A longitudinal study of cognition change during early menopausal transition in a rural community

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Abstract

Objective: To characterize changes in cognition that occur during the hormonal transitions of menopause.

Method: We conducted a longitudinal population-based study in Kinmen, Taiwan, recruiting all women age 40–54 years who were premenopausal and without a history of hormone replacement therapy (HRT) or hysterectomy. The cognitive measures used to assess function included the Auditory–Verbal Learning Test, visual memory, verbal fluency, Trail Making Test and digit span.

Results: A total of 694 eligible women participated in the baseline study, and 573 women (83%) completed follow-up 18 months later. After excluding 78 women who received hysterectomy or HRT, the final sample was composed of 495 subjects, of whom 114 (23%) progressed to perimenopause during follow-up. Women who remained premenopausal were younger than those who became perimenopausal (44.7 ± 2.3 years versus 47.1 ± 3.0 years, p < 0.01). All follow-up cognitive scores in women who entered perimenopause were slightly better than baseline measures except for Rey Auditory–Verbal Learning Test, which decreased by 0.23 (S.D. = 2.9, p = 0.3). At follow-up, cognitive function except for verbal fluency did not differ significantly between women who stayed premenopausal and those became perimenopausal after controlling for age, education, and baseline cognitive scores. Women who entered perimenopause have an average of 1.3 items (S.D. = 0.4) less in verbal fluency measures as compared with their premenopausal peers at the follow-up period.

Conclusions: The menopausal transition might not accompany significant cognitive decline except for verbal fluency.

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1. Introduction

Memory decline is a very common complaint during the menopausal transition [1]. Neurobiologists have provided clinicians with much evidence of estrogen’s effects on neuronal structure and function, including enhancement of cognitive function via acetylcholine and serotonin that increases synaptogenesis and neuron protection [2]. Nevertheless, results of these studies as conducted in humans are controversial. Some studies suggest that estrogen can improve or preserve cognitive function in postmenopausal women [3], whereas others indicate that estrogen does not maintain or enhance cognitive function in these women [4]. Some authors have asserted that different psychometric tests are the basis for differences in results [5].

Our previous cross-sectional study [6] showed most cognitive functions significantly decreased from the premenopausal to the postmenopausal stage. However, almost all of these differences were lost after adjusting for age and education. The exception was the Trail Making Test, part A, but its rate ratio of decrease was quite small.

The cross-sectional study could not distinguish cohort effect from aging effect; therefore, a longitudinal study could provide additional information about this issue. There is only one longitudinal study conducted in a metropolitan area with well-educated American women, which measured changes in cognitive function during the menopausal transition [7]. This study reported that the transition through menopause was not accompanied by a decline in working memory and perceptual speed. Whether these results could apply to other cognitive functions and different ethnic and educational groups is unknown.

In order to investigate whether the menopausal transition is associated with various cognitive changes in Taiwanese women, we conducted a follow-up study in the cohort of the Kinmen Women-Health Investigation (KIWI) [8].

2. Methods

2.1. Kinmen and its participants

Kinmen is a 176 km² island located 154 miles (248 km) west of Taiwan and 25 miles (41 km) east of mainland China. The people of Kinmen are Han Chinese, and most are involved in farming. There are four townships in Kinmen (total population 51,060 [1998]) with similar demographic compositions. Based on logistic convenience, the townships of Kin-Hu and Kin-Cheng were chosen for the study. From 1998 registration records, there were 2256 women aged 40-54 years living in these two townships and all of them were invited to participate in this longitudinal study without use of a sampling framework.

2.2. Procedures

The Kinmen Women-Health Investigation cohort was established in 1998 [8]. The study protocol was approved by the institutional review board of Taipei Veterans General Hospital. The details of the KIWI have been described elsewhere [8].

From July 1998, all targeted subjects were screened through an interview, at which time they were asked about their demographics and medical and reproductive history. In particular, each was asked about the presence or absence of menopausal or perimenopausal symptoms. Each subject also received a 45 min battery of neuropsychological tests. Women who were premenopausal at the baseline survey were followed up 18 months later with the same instruments. The range of follow-up time was from 18 to 24 months with a mean of 20 months.

2.3. Definition of menopausal status

Women were classified as premenopausal, perimenopausal or postmenopausal. The premenopausal period was defined as regular menstruation. A woman was considered perimenopausal if her menstrual cycles had been irregular or her last menstrual bleeding occurred >3 and ≤12 months prior to study baseline. Women who had not menstruated within the previous 12 months were categorized as postmenopausal. Women with surgically induced menopause were excluded from this study.

2.4. Measures

We conducted neuropsychological tests in the following order:
The Rey Auditory–Verbal Learning Test (RAVLT) [9]:

The subject memorizes a series of 15 words in 5 learning trials. Following a 15 min delay, the subject is asked to recall the word list, followed by a recognition trial in which the subject is presented with the 15 target words and 15 foils. Raw scores of the delayed recall are used for statistical analysis. The RAVLT measures learning, immediate memory, and delayed memory.

Continuous recognition paradigm of Kimura (CRP) [10]:

The CRP involved the sequential presentation of 70 nonsensical figures. Four figures were repeated seven times within the test. The subject was instructed to answer “yes” or “no” as to whether the figure had been seen before or not. The score is the number of correctly recognized repeated figures. The CRP is a measure of visual recognition memory.

Verbal fluency [11]:

In this test, the subject names as many animals as possible in 1 min. The score is the number correctly named. This test measures verbal production, semantic memory and language.

Trail Making Test, parts A and B [12]:

The task is to connect numbers (part A) and numbers alternating with letters (part B) on a sheet of paper. This is a test of visual scanning, visuomotor and conceptual tracking, mental flexibility and motor speed. The score is the time to completion in seconds. A maximum of 300 s is allowed for part B.

Digit span subtest of the Wechsler Adult Intelligence Scale—Revised (WAIS-R) [13]:

The WAIS-R is the most widely used and well-respected measure of general intelligence. The digit span subtest of the WAIS-R is a measure of basic attention in which the patient is required to repeat digits in forward and reverse order.

Statistical analysis

The main interest of the analysis was to compare cognitive changes in women who remain premenopausal (pre group) to those who became perimenopausal (peri group) during the follow-up period. Demographic and baseline information for premenopausal and perimenopausal groups were compared using the t-test, signed-rank test and Chi-square test as appropriate. The outcomes of interest were the cognitive function at follow-up as measured by five instruments: Auditory–Verbal Learning Test, visual memory, verbal fluency, trial making test and digit span.

Multiple linear regression (PROC GENMOD, SAS v8.1) was used to compare the mean change in cognitive function between the two groups while adjusting for baseline score, age and education. Education was coded as 1 (illiterate), 2 (literate), 3 (complete elementary school), 4 (complete junior high), 5 (complete high school) and 6 (complete 2 years of college or more). All statistical tests were two-sided. A p-value less than 0.05 was considered to be statistically significant.

Results

Characteristics of the study population

A total of 694 premenopausal women participated in the baseline study, and 573 women (83%) completed follow-up 18 months later. The remaining 121 women did not complete the study for the following reasons: (1) 78 subjects (64.5%) were not at home for at least three house calls; (2) 39 subjects (32.3%) refused to participate at follow-up; (3) 2 subjects (1.6%) moved; (4) 2 subjects (1.6%) died. The participants and non-participants did not differ in age and educational level. After excluding 78 women who received hysterectomy or HRT, the resulting sample was composed of 495 subjects, of whom 114 (23%) progressed to perimenopause during follow-up. Table 1 shows the demographic characteristics of women who remained premenopausal and the women who became perimenopausal during follow-up. The only significant difference was that the women who became perimenopausal were older than the women who remained premenopausal (p < 0.001, t-test) (per reviewer, add comments for the education differences between two groups, i.e. the perimenopausal group has higher illiteracy rate). It was also noticed that women who became perimenopausal have higher illiteracy rate (19.3%) as comparing to women who remained premenopausal (12.9%) even though this difference did not reach statistical significance (p = 0.09).

Results of neuropsychological testing

Table 2 lists the results of neuropsychological tests by menopausal status at baseline and follow-up. In the premenopausal group, the change from baseline
Table 1
Demographic characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Premenopausal group (N = 381)</th>
<th>Perimenopausal group (N = 114)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.7 ± 2.3</td>
<td>47.1 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at menarche</td>
<td>15.4 ± 1.6</td>
<td>15.4 ± 1.7</td>
<td>0.78</td>
</tr>
<tr>
<td>Education (years)</td>
<td>6.8 ± 4.5</td>
<td>6.0 ± 4.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Percentage of illiterate</td>
<td>12.9</td>
<td>19.3</td>
<td>0.09</td>
</tr>
<tr>
<td>Percentage of married</td>
<td>95.8</td>
<td>94.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Percentage with smoking habit</td>
<td>10</td>
<td>7</td>
<td>0.48</td>
</tr>
<tr>
<td>Percentage with an alcohol drinking habit</td>
<td>1.6</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Self-reported health status</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Excellent/very good (%)</td>
<td>22.3</td>
<td>30.7</td>
<td></td>
</tr>
<tr>
<td>Good (%)</td>
<td>37.9</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td>Fair (%)</td>
<td>37.1</td>
<td>38.6</td>
<td></td>
</tr>
<tr>
<td>Poor (%)</td>
<td>2.6</td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

was significantly different from zero for most cognitive functions with the exceptions of RAVLT and backward digit span. In the perimenopausal group, the change from baseline was significantly different from zero for Trail Making (parts A and B) and forward digit span. For all scores except Trail Making, the higher the score the better the performance. In contrast, a higher score on the Trail Making Test indicated a poorer response. Therefore, the cognitive function as measured by CRP, verbal fluency, Trail Making (A and B), and forward digit span was improved significantly (all p-values < 0.001) for women who stayed premenopausal. For women who entered perimenopause, the cognitive function as measured by Trial Making (A and B) and forward digit span was also improved (p < 0.001 for Trial Making A and B, and p = 0.03 for forward digit span). Most of the univariate comparisons between premenopausal and perimenopausal groups on cognitive function changes from baseline showed no difference except for CRP (p = 0.02) and verbal fluency (p = 0.02). Women who stayed premenopausal improved more in CRP and verbal fluency than those who entered perimenopause.

Univariate analysis also indicated that age and education were two important factors significantly associated with cognitive function. With menopausal status, age, education, and baseline cognitive scores within the model, we found that the cognitive function at follow-up did not differ significantly between women who stayed premenopausal and those who became permenopausal.

Table 2
Comparison of the cognitive tests on two menopausal groups

<table>
<thead>
<tr>
<th></th>
<th>Premenopausal status (N = 381)</th>
<th>Perimenopausal status (N = 114)</th>
<th>p-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Follow-up</td>
<td>Differences</td>
<td>Baseline</td>
</tr>
<tr>
<td>RAVLT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.8 ± 2.5</td>
<td>10.7 ± 2.3</td>
<td>10.7 ± 2.6</td>
</tr>
<tr>
<td>CRP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>69.7 ± 6.8</td>
<td>72 ± 6.0</td>
<td>70.7 ± 5.1</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>14.9 ± 4.1</td>
<td>16.1 ± 4.1</td>
<td>14.5 ± 3.8</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>640 ± 35.1</td>
<td>59.1 ± 31.8</td>
<td>71.5 ± 38.9</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>101.5 ± 46.9</td>
<td>89.9 ± 35.8</td>
<td>115.4 ± 57.0</td>
</tr>
<tr>
<td>Forward digit span</td>
<td>9.9 ± 2.6</td>
<td>10.5 ± 2.4</td>
<td>9.9 ± 2.4</td>
</tr>
<tr>
<td>Backward digit span</td>
<td>3.9 ± 2.4</td>
<td>4.0 ± 2.2</td>
<td>3.6 ± 2.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> CRP—continuous recognition paradigm of Kimura.<br><sup>b</sup> RAVLT—Rey Auditory–Verbal Learning Test.<br><sup>*</sup> p-Value derived from comparisons between premenopausal and perimenopausal groups on the differences of baseline and follow-up using Wilcoxon rank-sum test.<br><sup>**</sup> p < 0.05.<br><sup>***</sup> p < 0.001.
Table 3
The results of multiple linear regression analyses to test the menopausal transition as a predictor of cognitive function tests at follow-up^a

<table>
<thead>
<tr>
<th>Intercept</th>
<th>Menopausal groupb (95% CI)</th>
<th>Age (years)</th>
<th>Education (category)c</th>
<th>Baseline score</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA VLT</td>
<td>5.29</td>
<td>0.29 (−0.7, 0.2)</td>
<td>0.03</td>
<td>0.48**</td>
</tr>
<tr>
<td>CRP</td>
<td>69.9</td>
<td>0.98 (−1.3, 0.7)</td>
<td>−0.06</td>
<td>0.60</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>9.0</td>
<td>1.3 (−2.1, −0.6)</td>
<td>0.01</td>
<td>0.08**</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>84.8</td>
<td>−1.5 (−3.7, 0.7)</td>
<td>−0.50</td>
<td>−8.8**</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>84.4</td>
<td>−1.0 (−6.0, 8.1)</td>
<td>0.19</td>
<td>−8.2**</td>
</tr>
<tr>
<td>Forward digit span</td>
<td>4.9</td>
<td>0.1 (−0.5, 0.3)</td>
<td>0</td>
<td>0.56**</td>
</tr>
<tr>
<td>Backward digit span</td>
<td>1.01</td>
<td>0.18 (−0.6, 0.2)</td>
<td>0</td>
<td>0.62**</td>
</tr>
</tbody>
</table>


^a Intercepts and regression coefficients of the variables in the multiple regression model of each cognitive function test.

^b In comparison with women who stayed premenopausal during follow-up as a reference group.

^c Education categories: 1—illiterate; 2—literate; 3—completed elementary school; 4—completed junior high; 5—completed high school; 6—completed 2 year college or more.

* p < 0.01.

** p < 0.001.

imenopausal except for verbal fluency (Table 3). For verbal fluency, change of menopause status resulted in an estimated difference of 1.3 items less at follow-up from the GLM model after controlling for education, age and baseline score. Education is a significant factor in all models, which means that cognitive function at follow-up is mostly attributed to education, with higher educational levels leading to higher follow-up cognitive function scores. Age was not a significant factor.

### 4. Discussion

In our previous cross-sectional study [6], we found that most cognitive functions significantly decreased from the premenopausal to postmenopausal stages. However, that difference was lost after adjusting for age and education with the exception of Trail Making Test, part A. In this longitudinal study, we found that performance on almost all of the cognitive tests (the exception was RA VLT) was better at follow-up in women who became perimenopausal compared with their baseline data in terms of raw scores. The multivariate analysis suggested that the improvement in verbal fluency at follow-up was significantly less (estimated difference 1.3 items) in women who remained premenopausal compared with women who remained perimenopausal after adjustments for age, education and baseline score. The better performance in the follow-up examination might be attributed to learning effects [14] or inter-rater difference.

Findings from both our previous cross-sectional study and the current longitudinal study support the same conclusion: most cognitive functions do not significantly decline during the menopausal transition. The main difference between the two studies was the variance in significant cognitive functions revealed during the menopausal transition. The longitudinal data provide a more robust understanding of changes for each individual over time. The differences in cognitive test data found between the cross-sectional and longitudinal studies might be due to cohort effect. A 10-year longitudinal community study of cognitive change found the most marked decline over time was seen on the Trail Making tests [15]. The mean age difference between the premenopausal and the postmenopausal women was 7 years in the cross-sectional study. In contrast, the difference between premenopausal and perimenopausal women was only 3 years during the longitudinal study. The age difference might explain in part the differences in cognitive function test results between the cross-sectional and the longitudinal studies.

Our study showed that one category advance in education was associated with one item improvement in verbal fluency. Although not statistically significant, is associated with only 0.1 item improvement in verbal fluency. After controlling for age, education and baseline verbal fluency score, women who became peri-
menopausal did not improve in verbal fluency as did their premenopausal peers. Although the results of the past studies were not consistent [16,17], one recent study [17] showed that performance of verbal fluency and Trail Making tests among postmenopausal women who received estrogen treatment was significantly improved and positron emission tomography studies revealed that estrogen induced increases in 5-HT receptor binding in human prefrontal regions. It is hard to say the clinical significance of 1.3 items differences during the menopausal transition. Our results are in line with the above findings with performance in frontal lobe functions such as verbal fluency somewhat worse among perimenopausal women, whose estrogen levels would be lower than those in premenopausal women.

In contrast to previous studies [18,19] indicating that estrogen might influence verbal memory, we did not find a greater decline in verbal memory in perimenopausal women. A recent review article [20] found that studies assessing attention and concentration have inconsistent results with regard to hormone levels or menopausal status and thus no strong association between estrogen level and visual memory was identified.

Our findings are consistent with Meyer’s study [7], which showed small but significant increases in cognitive function test scores involving working memory and perceptual speed in American women. The similarity in findings implies cognitive function within one individual over time might not be affected significantly by culture and ethnicity. Our study also demonstrated there were no significant changes in other cognitive domains except for verbal fluency. In contrast to Meyer’s study, our study focused on the women from premenopausal to perimenopausal, rather than several different stages during the menopausal transition in Meyer’s study.

One limitation of the current study was the relatively short interval of follow-up. The mean duration of perimenopause was established as 3.8 years from a large study [21]. The 20-month interval in our study design might not be long enough to detect significant differences in cognitive change during the whole menopausal transition. Nevertheless, our study supported that the menopausal transition might not accompany significant cognitive decline except for verbal fluency.

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References


