

Effect of Menopause on Cognition in Post-menopausal Women

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ABSTRACT

Introduction: Menopause is the end of women's reproductive capacity, but it signals more than end of fertility. Health issues such as low bone mineral density, sexual problems, mood disorders and disturbed sleep increase around menopause, although the extent to which these problems are associated with diminished ovarian reserve is not well understood. Associations between hormone changes, menopausal symptoms and other health issues associated with menopause have been aided by staging the menopausal transition. Thus this study is an initiation to check cognitive function changes in later period of life after menopause.

Methods: Based on Inclusion and Exclusion criteria 100 subjects above the age of 50 years was selected by purposive sampling and informed consent was taken. Groups were divided into four categories Group A, B, C and D and assessed on the basis of ACE-R questionnaire. The data was then be collected, compiled and analyzed.

Measuring Scale: ACE-R Questionnaire

Results: Data was meaningfully assorted through calculation of mean & standard deviation. The p value for age and menopause was 0.879 which was >0.001. There was negative correlation between age and menopause. Result was non-significant for attention and concentration within the groups of menopausal stages with p value 0.120 which is >0.001. The p value for menopause and memory was <0.001 which signified that the relation between menopause and memory was significant. The p value for the language and menopausal stages was <0.001, which stated the result was significant between language and advancing menopausal stages. Menopause and visuospatial ability showed significant correlation with the p value <0.001, signified that the visuospatial abilities decline in a women with advanced menopausal stage.

Conclusion: In this study we found that there was significant decline in the various parameters of cognition including memory, verbal fluency, language, visuospatial abilities whereas age and attention concentration has negative correlation.

Keywords: Menopause; Post-menopausal women; Cognition

Abbreviations: FSH-Follicular Stimulating Hormone; WHO-World Health Organisation; FMP-Final Menstrual Period; BMI-Body Mass Index; ACER-Addenbrooke's Cognitive Examination Revised; STRAW-Stages of Reproductive Aging Workshop; MCI-Mild Cognitive Impairment; FSH-Follicular Stimulating Hormone; LH-Luteinizing Hormone; PFC-Prefrontal Cortex; MRI-Magnetic Resonance Imaging; VLFC-Ventrolateral Frontal Cortex

INTRODUCTION

Menopause and its classification

Menopause signifies as the permanent cessation of menstruation and the end of reproductive potential [1]. Study of Women's Health Across the Nation defined four menopausal status categories: premenopausal, 3 months of amenorrhea and no increase in menstrual irregularity in the past year; early peri-menopausal, 3

months of amenorrhea with some increase in menstrual irregularity; late peri-menopausal, between 3 and 11 months of amenorrhea; post-menopausal, 12 or more consecutive months of amenorrhea with no medical cause other than menopause [2]. Post-menopause is classified further into stages as Stage 1 (early) and stage 2 (late) encompass the post-menopause. The early post-menopause is defined as 5 years since the FMP. Stage 1 was further subdivided into segment "a", the first 12 months after the FMP, and segment

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“b”, the next 4 years. Stage 2 has a definite beginning but its duration varies, since it ends with death [3]. WHO (World Health Organization) proposed the average age of natural menopause in healthy women was considered to be between 45 to 55 years of age [4]. Reproductive hormonal levels, age, race; smoking, body mass index (BMI), alcohol use and age at menopause are the predictors of transition from one menopausal stage to the next [5].

Effect of Menopause

There are various effects of menopause on women's health including health issues such as low bone mineral density, mood disorders and disturbed sleep and problematic symptoms such as weight gain, anxiety, depression, sexual dysfunction, vasomotor irregularities [6]. The changes occurring during and after menopause are due to changes in various hormones such as follicular stimulating hormone (FSH) [7]. FSH levels were associated with bleeding criteria proposed to identify the STRAW (Stages of Reproductive Aging Workshop) early transition stage and indicated that a persistent more than 6-day difference in cycle length was the earliest of the studied criteria [8]. FSH (Follicular Stimulating Hormone) levels predicted time to menopause where FSH levels predict entry into each stage of the menopausal transition [9].

Role of Estrogen

Estrogen hormone that plays various roles in the body, especially in female reproductive system also influences hippocampus and prefrontal cortex function and the cognitive functions promoted by these brain regions, including verbal memory and executive function [10]. Estrogen directly affects the brain function by having an effect on the vascular and the immune system [11]. Changes in endogenous estrogen levels and symptoms associated with the menopausal transition, such as depression, sleep disturbance and hot flashes, may also occur independently [12]. Potential association of menopausal hormonal changes with brain function may therefore be approached in two ways: directly, i.e., effects on neural cells and systems, and indirectly, effects of hormonal changes on evidenced functions, mainly cognition and mood [13].

Cognitive changes

Age-related cognitive changes may progress from mild cognitive impairment (MCI) to dementia—a condition in which memory, behavior, and cognition are impaired secondary to neurodegeneration in the brain, researchers have determined the various cognitive aspects included in problematic symptom [14]. Cognition is the act of process of knowing including awareness, reasoning, judgement and memory [15]. Higher cortisol levels or greater cortisol reactivity may be one mechanism that links hot flashes, depressive or anxiety symptoms to peri-menopausal decrements in cognitive performance. Cortisol increases after a hot flash, experimental administration of corticosteroids produces verbal memory impairment, and higher endogenous cortisol levels are associated with poorer performance on memory tasks [16,17]. Changes in cognitive abilities are also associated with the process of aging, with memory difficulties increasing as women approach menopause [18,19]. Although it can be difficult to distinguish between effects of chronological versus reproductive aging, the transitioning hormonal environment leading to menopause may have various effects on specific cognitive domains [20,21]. The most common complaints were difficulty recalling words or

numbers, needing memory aids, and forgetting why one with peri-menopause was involved in a certain behavior. Thus this study was an initiation to check cognitive function changes in later period of life after menopause and to compare the level of cognitive functions in various stages of menopausal transition [22]. Although there have been many studies done on effect of menopause on women as on musculoskeletal disorders also cognitive decline in peri-menopausal women have been identified in some studies. But there was no clear evidence on the effect of menopause on cognition which is an important aspect of all the brain functions in post-menopausal women neither the duration of menopause have been considered this study was an initiation to check cognitive function changes in later period of life after menopause. The aim was once the cognitive function is known and in case it goes for a decline, cognitive rehabilitation exercises can be prescribed and taught to post-menopausal females. This in turn can improve their quality of life.

MATERIAL AND METHODS

This was a descriptive study (health survey). The samples were selected through purposive sampling. The study was done in the time period of September 18, 2019 to March 2, 2020. Subjects were taken from in and around Ludhiana. Females with age 35 years or above, housewives, with minimum qualification of graduation were included. Females with surgical menopause, hormonal therapy, Non cooperative, working women and with psychological problems were excluded from the study.

PROCEDURE

There were taken 100 subjects in total. The subjects were inquired some questions. The subjects were firstly asked about their demographic data including name, age and occupation, and then they were inquired about their last menstrual period and were rejected as had hysterectomy and were on hormonal therapy after taking their informed consent. The groups were named as group A as premenopausal women, group B as peri-menopausal women, group C as post-menopausal stage-1 women and group D as post-menopausal stage- 2, they were divided in the classification of menopausal status on the basis of the information they provide of last menopausal period.

The subjects were started with the interview and were asked questions according to the addenbrookes-revised scale (ACE-R) Questionnaire with reliability of alpha coefficient $\frac{1}{4}$ 0.8. The scale includes mainly 5 domains of cognition which are further divided into questions. Total score is 100, higher scores indicates better cognitive functioning. First section of the scale includes the question that inquires orientation, registration, attention and concentration of the subject with the scoring of 0-18. Next section includes the question testing the memory: recall, anterograde and retrograde with the scoring of 0-26. Then next section was of verbal fluency determined by asking the subject to list names of objects and animals in a given time which is 0-14 scores. The next section involves the queries determining language which is of total score of 0-26. The last section of the questionnaire includes the queries that test the visuospatial parameter of the addenbrookes-revised scale with scoring of 0-16. Each section was then scored accordingly and was summarized [23].

All the data was compiled and was analyzed using ANOVA and was compared in between the groups namely A, B, C and D. The

mean and standard deviation of the groups are 7.3+1.93, 6.9+1.76, 6.1+2.58 and 4.4+2.36 respectively. The p value comes out to be <0.001 which shows the significant relation between menopause and verbal fluency. It signifies that the verbal fluency in the women with the advancing stages of menopause is decreased.

RESULTS

Table 1 shows the demographic data which represents the educational status of females. (In India the primary education means the person has passed the 12th standard. Secondary education means the person has completed her higher education. The tertiary education means the person educated with specialization in particular field). The number of females having senior secondary education was 53, and the number of graduate females was 35 and the postgraduate females were 12 in total. Also as shown in percentages the females with primary education were 28% in group A, 56% in group B, 64% in both group C and D. Similarly females with secondary education were 52% in group A, 28% in group B and C and 32% in group D. Females with tertiary education were 20% in group A, 16% in group B, 8% and 4% in group C and D respectively. Table 2 represents the other demographic data of age of females, the number of females upto 40 years of age were 26, total number of females 41-50 were 45, 23 were the number of females with age 51-60, and there were 10 number of females with age above 60 years. Figure 1 represents the relation between the age and cognition within the four groups A, B, C and D. the mean and standard deviation for group A, B, C and D comes out to be 48.9+9.76, 47.6+9.93, 48.8+7.08, 49.5+7.39 respectively. The p value is 0.879 which is >0.001 and thus the correlation between age and cognition is non-significant. It means that decline in cognitive ability does not depend on increase in age. Figure 2 represents the relation between attention and concentration and cognition. The mean and standard deviation for group A, B, C and D were calculated as 7.7+0.75, 17.5+0.82, 17.6+0.99 and 17.1+1.26 respectively. The p value is 0.120 which is >0.001 and the result is non-significant for attention and concentration within the groups of menopausal stages. Figure 3 represents the relation between menopause and effect on memory which is a parameter for cognitive skills. The mean and standard deviation for group A, B, C and D are 25.0+1.49, 23.1+2.77, 21.5+3.37 and 19.6+ 3.20

respectively. The p value is <0.001 which signifies that the relation between menopause and memory is significant. Figure 4 represents the relation between verbal fluency and advancing menopausal stages named as group A, B, C and D. The mean and standard deviation of the groups are 7.3+1.93, 6.9+1.76, 6.1+2.58 and 4.4+ 2.36 respectively. The p value comes out to be <0.001 which shows the significant relation between menopause and verbal fluency. It signifies that the verbal fluency in the women with the advancing stages of menopause is decreased. Figure 5 represents the relation between menopause and language. The mean and standard deviation of group A, B, C and D are 19.6+2.46, 19.1+1.75, 16.6+3.23 and 15.5+3.06 respectively. The p value for the given data is <0.001, which states the significant result of the relation between language and advancing menopausal stages. Figure 6 represents the relation between visuospatial abilities and stages of menopause grouped as group A, B, C and D. The mean and standard deviation are 15.6+0.87, 15.7+0.74, 15.0+1.27 and 13.8+2.27 respectively. The p value is <0.001 which states the significant correlation between menopause and visuospatial ability. This signifies that the visuospatial abilities decline in a women with advanced menopausal stage.

DISCUSSION

The study was carried out to determine the effect of menopause on cognition in post-menopausal women. The result of the present study showed that there occurs decline in various parameters of cognition in women, which include verbal fluency, memory, language, visuospatial abilities.

Menopausal Transitions decline the cognitive ability

These cognitive changes occur with the effect of advancing menopausal status of women called the menopausal transitions. Menopausal transitions can be divided into stages. The stages have been divided on the basis of reproductive aging including oocyte number [24]. The changes in the oocyte number or advancing reproductive age, there occurs various changes in the levels of hormones. The hormones may include follicular stimulating hormone (FSH), luteinizing hormone (LH), estrogen and progesterone which are also called the ovarian hormones [25]. The

Table 1: Represents the educational status of females.

Section-1 Socio Demographic Proforma	Opts	Group A (%)	Group B (%)	Group C (%)	Group D (%)	Group A (N=25)	Group B (N=25)	Group C (N=25)	Group D (N=25)
Educational Status	Primary education	28%	56%	64%	64%	7	14	16	16
	Secondary education	52%	28%	28%	32%	13	7	7	8
	Tertiary education	20%	16%	8%	4%	5	4	2	1

Table 2: Represents the status of female Age.

Section-1 Socio Demographic Proforma	Opts	Group A (%)	Group B (%)	Group C (%)	Group D (%)	Group A (N=25)	Group B (N=25)	Group C (N=25)	Group D (N=25)
Age(in years)	Upto 40 Years	20%	36%	16%	16%	5	9	4	4
	41-50 Years	52%	32%	52%	44%	13	8	13	11
	51-60 Years	12%	24%	28%	28%	3	6	7	7
	51-60 Years	12%	24%	28%	28%	3	6	7	7
	Above 60 Years	16%	8%	4%	12%	4	2	1	3

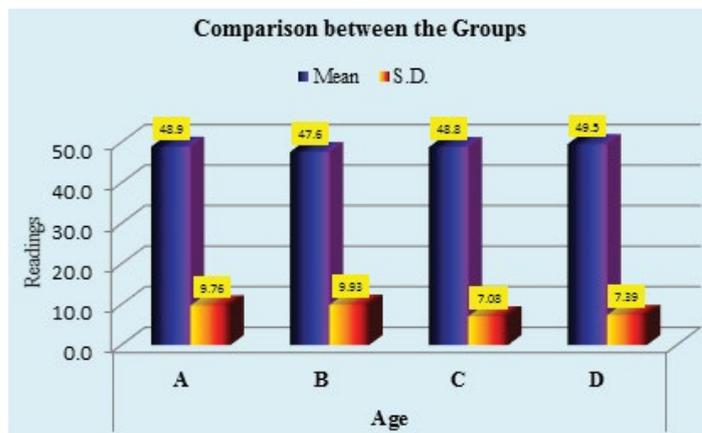


Figure 1: Represents that age does not affect decline in cognitive ability.

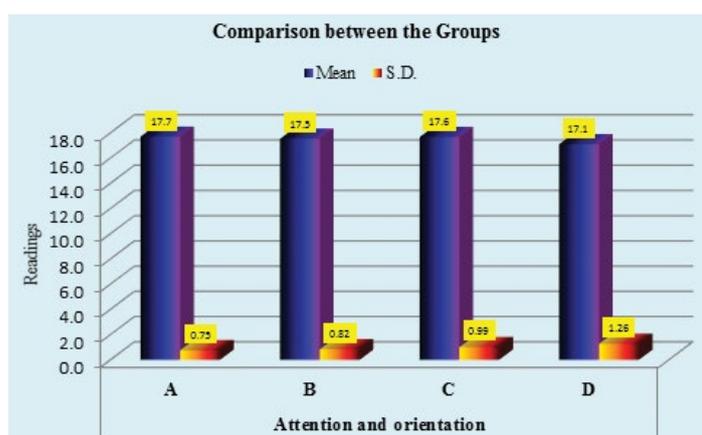


Figure 2: Represents the attention and concentration and menopause within the groups.

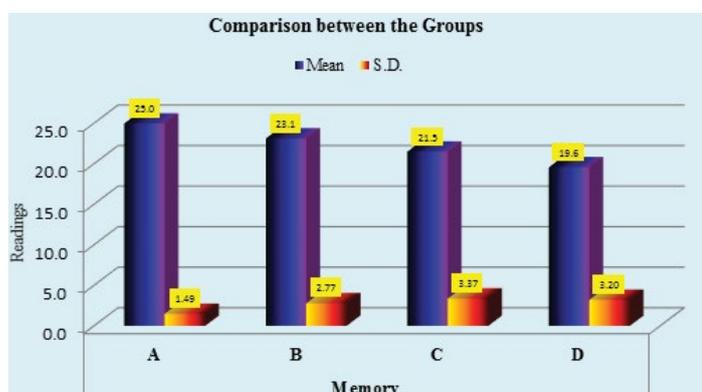


Figure 3: Represents relation of memory and menopause within the group.

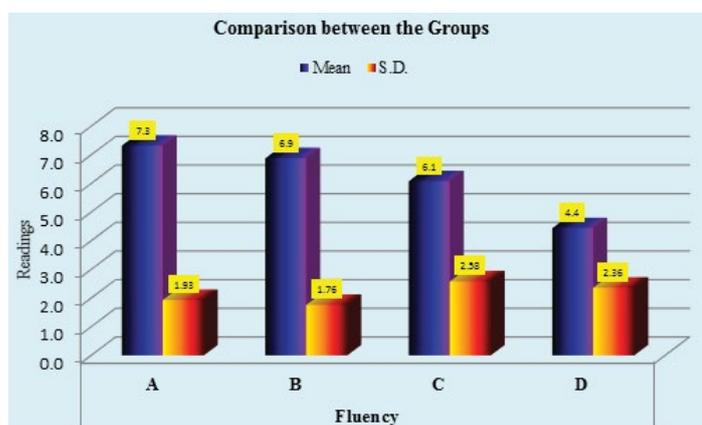


Figure 4: Represents relation between memory and verbal fluency.

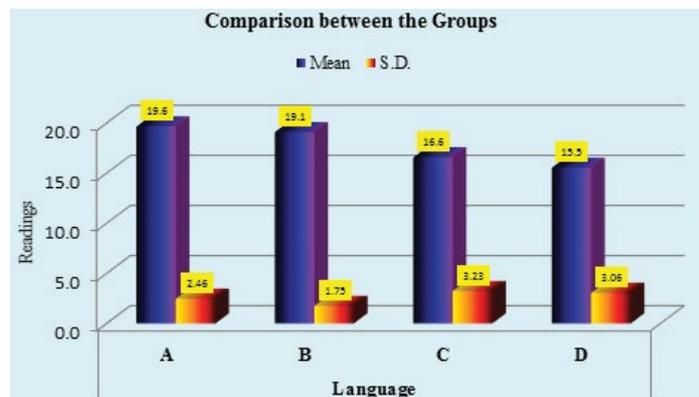


Figure 5: Represents the relation between the menopause and language within the groups.

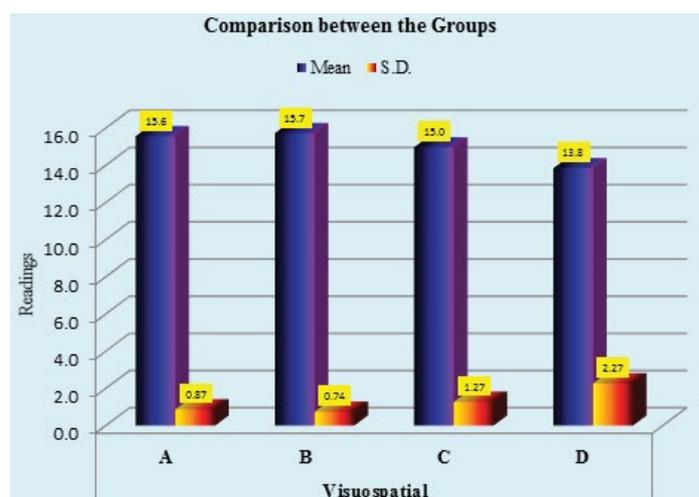


Figure 6: Represents the relation between visuospatial abilities with change in menopausal stage.

levels of these hormones during transition stages changes and result in various effects or symptoms of menopause which also includes cognitive changes. According to the report by WHO in 1990, it was suggested that the estrogen levels decrease during the menopausal transitions which plays a vital role in the cognitive decline.

Estrogen and Brain activities

Estrogen influences the brain activity due to its effects on vascular and immune response. Estrogen protects against apoptosis and against neural injury and enhances various neurotransmitters like acetyl choline which is important in memory processing. [26,27]. (Table 1 and Figure 3) represents that the relation between the menopause and memory is significant, It means that there is decline in memory due to advancing menopausal stage. Estrogen receptors present in the various parts of brain mostly in the prefrontal cortex and hippocampus. These areas are responsible for various cognitive skills such as memory processing, and thus due to decline in estrogen level causes changes in the parts of the brain and shows the symptoms of memory alterations. The hippocampus plays a critical role in verbal episodic memory, including memory encoding and storage [28]. The PFC also plays a critical role in early memory processing and is consistently activated on tasks of memory encoding and working memory which was confirmed with a functional MRI in study [29]. There was significant decline in verbal fluency in our study shown in Table 1 and Figure 4. The reason is being, the decline in estrogen and estrogen receptors in

the frontal areas causing suppression in the function of frontal area including the verbal fluency. The areas in the frontal lobe precisely to the ventrolateral frontal cortex (VLFC) include Brodman areas 44/45 and 42/22 (Broca's and Wernicke's area) which are responsible for comprehension and speech and broadly controlling language and verbal fluency [30]. The changes in the structures due to decline in the estrogen levels thus cause the decline in verbal fluency and language being the other parameter of cognition.

Verbal memory, recall and visuospatial abilities

The cognitive problems were associated with declines in verbal memory, and with declining performance on reaction time measures of attention, with small-to-medium effect sizes. Subjective cognitive complaints are also associated with decline in verbal memory [31]. Menopausal transition has an adverse effect on immediate and delayed verbal memory and recall [32]. This study provides an evidence of the significant decrease in verbal memory with the increase in age in females. Another parameter of cognition namely visuospatial abilities declines with advanced menopausal stage (Table 2 and Figure 6). Visuospatial function or ability refers to identify, integrate, and analyze space and visual forms, details, structures and spatial relations in more than one dimension [33].

Changes that occur in the areas of brain due to decreased estrogen

In this study the questionnaire (ACE-R) asked to draw various shapes, identify various picture for identification of change in visuospatial abilities or function in various groups of menopausal women. It was significant that there were changes in the outcomes of the result. The reason behind this change is that the estrogen decline causes the lesions and changes in the structure of hippocampus which is responsible for spatial memory and the connections between hippocampus and other areas of brain like areas in the frontal cortex causes alterations in the visuospatial memory or function [34]. Change in the concentration of 17-estradiol are related to the alterations in hippocampal connectivity and performance is poor for subsequent memory task across women taking sex steroids in the modulation of hippocampal function which confirms the above hippocampal involvement in the menopausal symptoms [35].

Age does not affect the cognitive abilities

The study revealed that menopause does not cause changes in the attention and orientation when compared between the groups of various menopausal stages of women. As mentioned above, the criteria for staging of menopause is the reproductive age. The relation between ages and various menopausal stages and symptoms have a negative effect on each other. This reveals that age does not determine the onset of menopausal transitions and their symptoms. Another longitudinal study showed that there were changes in the cognitive skills independent of age and education [36]. It was noted in this study while doing comparison in between the groups of women divided on the basis of menopausal transition stages, that each stage cause decline in cognitive ability of a women.

CONCLUSION

In this study we found that there was significant decline in the various parameters of cognition including memory, verbal fluency, language, visuospatial abilities. There were suggested changes in the memory of the women with advanced menopausal stage and

the changes in the menopausal status. There are various changes in the brain specially the prefrontal cortex which loses its vascularity with changes in the levels of hormones and there occurs the decline in verbal fluency or word fluency. There is no significant difference in the age and other demographic data variable with the changes in menopausal stages.

LIMITATIONS

- Only one scale was used for assessing cognitive ability of subjects
- Only educated females were included for evaluation and illiterate people were not taken which may show variations in results
- Women with surgical menopause and women on hormone therapy were excluded which may show variations
- Limited participants were included

FUTURE SCOPE OF THE STUDY

In this study there was only one scale used for the determination of the cognitive changes in the females with menopausal transition. In future use of any other scale can be done for further studies. A longitudinal study can be conducted which may include more participants and follow up can be done for more precise results.

DISCLOSURES

There are no conflicts of interests.

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