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RESEARCH ARTICLE

Auditory brainstem responses during menstrual cycle and pregnancy

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Abstract

Background and Aim: The sexual hormones alter during menstrual cycle and pregnancy. Despite the physiological benefits of these changes, their adverse effects on hearing system such as hearing loss and vertigo have been reported. Therefore, in this study, the auditory brainstem responses (ABR) were investigated during physiological hormonal variations in the menstrual cycle as well as pregnancy.

Methods: In this comparative-cross sectional research, the ABR was assessed in 25 women, including 17 pregnant and 8 non-pregnant women. The assessment was conducted at 24th week of pregnancy and in two stages of the menstrual cycle, on the 1st-3rd day and once again during the 12th-15th day in non-pregnant women (control group). Click stimuli ABR was recorded and compared between aforementioned groups.

Results: According to our results, ABR wave V absolute latency, III-V and I-V interpeak latencies were significantly longer during the 12th-15th day of menstrual cycle compared to 1st-3rd day results ($p<0.05$). These significant increases were observed between pregnant women and control groups ($p<0.05$).

Conclusion: The research revealed the influence of hormonal changes during menstrual cycle and pregnancy on brainstem and auditory pathways. We concluded that the brainstem auditory pathways processing decelerates with the increase of estrogen and progesterone hormones.

Keywords: Auditory brainstem response; estrogen; progesterone; menstrual cycle; pregnancy

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Introduction

The menstrual cycle is a series of recurring events over an average of 28 days in women occurring from puberty to menopause. The menstrual process is a 28 day periodic cycle consisting of follicular and luteal stages. The follicular stage starts with menstrual bleeding. Then, due to maximal estrogen secretion, luteinizing hormone secretion increases in the middle of the process which leads to ovulation (follicular phase). Second phase starts immediately after ovulation with the rise of progesterone. A high level of progesterone remains constant until 23rd or 24th day of the cycle. If the fertilizing does not occur, the next cycle starts on the 29th day with the start of the next bleeding [1]. At the beginning of pregnancy, the amounts of estrogen and progesterone are a lot lower than the last days. These two hormones show significant increase specifically between weeks 12 to 24 of pregnancy compared to early pregnancy [2]. Interestingly, the recent reports indicate that, there are estrogen and progesterone hormone's receptors in the hearing system [3,4].

Auditory brainstem responses (ABR) represent the extensive majority of neurons activity in the auditory brainstem by a sound stimulus and show the neural processing, synaptic transmission and the condition of auditory neurons [5,6]. ABR includes 5 to7 waves, which are labeled with roman numerals. For clinical purposes, waves I, III and V are more acceptable. A more recent study attributed wave I to the spiral ganglion cells of the cochlea, wave II to the cochlear nucleus, wave III to the cochlear nucleus and contralateral superior olivary nucleus (SOC), wave IV to SOC, and wave V to the lateral lemniscus and inferior colliculus [1]. In this model, waves VI and VII are attributed to the MGB of the thalamus. The ABRs are measured by electrodes placed on the skull. For more clinical uses, the electrodes are generally placed on the vertex of the skull and the mastoid or the ear (pinna) ipsilateral to the stimulus [1].

The interpeak latency (IPL) has a high diagnostic value. The IPL between I-V is representative of the nerve time conduction from the distal parts of the cochlear nerve to superior olivary nucleus/lateral lemniscus. The I-III IPL shows primary auditory neuron activity in the cochlear nerve and low levels of brain stem, while the III-V IPL represents the time conduction in the brain stem from the cochlear nerve nucleus to the lateral lemniscus [6].

Lots of efforts have been made using ABR to prove the relationship between auditory brainstem function in the menstrual cycle and during the pregnancy. However, conflicting results have been obtained [7-18]. Resende et al. in their study about the effects of menstruation in young women on the results of ABR found no relation between hormones and ABR results. They reported that sex hormones have no effect on the peripheral and central auditory system [7]. Yadav et al. reported that at different times of the menstrual cycle, the latency and IPL of waves increase [8]. Serra et al. investigated the effects of the menstrual cycle on the results of ABR, they indicated the reduction of wave latency and IPL before the ovulation phase compared to the luteal phase [9]. Although Upadhaya et al. reported prolongation of latency waves and IPL before ovulation phase compared to the luteal phase [10]. In a similar study Mann et al. reported a significant increase in IPL during the time of ovulation and decrease in the luteal phase [11]. Natarjan et al. examined four stages of the menstrual cycles and reported significant increase in the wave IV and no change at IPL in the stage of ovulation, although there was an increase in absolute latency [12]. Only two articles focused on the effects of pregnancy on the ABR waves which the results of these studies were not well aligned. Tandon et al. performed ABR on eight pregnant women in their third trimester of pregnancy, and eight non-pregnant women. They found that absolute latency of ABR waves were shortened, but these differences were not significant, and also significant increasing was observed in the interval interpeak of waves I-III, III-V and IV compared to the control group [13]. Sennaroglu et al. have tested ABR on 20 women in different stages of pregnancy and after delivery, and 18 non-pregnant women. There are no significant differences between the mentioned groups [14]. At these studies, the results of ABR in different phases of the menstrual cycle and during the pregnancy were assessed, separately. Based on our knowledge, there is no ABR study of the menstrual cycle on control group compared to pregnant group. Therefore, a research program was designed to determine ABR changes in the menstrual cycle and during the pregnancy.

Methods

This comparative, cross-sectional study was conducted on 25 women aged 20-34 years old, including 17 pregnant (34 ears) and 8 non-pregnant women (16 ears) as control group.

Specific inclusion criteria for non-pregnant women were non-lactating, natural menstrual cycle of 28 to 31 days and no previous use of oral contraceptives during the last 6 months prior to the study. For pregnant women, no experience of eclampsia, pre-eclampsia, abortions and stillbirth, and no history of dizziness, tinnitus and ear fullness before and after the pregnancy and existence of single fetus were considered. General inclusion criteria for both experimental groups were: no history of any hormonal disorders, high blood pressure, high blood fat, no history of head injury resulting in unconsciousness or neurological disorder, no history of mental and neurological illnesses, renal, hepatic, cardiovascular, ear and diabetes, no history of smoking and no consumption of sleeping drugs, psychotropic drugs and ototoxin drugs during the past 6 months, and no exposure of noise (NIHL). Also, they should have normal otoscopic examination, normal hearing (threshold level better than 25 dB HL, and air-bone gap less than 10 dB) and type A tympanogram [5]. Participants should have the body temperature of less than 38°C during the test [6]. The mentioned inclusion criteria was determined through filling out medical records by gynecologists and audiologists.

This study was designed for pregnant women in their second trimester (at 24th week of pregnancy), which the level of sex hormones is physiologically sufficient and the person's physical condition is suitable for recording. ABR was performed. The control group (non-pregnant women) was evaluated in two stages, once in days 1 to 3, because of the minimum levels of estrogen and progesterone and a retest was performed in days 12 to 15 of the menstrual cycle, due to the peak of estrogen.

ABR test was performed in Shahid Akbarabadi Hospital, Tehran, Iran with E-CLIPS (Interacoustic, Denmark). Considering the probability of hypotension in pregnant women in the supine position, the test was performed in a comfortable and suitable chair. Recording was done by a single-channel with ipsi-vertical electrode array. Impedance of electrodes was less than 5 kΩ. Type of stimulus was a 100 µs duration click; repetition rate was 11.3 cycles per second, the polarity was alternating, and 80 dB HL intensity was applied with inserted earphone. Time window was 15 ms, amplification was 100,000, filtration was 100 to 3000 Hz, average response with 2000 sweeps was applied and notch filters were off. To ensure the repeatability of the waves, a recorded process was repeated. The absolute latency of waves was considered from the start of stimulus to the highest peak of each wave in millisecond. Intervals between waves were measured in millisecond; this interval was the distance between the peak to peak latency [5,6].

For statistical analysis, due to the low sample size of cases in menstruation, non-parametric Wilcoxon test was used to compare ABR wave latencies between two stages in control group. Mann-Whitney test was used to compare ABR wave latencies between pregnant group and each of the two stages of menstrual cycle in control group. We used SPSS17 and the significance level was 0.05.

Results

At the present study, the average age range of the control group was 20-28 years old (mean 24.50, SD=2.33) and age range of pregnant women was 20-34 years old (mean 25.59, SD 2.33).

Comparing the difference between absolute latency of waves I, III, V and intervals between waves I-III, III-V, IV, in non-pregnant group at first phase of the menstrual cycle (days 1-3) and the second phase of the menstrual cycle (day 12-15), we found a significant difference in absolute latency of wave V and interval between waves III-V and I-V in both ears ($p<0.05$). There were no significant differences among absolute latencies of waves I, III and intervals between waves I-IV ($p>0.05$). Table 1 shows these results. Also on the effect of pregnancy,

Table 1. Mean (standard deviation) of ABR wave latencies recorded in the 1st-3rd days and the 12th-15th days of menstrual cycle in non-pregnant women (n=8)

Latency (ms)	Right ear			Left ear		
	1st-3rd days of menstrual cycle	12th-15th days of menstrual cycle	p*	1st-3rd days of menstrual cycle	12th-15th days of menstrual cycle	p*
Wave I	1.52 (0.08)	1.52 (0.08)	0.78	1.52 (0.08)	1.52 (0.08)	1.00
Wave III	3.53 (0.14)	3.54 (0.14)	0.18	3.53 (0.13)	3.53 (0.13)	0.10
Wave V	5.26 (0.11)	5.30 (0.12)	0.02	5.27 (0.12)	5.31 (0.12)	0.01
I-III interpeak latency	2.01 (0.09)	2.02 (0.10)	0.58	2.01 (0.10)	2.01 (0.10)	0.25
III-V interpeak latency	1.72 (0.11)	1.76 (0.14)	0.02	1.74 (0.14)	1.77 (0.16)	0.01
I-V interpeak latency	3.73 (0.11)	3.78 (0.12)	0.02	3.75 (0.13)	3.79 (0.14)	0.01

*Wilcoxon test

the results indicate a significant increase in absolute latency of wave V and the interval between wave III-V and IV in both ears between the first and second phases of the menstrual cycle in non-pregnant women compared to a pregnant person at week 24th of pregnancy ($p<0.05$). There were no significant differences among absolute latencies of waves I, III and intervals between waves I-IV ($p>0.05$). Results are shown in Tables 2 and 3.

Discussion

In this study, the absolute latency of wave V and the interval between wave III-V and IV in non-pregnant women, at the days 12-15 of menstruation, was significantly longer compared to the days 1-3 in the menstruation on the same sample. This finding was consistent with the study of Yadav et al. but not with the findings of Resend et al, and Serra, which have contradicted it [7-9]. Also compared to the first phase of the menstrual cycle in non-pregnant women (days 1-3) and the second phase (days 12-15) in the same group, we found a significant difference in absolute latency of wave V and interval between waves III-V and I-V in both ears.

In days 12-15, which the estrogen levels are physiologically in the highest level, we observed increased absolute latency of wave V and interval between waves III-V and I-V. This is a sign of sensitivity of auditory brainstem pathway to sexual hormones. However, in previous studies, conflicting findings about the results of ABR test during the menstrual cycle was reported [7,11,12]. Resende et al. did not find any relationship between hormones and ABR results and concluded that sex hormones have no effect on the peripheral and central auditory system [7]. But, Serra et al. reported the reduction of latency and IPL of waves in the phase before ovulation compared to the luteal phase [9]. Also in an animal experimental study, Coleman et al. conducted an estrogen therapy on rats and reported decreased latency and intervals between waves with the increasing levels of estrogen [16]. Their hypothesis was that high levels of estrogen might cause changes in sensory nerve conduction velocity in the brainstem which occurs by mediator glutamate [17]. Therefore, glutamate-mediated excitatory type increases nerve conduction velocity and then reduction of waves latency occurs. In another investigation conducted by Yadav et al. they indicated an increase on absolute latency of wave III and V the interval between wave I-V at the midcycle and the reduction of latency of the waves in the middle of the luteal phase (a phase in which progesterone is at its maximum amount) [8]. Also in the study of Upadhayay et al. reduction of latency and IPL waves was reported in the luteal phase compared to the

Table 2. Mean (standard deviation) of ABR wave latencies recorded in the 1st-3rd days of menstrual cycle in pregnant women (n=8) and the 24th weeks of pregnancy in pregnant women (n=17)

Latency (ms)	Right ear			Left ear		
	1st-3rd days of menstrual cycle	24th weeks pregnant	p*	1st-3rd days of menstrual cycle	24th weeks pregnant	p*
Wave I	1.52 (0.08)	1.51 (0.07)	1.00	1.52 (0.08)	1.51 (0.08)	0.97
Wave III	3.53 (0.14)	3.53 (0.10)	0.71	3.53 (0.13)	3.53 (0.08)	0.71
Wave V	5.26 (0.11)	5.50 (0.11)	0.001	5.27 (0.12)	5.51 (0.13)	0.001
I-III interpeak latency	2.01 (0.09)	2.01 (0.10)	0.84	2.01 (0.10)	2.02 (0.07)	0.97
III-V interpeak latency	1.72 (0.11)	1.98 (0.14)	0.001	1.74 (0.14)	1.98 (0.14)	0.001
I-V interpeak latency	3.73 (0.11)	3.98 (0.13)	0.001	3.75 (0.13)	4.00 (0.12)	0.001

*Mann-Whitney test

phase before ovulation [10]. Mann et al. recorded ABR in 4 phases of the menstrual cycle. They reported that the increased IPL at the time of ovulation and its decrease in the luteal phase were significant. They observed that IPL increases between waves, amplitude and the ratio of the V/I at the time of ovulation, and then declines in the mid-luteal phase and then again rises before the next menstruation, although these changes were not statistically significant [11].

As mentioned, findings of the present study also showed an increase in latency. Increased ABR latency in the phase before ovulation can be attributed to the peak of estrogen levels. It is believed that high levels of estrogen enhance GABA levels in the auditory system and through it, affect synaptic transmission speeds [3,4]. GABA is an inhibitory mediator and exists at all levels of the brainstem. Stomati et al. demonstrated estrogen through increasing meditors levels like Allopregnalone, that which leads to GABA increases its the inhibitory effect of GABA on the ABR latency [17]. It seems that latency of waves in ABR during the menstrual cycle is different and must be considered in clinical interpretation results for women.

In the current study, the effects of pregnancy on the ABR component were also considered. Results indicated a significant increase in absolute latency of wave V and IPL of III-V and I-V in both ears among pregnant women at the 24th week of pregnancy compared to those in the first and second phases of the menstruation. Based on our current knowledge, a significant increase in sexual hormonal levels occurs in women up to 24 weeks of pregnancy. Therefore, findings of this study in terms of absolute latency of wave V and the IPL in wave III-V and I-V are consistent and emphasize on the effect of steroidal hormones on auditory system. Findings of this study, regarding the increase of IPL in waves III-V and I-V in comparison with control group is consistent with the study of Tandon et al., although IPL of wave I-III was not significant. These researchers tested ABR on 8 pregnant women in the third trimester of pregnancy and 8 non-pregnant women, they observed a significant increase in the IPL in I-III, III-V and I-V in comparison with control group, but slight increase in absolute latency in pregnant women; although, the difference was not significant [13].

Our findings, in terms of absolute latency of wave V and the IPL III-V and I-V, were not consistent with the Sennaroglu and Belgin. They measured ABR on 20 women at different stages of pregnancy and after childbirth, as well as 18 non-pregnant women, but found no significant

Table 3. Mean (standard deviation) of ABR wave latencies recorded in 12th-15th days of menstrual cycle in non-pregnant women (n=8) and the 24th week of pregnancy in pregnant women (n=17)

Latency (ms)	Right ear			Left ear		
	12th-15th days of menstrual cycle	24th weeks pregnant	p*	12th-15th days of menstrual cycle	24th weeks pregnant	p*
Wave I	1.52 (0.08)	1.51 (0.07)	1.00	1.52 (0.08)	1.51 (0.08)	0.97
Wave III	3.54 (0.14)	3.53 (0.10)	0.58	3.53 (0.13)	3.53 (0.08)	0.71
Wave V	5.30 (0.12)	5.50 (0.11)	0.001	5.31 (0.12)	5.51 (0.13)	0.001
I-III interpeak latency	2.02 (0.10)	2.01 (0.10)	0.79	2.01 (0.10)	2.02 (0.07)	0.84
III-V interpeak latency	1.76 (0.14)	1.98 (0.14)	0.001	1.77 (0.16)	1.98 (0.14)	0.001
I-V interpeak latency	3.78 (0.12)	3.98 (0.13)	0.001	3.79 (0.14)	4.00 (0.12)	0.001

*Mann-Whitney test

difference between these groups [14]. As we mentioned, the findings of the present study showed an increase in the latency of the wave V and III-V and I-V in both ears at the 24th week of the pregnancy. These longer latencies of ABR may be related to considerable increase in estrogen levels compared to control group. On the other hand, there is retention of salt and water in pregnant women [18]. Electrolyte imbalance also increases the volume of extracellular fluid and causes edema around the nerves [19]. This inflation might be another reason for reduction in nerve conduction and increase in latency.

What we observed in our study was an increase in the latency of the wave V and III-V and I-V in both ears in the pregnant group as well as the control group. But no significant changes were observed in absolute latency of waves I and III and IPL of these waves. IPLs show a primary auditory neuron activity in the cochlear nerve and low levels of the brainstem. The III-V IPL represents the nerve conduction in the brainstem from cochlear nucleus to external lemniscus, and I-V IPL also introduces a nerve conduction from distal portion of cochlear nerve to the superior olive/lateral lemniscus [5,6]. GABA mediator exists at all levels of the brainstem, it seems that estrogen probably affects the increasing inhibitory effect of rostral brainstem. Therefore, the influence of hormones occurs on the higher levels of brainstem, particularly above the cochlear nuclei. We suggest conducting further research in order to determine the relationship between estrogen and progesterone hormone levels, and obtaining physiological, electrophysiological and balance findings using larger sample sizes and longitudinal study on pregnant women.

Conclusion

Findings of this study show the effect of pregnancy and different phases of menstruation and the increased level of female sex hormones in these periods on ABR. Our results concluded the probable hormonal effect on brainstem and auditory pathways which the increase of these hormones leads to decrement of auditory brainstem processing function.

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