ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 09 | September - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EFFECT OF CHANGE IN ESTROGEN LEVELS ON COGNITIVE FUNCTIONS IN PREMENOPAUSAL, EARLY PERIMENOPAUSAL AND LATE PERIMENOPAUSAL FEMALES: A HOSPITAL BASED CROSS-SECTIONAL STUDY

Physiology

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ABSTRACT

Background: There is an established link between the change in levels of Estrogen and its affect on mental health in middle age females. Objective: To see the correlation between serum Estrogen levels and cognitive functions in the study groups. Methods: This was a hospital based cross-sectional study involving a total of 90 females who were divided into three groups of 30 females each, based on their age and menstrual history.These groups were premenopausal(31-35 years) ,early perimenopausal(36-40 years,),late perimenopausal (41- 45 years).The level of serum Estrogen was estimated in all the study subjects and their cognitive assessment was done using Montreal Cognitive Assessment scale(MoCA). One way ANOVA was used to asses the significance. Results: There is a correlation between cognitive decline and serum estrogen levels in late perimenopausal age group as compared to early perimenopausal and premenopausal age group. Conclusion: There is a significant relationship between estrogen levels and cognitive functions in middle aged females.

KEYWORDS

Estrogen, perimenopause cognitive functions, MoCA

INTRODUCTION

Aging is an inevitable biologic process where there is progressive decline in physiological function and increased susceptibility to disease (1) .Since ancient times it has been believed that the sudden behavioural changes in a female are related to their reproductive system. The perimenopausal changes in a female does not symbolize any "bad omen" but forms a part of reproductive aging which appears at an earlier age as compared to the somatic aging in various other physiological organ system in the body .Various events from basic physiology ,interventional studies and epidemiological data suggests that Estrogens positively influence the mental well being in females. Increase in depressive disorders and other mental health issues around late perimenopause and menopause suggests involvement of decreased levels of Estrogen on mental health. (2)

Perimenopause can be defined as the transition period prior to last menstrual cycle along with fluctuation in various hormonal level(3). The common symptoms reported in perimenopausal and menopausal age groups are vasomotor symptoms like hot flushes, vaginal dryness, insomnia, fatigue, joint pain ,urinary symptoms and mental illness like depression and dementia.(5) Cognition can be defined as a process in which conceptual comprehension of reality takes place. This is where fixation of close link of cognition and language comes from (8). Perimenopause may have temporary as well as long term effects on cognitive functions. The contemporaneous impact of perimenopause on cognition appears to be both transient (occurring only during perimenopause) and very subtle.

In both KIWI and SWAN study, the only published longitudinal studies of measured cognitive performance during the menopause transition, an absence of improved test scores with repeated annual measurements, not a decline in test scores, was evident during perimenopause.(9) The increases in anxiety and depressive symptoms that accompany the perimenopausal transition have an independent effect on cognitive performance.

This is consistent with the findings that the effects of Estrogen on depression and anxiety are largely mediated by estrogen receptor beta and its effect on serotonin and hypothalamic-pituitary-adrenal (HPA) axis function. Along with this, higher baseline cortisol levels or greater cortisol reactivity could link hot flushes, depressive or anxiety symptoms with perimenopausal decrements in cognitive performance.

MATERIAL AND METHOD

The study was done during the year 2020-2021 in the Department of Physiology and Department of Obstetric and Gynaecology ,Jawahar Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh.It was a hospital based cross -sectional study.

In this study a total of 90 cases were recruited who met the inclusion and exclusion criteria and had given consent. These 90 cases were divided into three groups of 30 cases each on basis of age and menstrual history .The premenopausal group aged between 31 to 35 years with regular cycles, acted as controls for the given study. Early perimenopausal group had females between 36 to 40 years of age with few interrupted cycles delayed by a week time, and late perimenopausal had females between 41 to 45 years of age with irregular cycles with period of upto 2 months of ammenorrhoea in between. The cases and controls were tested for their cognitive functions and serum Estradiol was measured for all the study cases and comparison was done.

The cases included were females with normal BMI ,in age group of 31 to 45 years and literate. Cases excluded were patients aged < 30 year and > 45 year, known case of thyroid disorders ,k/c/o any psychiatric illness,k/c/o any neurodegenerative disorder ,females with surgical menopause, females who have undergone u/l or b/l 00pherectomy ,females on any type of hormonal medication.

After approval from the ethical committee of J.N. Medical College,Proper history was taken and clinical assessment was done as in prescribed proforma after valid and informed consent. Blood samples were collected ,under all aseptic precautions in Na -EDTA vials for estimation of serum estradiol using XEMA ELISA kit for Estrogen. Patients were tested for cognition which was done by questionnaire method by the Montreal Cognitive Assessment scale(MoCA) in Hindi.

Time to administer the test was approximately 10 minutes. Total score was 30 points and a score of 26 or above was considered normal. One point was added for an individual who had a formal education of 12 years or less.

OBSERVATIONS

Table 1: Distribution of age in the study groups. [Premenopausal/ controls (n=30), Early perimenopausal (n= 30), Late perimenopausal (n=30)]

S. No.	Groups	Age				
		31-35 Year	36-40 Year	41-45 Year	Total	Mean ± SD
1	Control	30	0	0	30	32.73 ±1.31
2	Early Perimenopausal	0	30	0	30	39.07 ±1.26
3	Late Perimenopausal	0	0	30	30	44.07 ±1.17

Table 2: Mean Variation Of Serum Estradiol In Study Groups (n=30):

S. No.	Groups	Serum Estradiol Mean ± SD	F-Value	P-Value
1	Control	106.97 ± 62.59	8.616	*P < 0.001
2	Early Perimenopausal	109.86 ± 67.68		
3	Late Perimenopausal	55.54 ± 35.48		

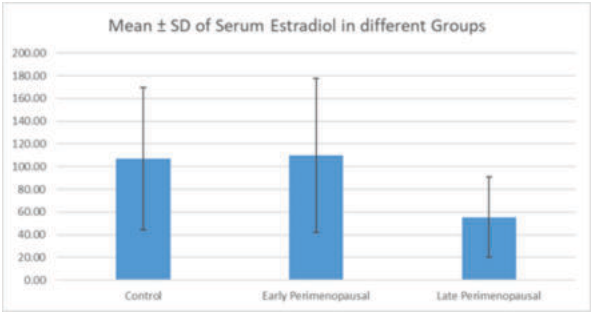

Fig.2a: Shows Mean Variation Of Serum Estradiol In The Study Groups

Table 3: Distribution Of Montreal Cognitive Assesment Scores (MoCA) In The Study Groups(n=30):

S. No.	Groups	MOCA Score			Ch^2-Value	P-Value
		Mild Cognitive Decline	Normal	Total		
1	Control	4	26	30	6.256	*P < 0.05
2	Early Perimenopausal	6	24	30		
3	Late Perimenopausal	12	18	30		
4	Total	19	71	90		

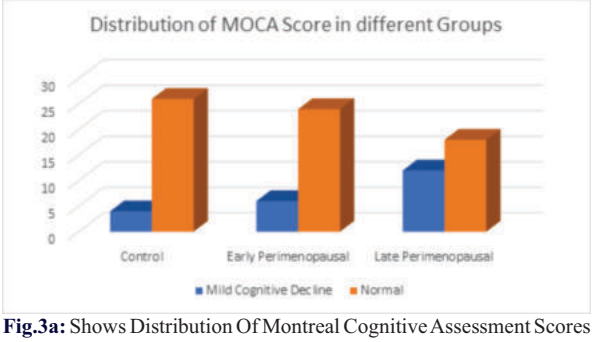

Fig.3a: Shows Distribution Of Montreal Cognitive Assessment Scores (MoCA) In The Study Groups

Table 4: Correlation Of Age With Serum Estradiol And Montreal Cognitive Assesment Score.

Pearson Corelation- Cofficient	Serum Estradiol	MOCA Score
	-.324**	-0.207
P- Value	*P < 0.01	P > 0.05

Table 5: Shows Correlation Of Serum Estradiol With Montreal Cognitive Assesment Score

Pearson Corelation- Cofficient	MOCA Score
	0.069
P- Value	P > 0.05

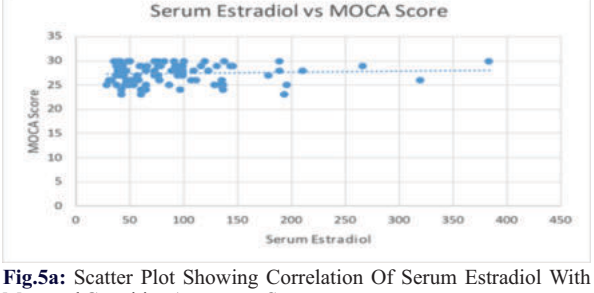

Fig.5a: Scatter Plot Showing Correlation Of Serum Estradiol With Montreal Cognitive Assesment Score

RESULTS

Table 1 shows the distribution of age in different study group.The mean age of control group is 32.73 ± 1.31 ,early perimenopausal group is 39.07 ± 1.26 and late perimenopausal group is 44.07 ± 1.17. Table 2 and fig.2a shows mean serum Estradiol in control group is 106.97 ± 62.59, in early perimenopausal group is 109.86 ± 67.68 and in late perimenopausal group is 55.54 ± 35.48 . P<0. 05, hence variation of mean serum Estradiol in study groups is statistically significant. Table 3 and fig.3a shows distribution of Montreal cognitive assesment scores in the study groups. P<0.05 shows that distribution of Montreal cognitive assessment scores is statistically significant. Table 4 shows that age has weak negative correlation with serum Estradiol(r = -0.324, P<0.01).The correlation of age with serum Estradiol is statistically significant. Age has weak negative correlation with Montreal cognitive assesment scores (r = -0.207 , P>005).The correlation witn Montreal cognitive assesment scores is statistically not significant. Table 5 shows that levels of serum Estradiol is positively correlated with Montreal cognitive assesment scores (r = 0.069 ,P> 0.05).The correlation of serum Estradiol with Montreal cognitive assesment scores is statistically not significant. Fig.5a is scatter plot showing correlation of Serum Estradiol with Montreal cognitive assesment score

DISCUSSION

Age-related cognitive impairment may progress from mild cognitive impairment (MCI) to dementia, a condition in which memory, behaviour, and cognition are impaired secondary to neurodegeneration in the brain. (7) Cognition is the act of process of knowing including awareness, reasoning, judgement and memory. Higher cortisol level or greater cortisol reactivity may be one mechanism other than decrease in estradiol levels that links hot flashes, depressive or anxiety symptoms to peri-menopausal decrements in cognitive performance. Cortisol increases after a hot flush. Exogenous administration of corticosteroids produces verbal memory impairment, and higher endogenous cortisol levels are associated with poorer performance on memory tasks. (8) Changes in cognitive abilities are also associated with the process of aging, with memory difficulties increasing as women approach menopause. (9) Although it can be difficult to distinguish between effects of chronological or reproductive aging, the transitioning hormonal environment leading to menopause may have various effects on specific cognitive domains. (10)

The most common complaints were difficulty recalling words or numbers, needing memory aids, and forgetting why one with perimenopause was involved in a certain behaviour. In this study as we could see in table 2, we have found that levels of serum Estradiol have decreased significantly in late perimenopausal age group as compared to control and early perimenopausal age group females.Further it is evident that in early perimenopausal group the serum Estradiol level is slightly more than the control group. There has been a significant negative correlation of age with serum Estradiol. My finding are similar to the findings seen in work of *sowers et all in 2008.* (11)

In this study we have seen in table 3 that number of women with Montreal cognitive assesment score of< = 26 are significantly more in late perimenopausal group as compared to control and early perimenopausal age group The correlation with Montreal cognitive assesment score is not significant whereas with Mini-mental scale examination score is significant. Lots of studies done previously have shown a significant decline in cognition in midlife as well as post menopausal life of women.My findings are similar to findings seen in work of *Karmangla et al.,2017.* (12)

There was no significant relation between cognitive decline and education status of females *Lovden et al.,2020* (13) wherein it says there is strong association between cognition and education in adulthood irrespective of gender but the decline in cognitive status in later age cannot be consistently related to education. There can be various other factors which could influence the cognitive status in mid life.

Our study also shows a negative correlation of age with cognition as seen in table 4,though the correlation is not very strong .Our findings are consistent with the findings seen in the study by *Conde et al in 2021* (14), which was done in postmenopausal females. They found a strong association of age with mild cognitive decline which can be attributed to the decreased levels of estradiol in postmenopausal age .Though our study found a significant decline in serum Estradiol levels

with age but we did not find a strong correlation between serum estradiol levels and cognitive decline as seen in table 5 among the premenopausal ,early perimenopausal and late perimenopausal groups.

CONCLUSION

Data obtained in our study showed a significant change in serum Estradiol levels with age but it did not show a strong correlation between serum estradiol levels and cognitive decline among the premenopausal ,early perimenopausal and late perimenopausal groups.Though the decreasing levels of serum Estradiol play a major role in affecting the cognitive status in females, it is more evident in the post menopausal age females.There are various other factors which may affect cognitive functions during menopausal transition .These factors are sleep loss, mood disorders, and hot flashes .

Further detailed and extensive studies are needed to deeply analyze the relationship of these hormone with the cognitive functions, which will pave the path for usage of these hormones during hormone replacement therapy in specific patients with cognitive decline.

No studies are done without limitations.The limitations in my study were, first only limited number of participants were included in each study group. Further research with more number of participants is needed for better understanding of the research. Secondly we included only literate females in our study.Such tools are needed which can identify the cognitive status in literate as well as illiterate population without differentiating on the basis of education. More extensive studies with more number of participants and more better methods to detect cognitive decline should be taken up for more precise results.

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