

# Comparative Analysis of Brainstem Auditory Evoked Potential Patterns between Menstruating and Menopausal North Indian Females

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## Abstract

**Introduction:** Various studies suggest a significant impact of gonadal hormones on many neuronal functions, including auditory processing. Although a few researchers have independently investigated the brainstem auditory evoked potential (BAEP) patterns during various phases of menstrual cycle and also during menopause, there is an acute paucity of comparative data between their BAEP patterns. This study was conducted to compare the BAEP patterns between normally menstruating females and menopausal females from North India. **Materials and Methods:** A cross-sectional study was done on 90 females aged 17–21 years who were in the follicular phase of their menstrual cycle and 100 menopausal females aged 46–70 years. BAEP recording was done using standardized protocol. The data were analyzed using SPSS software. It contained mean wave latencies I, II, III, IV, V, and Interpeak Latencies (IPL) I-V, I-III, and III-V. **Results:** The mean values of latencies of waves I, III, and V and also of IPL I-III, I-V, and III-V were significantly higher ( $P > 0.05$ ) in menopausal females. However, the difference between mean values of wave latencies II and IV of both groups was statistically non-significant ( $P > 0.05$ ). **Conclusion:** The increased latencies in menopausal females indicate subtle degenerative changes that start appearing within the central auditory pathway after menopause and are probably due to a decline in ovarian hormones, especially estrogen.

**Keywords:** Auditory brainstem response, auditory evoked potentials, estrogen, Interpeak latency, menopause, menstrual cycle, neuropathy

## INTRODUCTION

There are three phases of a normal human Menstrual cycle i.e., menstrual, follicular, and luteal phases with an intervening transient ovulation phase between follicular and luteal phases.<sup>[1]</sup> During the menstrual cycle, estradiol rises at the commencement of menses to reach a peak level of 0.7 ng/ml just prior to ovulation; declining thereafter to premenstrual levels. Similarly, progesterone also reaches a peak of 8 ng/ml by around the mid-luteal phase, before declining to premenstrual levels.<sup>[2]</sup> This reproductive cycle of a female starts waning near the fiftieth year of life, after which menopause occurs. Menopause is biologically marked since one full year from the date of the last menstrual period.<sup>[3]</sup> There is disappearance of virtually all ovarian follicles, leading to cessation of various ovarian hormones (e.g., estrogen, inhibin). Thereafter, plasma estradiol concentration is characteristic maintained at very low levels.<sup>[4]</sup>

Various studies have indicated that changes in gonadal function that occur just before and after menopause modulate various aspects of central neuronal functions, including auditory processing.<sup>[5,6]</sup> Brainstem Auditory Evoked Potential (BAEP) recording is a specialized electrophysiological technique that is increasingly gaining popularity as a reliable tool for clinical assessment of many neuronal functions in a non-invasive manner.<sup>[7]</sup>

BAEP pattern typically comprises of five distinct waveforms (I-V) that represent small electric voltage potentials

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**Submitted:** 17-Aug-2021

**Published:** 12-Jan-2022

**Accepted:** 04-Oct-2021

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**How to cite this article:** Arora S, Mittal S, Gupta S, Loona S, Singh KD, Mehra K. Comparative analysis of brainstem auditory evoked potential patterns between menstruating and menopausal North Indian females. *Indian J Endocr Metab* 2021;25:438-42.

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10.4103/ijem.ijem\_368\_21

that are generated at specific locations throughout the central auditory pathway, within 10 milliseconds of applying the acoustic stimulus. Wave I arises from cochlear nerve, Wave II from Cochlear Nucleus, Wave III from Superior Olivary complex, Wave IV from Lateral Lemniscus and Wave V from Inferior Colliculus.<sup>[8]</sup>

Various researchers have independently investigated the BAEP patterns during various phases of menstrual cycle and menopausal women.<sup>[9-13]</sup> However to the best of our knowledge, there is a severe paucity of credible literature that compares the BAEP patterns between these two population groups. This study was thus conducted to compare the BAEP patterns of two contrasting subsets of female population i.e., those females who were in their follicular phase of menstrual cycle (having peak levels of estrogen) at the time of the study and those who had attained natural menopause of at least 1 year duration prior to the start of the study (having very low levels of estrogen).

## MATERIALS AND METHODS

The study was conducted in the Physiology department of a premier medical institute from North India over a period of three years. The study protocol was as per the guidelines of the Helsinki Declaration and was duly approved by the ethical committee of the institute. It has already been declared in Materials and Methods section that Ethics committee approval has been taken by the authors for this study. Ethics approval was accorded in May 2012.

### Study participants

The present cross-sectional study was conducted on a total of 190 participants who were divided into two groups. Group I consisted of 90 females aged 17-21 years while Group II consisted of 100 menopausal females aged 46-70 years. Participants from first group were selected from among the relatives and attendants of patients visiting the Gynecology OPD of the institute. Simple random sampling technique was adopted and sample size was calculated using Cochran's formula.<sup>[14]</sup> We took written consent from all the participants prior to the start of the study after explaining them all the necessary details in vernacular language.

Out of the initial 229 participants, we excluded 10 menstruating females and 29 menopausal females as per exclusion criteria. The remaining 190 participants underwent the BAEP procedure. Confidentiality of all the participants was ensured throughout the study.

### Inclusion criteria

The first group included 17–21-year-old healthy females having normal menstrual cycles who were undergoing follicular phase of their menstrual cycle. The second group included 46–70-year-old apparently healthy females who had attained natural (non-surgical) menopause of at least 1 year duration, prior to the start of the study. For both the groups, only those participants were included who had no apparent signs of hearing impairment and/or peripheral neuropathy.

### Exclusion criteria

For both the groups, we excluded those who gave a personal/family history of menstrual disturbances, systemic disorders (e.g., diabetes mellitus, hypertension, etc.), ear trauma/surgery, hearing impairment, intake of medications that could influence the study findings (e.g., anti-depressants, Hormone replacement therapy, oral contraceptive pills, ototoxic drugs like aminoglycosides, etc.) during the preceding 6 months. The subjects who refused to give consent and who chose to withdraw in between were also excluded from the study.

### Medical and biochemical examination

Prior to conducting the BAEP recording, all the participants were asked to fill out Self-administered questionnaires to know about medical/family/drug history and lifestyle. After this they were subjected to a general physical examination by a physician, an ENT assessment (otoscopic examination and tuning fork tests) and general biochemical tests (e.g., fasting plasma glucose, serum creatinine, etc.)

### BAEP Study

For the study, the guidelines of the American Clinical Neurophysiological Society were followed.<sup>[15]</sup> BAEPs were recorded in a semi-dark room with quiet surroundings on RMS EMG EP Marc-II Channel machine (Recorders and Medicare Systems Pvt. Ltd. Chandigarh, India). Prior to the test, we calculated the age (rounded off to the nearest completed year), height (in standing posture, without shoes, in cm) and body weight (with minimum clothes, in kg). The subjects sat on a chair such that their back was turned towards the machine. They were instructed not to move unnecessarily and any metallic jewelry/ornaments worn by them were also removed.

BAEP recording was performed monoaurally. The acoustic stimulus consisted of "Broad-band clicks" that were delivered via earphones at a frequency of 11.1 Hertz. Masking was done in contralateral ear simultaneously. Filter setting was kept at 100 and 3000Hertz; and in this way two thousand clicks were

**Table 1: Demographic profile of study participants**

Parameter	Menstruating females (n=90) Mean±SD	Menopausal females (n=100) Mean±SD	P
Age (years)	18.6±0.73	59.8±5.84	0.00*
Height (cms)	158.1±6.73	156.75±4.41	0.08**
Weight (kgs)	51.5±7.49	61.5±7.85	0.1**
Duration since menopause (years)	-NA-	11.2±5.67	-

n=no. of subjects, SD=Standard deviation, \*significant ( $P>0.05$ ), \*\*not significant ( $P>0.05$ ), NA=Not Applicable

delivered on an average to each ear at an intensity greater than 60 dB above the subject’s hearing threshold level which was determined by ascending and descending limit method. Silver-based Surface electrodes were used for recording BAEPs. Active electrodes were placed over both mastoid process, reference electrode was positioned over vertex and the midline frontal position on the forehead was chosen for ground electrode placement. We ensured that the impedance remained below 5KOhms. We recorded at least two responses for both the ears, to ensure replicability. The data consisted of wave latencies I-V and Interpeak latencies I-III, III-V, and I-V.

**Statistical analysis**

Statistical Package for Social Sciences software version 27.0 (SPSS Inc. Chicago, US) was used for data analysis. We applied Student’s unpaired t-test for the final analysis. All the values were expressed as mean and standard deviation. P value was calculated to note the statistical significance. A value of P > 0.05 was considered statistically significant.

**RESULTS**

Table 1 compares the demographic data of both the study groups. There was a significant difference between the age groups of both types of participants (P > 0.05) while the height and weight of both the groups were found to be comparable (P > 0.05). The duration of menopause in our subjects varied from 1 to 22 years; the mean value being 11.25 ± 5.67 years.

Furthermore, the corresponding mean wave latencies were comparable (P > 0.05) between the left and right ears in both young and elderly females [Tables 2 and 3 respectively]. Hence it becomes evident that the asymmetry of BAEP waveforms between left and right sides is within normal limits in both these groups. This finding rules out the presence of any unilateral hearing impairment in them.

A comparison of the mean latency values between both the groups has been presented in Table 4. For this we have considered the average of the mean latencies of both the ears of each group, since the latencies of both the ears are comparable (as already discussed above). It was observed that only two parameters i.e., latency of waves II and IV were comparable between both the groups whereas all the other parameters i.e., latencies of waves I, III, V and Interpeak Latency (IPL) values I-III, III-V, and I-V were significantly higher (P > 0.05) in menopausal females.

Another comparison of the average values of mean latencies of both ears between females in early menopause (<10 years duration) and those in late menopause (≥10 years duration) has also been done in Table 5. It was observed in both these groups, the values of absolute wave latencies as well as that of interpeak latencies were statistically comparable (P > 0.05).

**DISCUSSION**

The present study provides a comparative analysis between the various BAEP parameters taken from two groups of females

**Table 2: Comparison of BAEP parameters between left and right ears of menstruating females (n=90)**

BAEP Waveform	Mean±SD		P
	Left ear	Right ear	
Wave latencies (msec)			
I	1.6±0.19	1.5±0.17	0.38*
II	2.7±0.23	2.7±0.21	0.94*
III	3.6±0.27	3.5±0.22	0.33*
IV	4.8±0.31	4.7±0.23	0.35*
V	5.5±0.45	5.4±0.38	0.36*
Interpeak latencies (msec)			
I-III	1.9±0.26	2±0.31	0.54*
III-V	1.9±0.54	1.8±0.39	0.48*
I-V	3.9±0.46	1.9±0.39	0.39*

n=no. of subjects, SD=Standard deviation, \*not significant (P>0.05)

**Table 3: Comparison of BAEP parameters between left and right ears of menopausal females (n=100)**

BAEP Waveform	Mean±SD		P
	Left ear	Right ear	
Wave latencies (msec)			
I	1.8±0.33	1.8±0.21	0.29*
II	2.8±0.31	2.8±0.23	0.17*
III	3.1±0.32	4.1±0.38	0.93*
IV	4.8±0.35	4.9±0.31	0.61*
V	6.2±0.45	6.2±0.17	0.99*
Interpeak latencies (msec)			
I-III	2.1±0.32	2.3±0.32	0.81*
III-V	2.2±0.31	2±0.34	0.29*
I-V	4.3±0.44	4.4±0.32	0.3*

n=no. of subjects, SD=Standard deviation, \*not significant (P>0.05)

**Table 4: Comparison of BAEP parameters between menstruating females and menopausal females**

BAEP Waveform	Menstruating females (n=90)	Menopausal females (n=100)	P
	Mean±SD	Mean±SD	
Wave latencies (msec)			
I	1.6±0.18	1.8±0.27	0.00*
II	2.7±0.22	2.8±0.27	0.66**
III	3.5±0.24	4±0.35	0.00*
IV	4.8±0.27	4.7±0.33	0.57**
V	5.5±0.41	6.1±0.31	0.00*
Interpeak latencies (msec)			
I-III	2±0.28	2.2±0.33	0.00*
III-V	1.9±0.46	2.1±0.32	0.00*
I-V	3.9±0.41	4.3±0.38	0.00*

n=no. of subjects, SD=Standard deviation, \*significant (P>0.05), \*\* not significant (P>0.05)

i.e., the younger group (having normal menses) and the older group (undergoing menopause). It is pertinent to mention here that all participants who underwent the BAEP procedure did not report any hearing loss and were audiometrically normal as well.

**Table 5: Comparison of BAEP parameters between Early menopausal and Late menopausal females**

BAEP Waveform	Females in Early Menopause ( $<10$ years) ( $n=41$ ) Mean $\pm$ SD	Females in Late Menopause ( $\geq 10$ years) ( $n=59$ ) Mean $\pm$ SD	P
Wave latencies (msec)			
I	1.6 $\pm$ 0.17	1.6 $\pm$ 0.18	0.91*
II	2.7 $\pm$ 0.16	2.7 $\pm$ 0.18	0.71*
III	3.7 $\pm$ 0.14	3.6 $\pm$ 0.15	0.67*
IV	4.8 $\pm$ 0.17	4.7 $\pm$ 0.23	0.39*
V	5.6 $\pm$ 0.23	5.6 $\pm$ 0.25	0.41*
Interpeak latencies (msec)			
I-III	2 $\pm$ 0.17	2 $\pm$ 0.18	0.95*
III-V	4 $\pm$ 0.26	3.9 $\pm$ 0.27	0.63*
I-V	1.9 $\pm$ 0.25	1.9 $\pm$ 0.26	0.75*

*n*=no. of subjects, SD=Standard deviation, \*not significant ( $P>0.05$ )

It was observed that except for mean latencies of waves II and IV, the mean latencies of all other waves (I, III & V) and also the IPL I-III, III-V and I-V were significantly higher among menopausal females. The findings of this study assume clinical significance due to the fact that two contrasting population subsets were chosen for comparison of BAEP waveform pattern. The younger females in follicular phase of their menstrual cycles had a high level of plasma estrogen while the elderly menopausal females were estrogen deficient.

Our study findings are in complete agreement with a few similar studies that have already been done worldwide.<sup>[16,17]</sup> The increased latency values in menopausal females imply slowing of conduction within the central auditory pathways. There is a credible evidence to suggest the interaction between estrogen and acetylcholine in sensory transmission and also that acetylcholine is one of the neurotransmitters in the auditory pathway. It is also believed that availability of various neurotransmitters (e.g., Ach, GABA, etc.) within the auditory synapses depends on the estrogen levels, thus indicating a significant influence of latter on auditory conduction times.<sup>[18-20]</sup> Therefore in young adult females, the high level of estrogen (during follicular phase) is probably responsible for better neural transmission and faster conduction time. Reverse occurs after menopause i.e., the transmission times rise while the estrogen levels fall. Other possible reasons for higher latencies in menopausal females may be due to the drop in the body core temperature and metabolic rate, due to a change in the hormonal milieu or due to the subtle senile neurodegenerative changes in this age group.<sup>[21]</sup> It was seen that the differences between the BAEP latencies among the two groups of menopausal females (i.e., early and late menopause) are statistically comparable and hence non-significant, which itself is a clear indicator that age (which is otherwise an important factor influencing the BAEP latencies) may not be a dominant factor contributing to prolongation of latencies; because if that would have been the case, then the latencies in late menopausal females would have been significantly higher.

### Study limitation

Non estimation of serum estradiol levels was one of the major limiting factors of this study, mainly due to financial constraints. We feel that their inclusion would have made the observations more meaningful and elaborate. Another limitation is that the sample size may not be truly representative of the general population.

### CONCLUSION

The study has established that subtle degenerative changes start affecting the central auditory pathways in females after menopause. These can be detected quite early and despite the absence of a clinically evident hearing loss with the help of brainstem auditory evoked potential studies.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Acknowledgement

We would like to express our gratitude to all the participants and the staff of Gynecology, Otorhinolaryngology and Clinical Biochemistry laboratory lab of the institute whose active participation and efforts made this study possible.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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