RESEARCH ARTICLE

Oxidative stress markers and brainstem auditory evoked potential in premenopausal, perimenopausal and postmenopausal females

Asma Ashraf[1], Seher Naeem[2], Madiha Akram[3], Muniza Saeed[4]

Abstract

Objective: To measure biomarkers of oxidative stress and to determine hearing sensitivity by auditory brainstem response in premenopausal, perimenopausal and postmenopausal women.

Method: The cross-sectional, comparative study was conducted in the departments of Physiology and Audiology at the Post-Graduate Medical Institute, Lahore, and the Lahore General Hospital, Lahore, Pakistan, from November 2020 to November 2021, and comprised healthy female subjects grouped into premenopausal group 1, perimenopausal group 2 and postmenopausal group 3 as per their menstrual history. Blood samples were taken for measuring biological indicators of oxidative damage, while auditory integrity was assessed by measuring absolute latencies of waves I, III, V and interpeak latency of waves III and V at an intensity of 80dB by performing brainstem auditory evoked potential. Data was analysed using SPSS 23.

Results: Of the 45 subjects, 15(33.3%) with mean age 41.3±1.9 years were in group 1, 15(33.3%) with mean age 46.7 ± 3.7 years were in group 2, and 15(33.3%) with mean age 55.8±2.7 years were in group 3. Significantly increased levels of thiobarbituric acid reactive substance were found in group 3 compared to groups 1 and 2 ($p<0.05$). Regarding auditory brainstem response, a significant increase was observed in absolute latencies of waves I, III, V and interpeak latency between waves III and V in group 3 compared to the other groups ($p<0.05$).

Conclusion: Oxidative stress had a debilitating impact on hearing sensitivity related to the menopausal status of women.

Key Words: Menopause, Oxidative stress, Brainstem auditory evoked potential.

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Introduction

Reproductive transitions in the later stages of female life occur as a result of sequential activation and deactivation of complex regulatory pathways. Small perturbations during the restructuring processes that regulate these transition states may shape women's wellbeing and quality of life in old age. Moreover, the presence, variability, intensity and duration of various neurological symptoms during these phases might foreshadow an increased risk of detrimental health outcomes in later life, especially neurodegenerative diseases.[1]

In accordance with the Stages of Reproductive Aging Workshop (STRAW) staging system, menopause/final menstrual period (FMP) is defined as the complete absence of menstrual bleeding for 12 consecutive months following a paucity of follicular reserve in females' ovaries. It constitutes the final stage of perimenopause, the first stage being the menopausal transition where regular menstrual cycles become more and more unpredictable or inconstant and features of approaching menopause commence. Postmenopause is referred to as a period of complete amenorrhea where symptoms, most notably vasomotor and symptoms related to female genitalia and urinary tract infections (UTIs) become more frequent and extensive along with stabilisation of follicle stimulating hormone (FSH) at higher levels compared to the premenopausal phase.[2]

Recent data suggests that marked hormonal aberrations around the time of menopause have pronounced negative impact on oxidative balance of the female body, contributing to the emergence of numerous neurodegenerative diseases that are observed in postmenopausal women. One of the suggested mechanisms explaining this link takes into account the loss of the protective effect of 17-beta-estradiol (E2) as its levels rapidly decline with the increasing reproductive age.[3,4] Oxidative stress (OS) is basically the consequence of an imbalance between the oxidants and antioxidants present naturally in the body. Altered redox status can inflict serious damage to body cells by inducing the degenerative changes in biological molecules, like lipid bilayer or deoxyribonucleic acid (DNA).[5,6] For this reason, the human body has been provided with its own naturally

[1-4]Post Graduate Medical Institute, Lahore, Pakistan.

Correspondence: Asma Ashraf. **Email:** asma.ashruf@yahoo.com

Current Affiliation (Author-1): Continental Medical College, Lahore, Pakistan

ORCID ID: 0009-0006-9549-2221

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occurring antioxidant enzymes that are responsible for maintaining the stable internal environment of body.[5]

Like many neurological symptoms, hearing impairment has a disabling impact on the lives of aging females. Though the high risk of mortality associated with such issues is usually not significant, it has repeatedly been linked with despair, seclusion, apprehension and cognitive deficit.[7] Regarding the pathophysiology of hearing decline in the absence of oestrogen, studies have confirmed that hair cells present in cochlea undergo eradication and programmed cell death in response to injuries mediated by reactive oxygen species (ROS). Since hair cells are believed to be very much dependent upon high levels of oxygen for their continuous working, therefore even minor hypoxias can initiate their death because of oxidative damage to lipids, amino acids and nucleic acids through generation of oxygen-free radicals.[8] In addition to the aforementioned facts, altered redox status has also been shown to contribute to some other audiological pathologies, such as noise-induced hearing loss, presbycusis, Meniere's syndrome and inflammatory diseases of the inner ear.[9] Thus, OS may be a common factor underlying these seemingly different causes of hearing loss.[10]

OS-induced hearing decline in females with reproductive aging is an important issue, but it has been relatively less explained. The current study was planned to measure OS biomarkers, and to determine hearing sensitivity by auditory brainstem response (ABR) in premenopausal, perimenopausal and postmenopausal women.

Subjects and Methods

The cross-sectional, comparative study was conducted from November 2020 to November 2021 at the Physiology Department of the Post-Graduate Medical Institute (PGMI), Lahore, and the Audiology Department of the Lahore General Hospital, Lahore, Pakistan. After approval from the PGMI ethics review board, the sample size was calculated in the light of literature[11] at 95% confidence interval and 90% power.

The sample was raised using non-probability convenience sampling technique.

Those included were women aged 40-60 years having body mass index (BMI) 18.5-24.9kg/m^2. The participants were grouped into premenopausal (regular menstrual cycle of 28±4 days) group 1, perimenopausal (irregular periods with amenorrhea for <12 months) group 2 and postmenopausal (amenorrhea ≥12 months) group 3[2]. Women fulfilling the criteria were assessed with pure tone audiometry, and those who had hearing threshold 0-20 decibels (dB) at routine frequencies were included.[12] Pregnant or lactating women, those with polycystic ovaries or who had undergone hysterectomy or endometrial ablation, those on chemotherapy, hormone replacement therapy (HRT) or antioxidant supplements, and those with history of diabetes, hypertension, renal diseases, smoking, alcohol consumption or any known otological disease or occupational noise exposure were excluded. Data was collected after taking informed, written consent from the subjects.

Blood sampling was done to measure OS markers total antioxidant capacity (T-AOC), total superoxide dismutase (SOD) activity and thiobarbituric acid reactive substances (TBARS) using commercially available kits. Hearing was assessed using ABR potential on computerised evoked potential recorder (Model Name Epicplus Pro, Company Labat Asia Private Limited, India). For electrode placement and other settings required for ABR testing, the International 10-20 system established for electroencephalography and polysomnography exams was used (Figure 1).[12,13] The principal measurements included absolute latencies of waves I, III, V and inter-peak latency between waves III and V at an intensity of 80dB.

Data was analysed using SPSS 23. After assessing data normality with Shapiro-Wilk test, multivariate analysis of

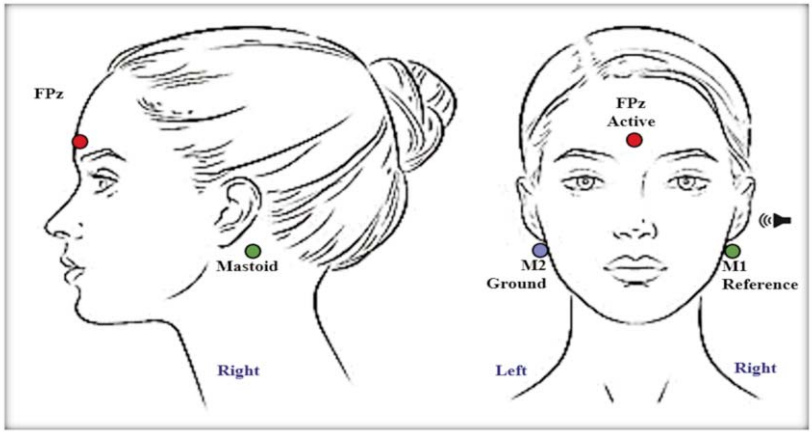

Figure-1: Electrode placement for one-channel auditory brainstem response (ABR) recording

One electrode was placed on the forehead (FPz) as active/non-inverting/+ve electrode, and the other two, the reference/inverting/-ve and ground electrodes were placed on mastoid processes of test and non-test ear, respectively (M1 and M2). Acoustic stimuli were delivered monoaurally through a headphone in the form of alternate clicks, 100 µsec in duration, intensity 80dB HL and at a rate of 11/s. Contact impedance was maintained at 1.7-2.2 kΩ throughout the procedure[12,13].

variance (MANOVA) was used for comparison of means among the groups, and Tukey's post-hoc test for pair-wise intergroup comparison. Pearson correlation test was used to look for linear relationship between OS markers[14], antioxidant status and absolute and interpeak latencies of ABR waves in all the groups. P≤0.05 was considered statistically significant.

Results

Of the 45 subjects, 15(33.3%) with mean age 41.3±1.9 were in group 1, 15(33.3%) with mean age 46.7 ± 3.7 years were in group 2, and 15(33.3%) with mean age 55.8±2.7 years were in group 3.

Significantly increased levels of TBARS were found in group 3 compared to groups 1 and 2 (p<0.001). A significant increase was noted in group 3 compared to group 2 (p<0.01). Serum SOD and T-AOC values were distinctly lower in group 3 compared to group 1 (Table 1).

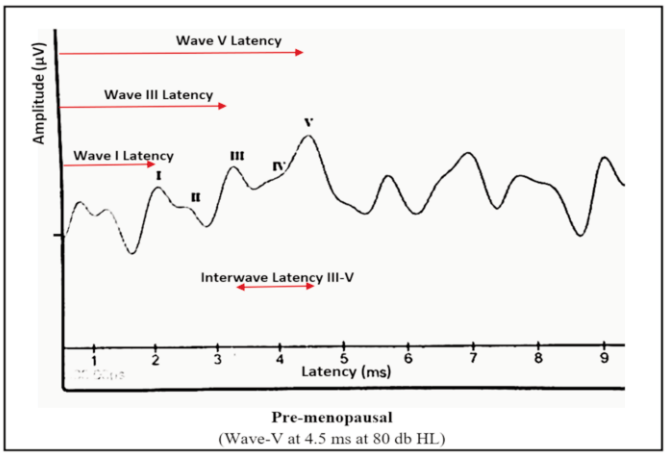

Figure-2: Auditory brainstem response (ABR) tracing of a subject in the premenopausal group.

Table-1: Comparison of oxidative stress (OS) markers.

	Premenopausal (n=15)	Perimenopausal (n=15)	Postmenopausal (n=15)	MANOVA p-value	Tukey's Post Hoc p-value
TBARS (µmol/L)	2.2 ± 0.9	5.5 ± 1.3	7.8 ± 1.5	0.000**	$P_{1-2} = 0.002$**
					$p_{1-3} = 0.000$**
					$p_{2-3} = 0.004$**
SOD (U/ml)	12.8 ± 1.6	12.8 ± 1.1	9.0 ± 1.7	0.000**	$p_{1-2} = 1.000$
					$p_{1-3} = 0.002$**
					$p_{2-3} = 0.002$**
T-AOC (mmol/L)	1.3 ± 0.3	1.1 ± 0.2	0.7 ± 0.2	0.000**	$p_{1-2} = 0.047$*
					$p_{1-3} = 0.02$*
					$p_{2-3} = 0.027$*

TBARS: Thiobarbituric acid reactive substance, SOD: Superoxide dismutase, T-AOC: Total antioxidant capacity, MANOVA: Multivariate analysis of variance.
**p-value <0.01 was considered highly significant

Table-2: Comparison of absolute latencies and interpeak latency of auditory brainstem response (ABR) waves.

Latency (msec)	Premenopausal (n=15)	Perimenopausal (n=15)	Postmenopausal (n=15)	MANOVA p-value	Tukey's Post Hoc p-value
Wave-I	1.3 ± 0.3	1.7 ± 0.5	2.0 ± 0.4	0.000**	$p_{1-2} = 0.070$
					$p_{1-3} = 0.000$**
					$p_{2-3} = 0.069$
Wave-III	3.2 ± 0.5	3.6 ± 0.5	4.1 ± 0.7	0.001**	$p_{1-2} = 0.294$
					$p_{1-3} = 0.001$**
					$p_{2-3} = 0.039$*
Wave-V	5.3 ± 0.5	5.5 ± 0.7	6.8 ± 0.8	0.000**	$p_{1-2} = 0.664$
					$p_{1-3} = 0.000$**
					$p_{2-3} = 0.000$**
III-V	2.1 ± 0.5	1.9 ± 0.5	2.7 ± 0.7	0.003**	$p_{1-2} = 0.789$
					$p_{1-3} = 0.023$*
					$p_{2-3} = 0.004$**

MANOVA: Multivariate analysis of variance.
**p-value <0.01 was considered highly significant
* p-value <0.05 was considered statistically significant
p1-2; premenopausal vs perimenopausal;
p1-3; premenopausal vs postmenopausal;
p2-3; perimenopausal vs postmenopausal..

Regarding ABR, a significant increase was observed in absolute latencies of waves I, III, V and interpeak latency between waves III and V in group 3 compared to the other groups (Table 2; Figures 2-3).

In group 1 subjects, a significant negative correlation was found between capacity-AOC and inter-peak latency of waves III-V (p<0.05; r=-0.591). In group 2 subjects, a significant negative association was seen between serum TBARS levels and serum SOD levels (p<0.05; r=-0.606). Moreover, a weak negative correlation was also found between capacity-AOC and inter-peak latency of waves III-V (r=-0.271). In group 3, a significant negative correlation was seen between capacity-AOC and interpeak latencies of waves III-V (p<0.05; r=-0.659). A moderate negative but non-significant correlation was present between T-AOC and latency of wave III (r=-0.438) (Table 3).

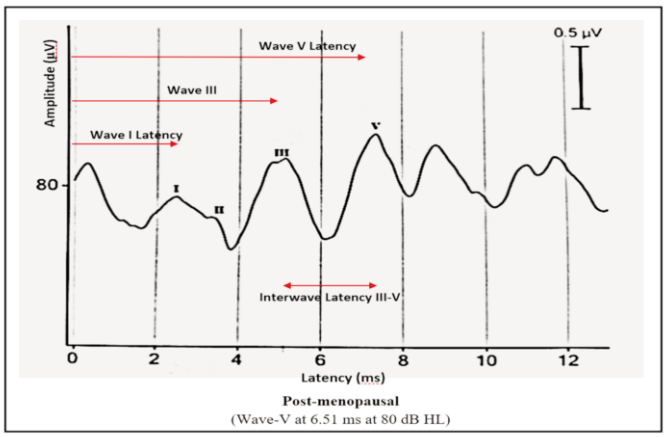

Figure-3: Auditory brainstem response (ABR) tracing of a subject in the postmenopausal group.

Table-3: Correlation analysis between oxidative stress markers and auditory brainstem response (ABR) waves.

	SOD	T-AOC	Wave I	Wave III	Wave V	III-V
Pre-Menopausal						
TBARS	0.060	-0.172	0.105	0.241	-0.210	-0.176
SOD		-0.088	0.153	-0.112	-0.405	
T-AOC		0.193	0.376	0.238	-0.591*	
Peri-Menopausal						
TBARS	-0.606*	-0.176	-0.450	-0.149	-0.136	-0.034
SOD		0.394	-0.070	0.180	0.327	
T-AOC		0.288	0.002	-0.20	-0.271	
Post-Menopausal						
TBARS	0.181	0.555*	-0.163	-0.287	-0.069	0.159
SOD		0.019	-0.044	0.368	0.394	
T-AOC		0.094	-0.438	-0.186	-0.659**	

TBARS: Thiobarbituric acid reactive substance, SOD: Superoxide dismutase, T-AOC: Total antioxidant capacity.
*Correlation is significant at 0.05 level (2-tailed)
** Correlation is significant at 0.01 level (2-tailed)
Correlation coefficient (r)= 1 = perfect correlation
(r)=0.9 to 0.99 or -0.9 to -0.99 = very strong correlation
(r)= 0.70 to 0.89 or -0.7 to -0.89 = strong correlation
(r)= 0.40 to 0.69 or -0.40 to -0.69 = moderate correlation
(r)= 0.10 to 0.39 or -0.10 to -0.39 = weak correlation
(r)= 0 = no correlation.

Discussion

The present study corroborates earlier findings[15] related to health issues encountered by postmenopausal women as a result of the altered redox status of the body in response to decreasing oestrogen levels, focussing on the integrity of the auditory pathway.

The mean ages of subjects in the three groups were 41.3 years, 46.7 years and 55.8 years, respectively. In most studies done on menopausal females, the average age of menopause is around 46-50 years with the perimenopausal period ranging 2-7 years.[16,17] To avoid any confounding factors, all women in the current study were normotensive and in the healthy BMI category.

The current findings show that the circulating level of OS marker TBARS was significantly increased during perimenopausal and postmenopausal phases compared to the reproductive phase of women. The finding is in agreement with earlier studies that have shown more pronounced OS in females with menopause because of compromised antioxidant defence mechanism of the body which tips the balance in favour of excess reactive oxygen and nitrogen species.[18,19] The T-AOC levels were also significantly reduced in perimenopausal and postmenopausal women as opposed to women in the reproductive phase. Likewise, regularly menstruating females showed remarkably elevated levels of serum SOD in contrast to the postmenopausal group. Results from another study revealed that by-products of lipid and protein peroxidation were increased in perimenopausal and postmenopausal women contrary to non-menopausal women along with altered lipid profile and inflammatory markers.[20,21] A considerable number of researches done previously have hypothesised that OS development around the time of menopause is linked to the declining levels of oestrogen since oestrogen has been shown to exert antioxidant actions owing to its hydroxyl-phenol structure and its ability to trigger cellular antioxidant enzymes of the body.[22,23]

In the context of menopause-related OS and rapid hearing decline in postmenopausal females, ample evidence[24,25] has already proven that generation of excessive amount of ROS can play a key role in the pathogenesis of hearing decline, such as in age-related or noise-induced hearing deficit. This can be attributed to the extreme vulnerability of the highly sensitive auditory system to the toxic effects of ROS which include not only inflammation, but also ischaemic changes, inner and outer hair cell death, and mitochondrial impairment.[24] Pertaining to that, ROS-induced lipid peroxidation has been shown to trigger apoptosis of cochlear hair cells and cochlear ischaemia.[25]

To see the effect of OS on the integrity of auditory pathway, the current study used ABR, and found an increasing trend in absolute latencies of waves I, III and V and inter-peak latency of waves III and V from premenopausal to postmenopausal group. Further analysis showed sharp contrast between groups 1 and 3, and between groups 2 and 3, indicating decreased hearing sensitivity in females as they pass from premenopausal to postmenopausal phase, or in females

passing from perimenopausal to postmenopausal phase. The results align perfectly with several other similar studies conducted globally.[26,27] In one study, menopausal women with normal hearing thresholds exhibited significantly longer ABR waves' latencies and experienced notably poor hearing in noisy environments compared to a similarly aged control group of menstruating women.[28]

Furthermore, correlation analysis showed a significant negative correlation between capacity-AOC and interpeak latencies of waves III and V in premenopausal and postmenopausal groups. Research has indicated that unopposed action of ROS in the absence of endogenous or exogenous antioxidants plays a role in the demise of inner and outer cochlear hair cells and in altering the synaptic transmission at various levels of auditory pathway, potentially resulting in reduced hearing sensitivity.[29]

The current study has limitations. Due to its cross-sectional design, the study could not determine temporal or causal relationship among the variables.

Conclusion

OS along with its debilitating impact on hearing sensitivity was noted in perimenopausal and postmenopausal women compared to premenopausal subjects.

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Conflict of Interest: None.

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AUTHORS' CONTRIBUTIONS:
AA: Concept, design, data acquisition and drafting.
SN: Concept and design.
MA: Data analysis, interpretation and drafting.
MS: Final approval.