±2.8</td>
<td>4.31±9.2</td>
<td>0.77</td>
</tr>
<tr>
<td>Days in the hospital</td>
<td>9.11±9.2</td>
<td>8.09±5.9</td>
<td>10.16±11.6</td>
<td>0.76</td>
</tr>
<tr>
<td>One-month mortality</td>
<td>5.9%</td>
<td>8.6%</td>
<td>3.3%</td>
<td>0.22</td>
</tr>
<tr>
<td>Six-month mortality</td>
<td>8.4%</td>
<td>10.3%</td>
<td>6.6%</td>
<td>0.46</td>
</tr>
</tbody>
</table>
4 to 6 weeks after surgery and in 20% to 40% of patients 5 months later. The relation between postoperative neurocognitive dysfunction and operative mortality, health resource consumption, diminished quality of life, and long-term cognitive decline underscores its importance in an increasingly aged surgical population.

A potential explanation for the failure of 17β-estradiol to lessen the frequency of cognitive decline in this study might be inappropriate dosing or duration of therapy. We targeted 17β-estradiol levels similar to those occurring in midcycle in ovulating women. Both pharmacological and physiological doses of 17β-estradiol limit experimental ischemic brain injury, whereas other data suggest a narrow therapeutic window in the low physiological range. The targeting of estrogen levels in this range in women nearly 20 years after menopause might further have contributed to our negative findings. The beneficial effects of hormone therapy on cardiovascular risk are suggested to depend on the initiation of hormone therapy early after menopause, whereas initiation of hormone replacement >10 years after menopause confers no benefit against coronary heart disease. In our study, 17β-estradiol was given only perioperatively, whereas our primary outcome was assessed 4 to 6 weeks after surgery. It is possible that ongoing neurological injury might have occurred after this short treatment period, masking any potential early benefits. We did not measure cognitive function early after surgery because, in our experience, those data are confounded by ongoing pain, fatigue, and other responses to surgery. In most series, though, cognitive performance tends to improve rather than decline in the first postoperative month. Perhaps another explanation for our findings is that in many experimental animal models of ischemic brain injury, 17β-estradiol is given for 1 week before the ischemic insult. This approach would be logistically difficult to implement owing to practice patterns in the United States, where cardiac surgery is typically performed after short preoperative waiting times. Regardless, we cannot exclude the possibility that a different 17β-estradiol dose or longer treatment might lead to benefit on cognitive outcomes after cardiac surgery.

### TABLE 3. Dichotomous Measures of Neurological Deterioration 4 to 6 Weeks and 6 Months After Surgery

<table>
<thead>
<tr>
<th>Type of deficit</th>
<th>Placebo Group</th>
<th>17β-Estradiol Group</th>
<th>Unadjusted $P$ Value</th>
<th>Adjusted $P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stroke</td>
<td>4.6%</td>
<td>4.7%</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>† NHSS &gt;2 from baseline</td>
<td>11.6%</td>
<td>26.2%</td>
<td>0.01</td>
<td>0.22</td>
</tr>
<tr>
<td>Cognitive decline 4 to 6 weeks after surgery</td>
<td>21.4%</td>
<td>22.4%</td>
<td>0.90</td>
<td>0.45</td>
</tr>
<tr>
<td>Cognitive decline 6 months after surgery</td>
<td>14.7%</td>
<td>23.2%</td>
<td>0.24</td>
<td>0.82</td>
</tr>
</tbody>
</table>

### TABLE 4. Psychometric Testing Results From Baseline and the 2 Postoperative Testing Sessions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Assessment Time</th>
<th>Placebo Group</th>
<th>17β-Estradiol Group</th>
<th>Unadjusted $P$ Value</th>
<th>Adjusted $P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit Symbol: total correct</td>
<td>Baseline</td>
<td>41.3±17</td>
<td>40.2±18</td>
<td>0.680</td>
<td>0.604</td>
</tr>
<tr>
<td></td>
<td>4–6 weeks</td>
<td>47.8±18</td>
<td>47.6±21</td>
<td>0.956</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>48.8±18</td>
<td>47.1±20</td>
<td>0.399</td>
<td>0.38</td>
</tr>
<tr>
<td>Trail Making A Time</td>
<td>Baseline</td>
<td>66.6±43</td>
<td>59.1±35</td>
<td>0.229</td>
<td>0.058</td>
</tr>
<tr>
<td></td>
<td>4–6 Weeks</td>
<td>54.8±29</td>
<td>58.2±36</td>
<td>0.006</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>53.2±25</td>
<td>61.5±41</td>
<td>0.010</td>
<td>0.006</td>
</tr>
<tr>
<td>Trail Making B Time</td>
<td>Baseline</td>
<td>169±119</td>
<td>171±116</td>
<td>0.933</td>
<td>0.471</td>
</tr>
<tr>
<td></td>
<td>4–6 Weeks</td>
<td>128±59</td>
<td>133±67</td>
<td>0.423</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>132±81</td>
<td>169±145</td>
<td>0.118</td>
<td>0.10</td>
</tr>
<tr>
<td>Pegboard Dominant Hand, s</td>
<td>Baseline</td>
<td>154±97</td>
<td>186±121</td>
<td>0.086</td>
<td>0.745</td>
</tr>
<tr>
<td></td>
<td>4–6 Weeks</td>
<td>127±78</td>
<td>147±105</td>
<td>0.824</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>128±66</td>
<td>149±92</td>
<td>0.603</td>
<td>0.832</td>
</tr>
<tr>
<td>Pegboard Nondominant Hand, s</td>
<td>Baseline</td>
<td>164±106</td>
<td>200±131</td>
<td>0.078</td>
<td>0.555</td>
</tr>
<tr>
<td></td>
<td>4–6 Weeks</td>
<td>127±49</td>
<td>135±62</td>
<td>0.276</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>136±74</td>
<td>166±107</td>
<td>0.859</td>
<td>0.86</td>
</tr>
<tr>
<td>Benton Visual Form Discrimination</td>
<td>Baseline</td>
<td>12.3±3.3</td>
<td>12.1±3.5</td>
<td>0.732</td>
<td>0.972</td>
</tr>
<tr>
<td></td>
<td>4–6 Weeks</td>
<td>13.5±2.5</td>
<td>13.2±2.8</td>
<td>0.846</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>14.1±2.1</td>
<td>13.2±2.6</td>
<td>0.272</td>
<td>0.37</td>
</tr>
<tr>
<td>Rey Auditory Test: sum A1–A7</td>
<td>Baseline</td>
<td>61.3±21</td>
<td>58.2±20</td>
<td>0.344</td>
<td>0.983</td>
</tr>
<tr>
<td></td>
<td>4–6 Weeks</td>
<td>57.4±19</td>
<td>56.6±20</td>
<td>0.959</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>69.6±18</td>
<td>65.1±23</td>
<td>0.447</td>
<td>0.39</td>
</tr>
</tbody>
</table>

The Trails tests and the Pegboard tests are timed tests, for which higher scores indicate worse performance. Lower scores on the other measures indicate worse performance.
Extensive laboratory evidence has convincingly shown that 17β-estradiol limits the extent of ischemic neuronal injury via multiple genomic and nongenomic mechanisms. It is plausible that the conditions under which estrogens are found experimentally to limit neuronal damage, for many reasons, do not replicate the clinical conditions of brain injury.\(^1\) In interpreting our data, though, consideration must be given to the possible low sensitivity of the primary end point of this study. Cerebrovascular disease predisposing to cognitive impairment is increasingly recognized in patients scheduled for cardiac surgery, likely due to hypertension, diabetes, and widespread atherosclerosis.\(^3\) A recognized limitation of psychometric testing is the low likelihood of identifying further decrements in cognition in individuals with low levels of baseline function (the "basement effect"). Studies evaluating neuroprotective strategies in patients with cerebrovascular disease might be more authoritative if brain imaging end points are included with clinical and neurocognitive outcomes.

Our results can be considered in the broader context of data from postmenopausal hormone replacement studies in nonsurgical patients. In the Heart and Estrogen/Progestin Replacement Study, hormone replacement therapy given after an acute coronary ischemic event had no effect on the risk of stroke after 4.1 years of follow-up.\(^10,11\) In the Women’s Estrogen for Stroke Trial, 17β-estradiol treatment started within 90 days of an ischemic stroke or transient ischemic attack did not affect the risk of death or stroke compared with placebo after a mean follow-up of 2.8 years.\(^12\) In contrast, 2 studies of the Women’s Health Initiative found that long-term estrogen replacement with or without progesterone increased the risk for stroke in postmenopausal women without established cardiovascular disease compared with placebo.\(^13\) Other randomized trials have shown no benefits or even deleterious effects of estrogen replacement on the progression of cognitive decline in elderly individuals, including those with Alzheimer’s disease.\(^14–18\)

Early termination of this trial resulted from the data and safety monitoring board’s concerns of potential harm to participants with continuation of the study when there was little likelihood of benefit. This safety concern was due in part to the finding of an unadjusted higher rate of postoperative increases in the NIHSS with 17β-estradiol treatment. These findings were considered in light of data that became available during the conduct of this trial, showing no benefit and possible harm of estrogen replacement for stroke prevention.\(^19–15\)

Thus, despite a sound experimental rationale and ensuring compliance, short-term 17β-estradiol treatment did not improve cognitive outcomes in postmenopausal women undergoing cardiac surgery compared with placebo. The data from this trial of short-term estrogen administration provide further evidence of the ineffectiveness and possible harm of estrogen replacement in reducing the extent of brain injury from a variety of causes in postmenopausal women.

Acknowledgments

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Disclosures

None.

References

and estradiol-17β during the menstrual cycle. J Clin Endocrinol Metab. 1972;34:312–316.


<table>
<thead>
<tr>
<th>Instrument</th>
<th>Cognitive Domain</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey Auditory Verbal Learning Test</td>
<td>Verbal memory</td>
<td>List of 15 words is presented over multiple trials and recall is tested after 30 minutes.</td>
</tr>
<tr>
<td>Digit Symbol subtest of Wechsler Adult Intelligence Scale</td>
<td>Complex attention</td>
<td>Participants transcribe number-symbol pairs under timed conditions.</td>
</tr>
<tr>
<td>Trail Making Test A and B</td>
<td>Psychomotor speed (Trails A) and Executive function (Trails B)</td>
<td>Participants connect numbered and then alternately numbered and lettered dots in order, under timed conditions.</td>
</tr>
<tr>
<td>Grooved Pegboard Test</td>
<td>Fine motor speed</td>
<td>Pegs are rapidly placed into fitted holes on a shallow box. Dominant and nondominant hands are tested separately.</td>
</tr>
<tr>
<td>Benton Visual Form Discrimination Test</td>
<td>Visual spatial processing</td>
<td>Participants match target and shapes visually.</td>
</tr>
</tbody>
</table>
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