

Auditory brainstem response in premenopausal women taking oral contraceptives

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BACKGROUND: The aim of this prospective study was to evaluate the effects of the new monophasic oral contraceptives on the audiological system in premenopausal women. **METHODS:** The auditory brainstem response (ABR) was measured in 94 women during the follicular, periovular and luteal phases of one menstrual cycle in which ovulation was confirmed using sonography and serum progesterone concentration. The latencies for waves I, III and V were determined, and the inter-peak intervals were calculated for waves I–III, I–V and III–V. All 94 women began taking oral contraceptives: 23 women used 20 µg ethinyl estradiol (EE) plus 150 µg desogestrel, 24 women used 30 µg EE plus 75 µg gestodene, and 47 women used 15 µg EE plus 60 µg gestodene. During the third month of contraceptive intake, each subject was again tested for ABR, as above. **RESULTS:** The wave latencies and inter-peak intervals showed shorter values during the periovular phase with respect to the luteal phase ($P < 0.05$), the follicular phase for wave I and for inter-peak interval I–V ($P < 0.05$) of the menstrual cycle. All of the ABR results in pill users were statistically different from those of the periovular phase ($P < 0.05$), though similar to those of both the luteal and follicular phases ($P = \text{NS}$). **CONCLUSIONS:** ABR seems to depend on the variations of ovarian steroids during the menstrual cycle and during oral contraceptive intake.

Key words: Auditory brainstem response/auditory evoked potentials/hearing/menstrual cycle/oral contraceptives

Introduction

Clinical observations strongly suggest that premenopausal and post-menopausal changes in gonadal function modify auditory (Sator *et al.*, 1999; Caruso *et al.*, 2000a), olfactory (Caruso *et al.*, 2001; Grillo *et al.*, 2001) and taste (Finger and Silver, 1991) thresholds, and the trophic aspect of the larynx (Caruso *et al.*, 2000b). However, the direct role of gonadal hormones on sensory processing, including the auditory system, has not been well studied. The influence of estrogen and other gonadal steroid substances may have direct effects upon the cochlea and various central auditory system pathways; they could indirectly influence central processing through other pathways and could also modulate blood flow in the cochlea and brain (Coleman *et al.*, 1994). A decrease in estrogen and decreased metabolism rates (Bruce and Russel, 1962) could influence the availability of neurotransmitters at the synapse and in turn influence neural conduction time (Haggard and Gaston, 1978; McEwen, 1991). Estradiol could modify the secretion of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) at auditory nerve synapses, leading to delayed synaptic conduction time (Elkind-Hirsch *et al.*, 1992a).

Advances in electronic and computing technology and their physiological application have made possible the detection of

small biological signals arising from within the nervous system. Since the brainstem potentials were first described during the 1970s (Jewett and Williston, 1971; Sohmer and Feinmesser, 1974), interest has continued to increase, both in the audiological and neurological fields (Nuwer, 1998). The auditory brainstem response (ABR) is a measure of the electrical activities generated in the brainstem auditory pathways after auditory stimulation and recorded superficially from the surface of the scalp. Classification of these auditory-evoked potentials has been based primarily on their latencies in relation to a previous stimulus. The response consists of five waves, designated I–V. The preponderance of experimental and clinical evidence suggests that wave I is generated by action potentials of the cochlear nerve, wave II by the cochlear nucleus, wave III by the superior olivary complex, wave IV by the nucleus of the lateral lemniscus, and wave V by the inferior colliculus (Jewett and Williston, 1971). Data demonstrate that post-menopausal women show increased ABR wave latencies and inter-peak intervals than do younger women or men (Jerger and Hall, 1980; Dehan and Jerger, 1990; Wharton and Church, 1990), and it has been hypothesized that ABR latencies could change with age (O'Donovan *et al.*, 1980; Rosenhamer *et al.*, 1980; Jerger and Johnson, 1988). The source of the

male–female related differences could also be factors such as hormones (McFadden, 1998), head size, skin thickness or gender-dependent sizes of the external acoustic meatus (Trune *et al.*, 1988), or even metabolic differences (Baker and Weiler, 1977). Hormones influencing the brain structures responsible for sexual orientation can provoke differences in ABR. Homosexual and bisexual females, and homosexual males have respectively masculinized and hypermasculinized ABRs, probably due to exposures to androgens during development (McFadden, 2002). It has also been reported that there is a fluctuation in behavioural auditory thresholds during the menstrual cycle (Haggard and Gaston, 1978; Fagan and Church, 1986; Elkind-Hirsch *et al.*, 1992b). Ovulatory women seem to have significant cyclic fluctuation in auditory sensitivity during the follicular, periovular and luteal phases of menstrual cycle, and less temporary threshold shifts during menstrual phase than women using the pill (Swanson and Dengerink, 1988).

One of the variables associated with changes in female hormonal status is oral contraceptive (pill) intake. There are currently ~400 million contraceptive users worldwide, with approximately one-sixth taking the pill. Use of the pill declines with age; 75% of users are aged 19–30 years. A review of medical literature shows that research is being carried out on ABR in oral contraceptive users (Swanson and Dengerink, 1988; Elkind-Hirsch *et al.*, 1992a,b, 1994; McFadden, 2000). The results of this research are not always in agreement, though this may be due to the use of non-standardized methodologies.

A prospective, within-subject study was designed to test whether ABRs are affected by oral contraceptives with respect to the different phases of the menstrual cycle.

Materials and methods

The study was performed at the Family Planning Centre of the Research Group for Sexology of the Department of Microbiological and Gynecological Science and at the Department of Otorhinolaryngology, School of Medicine, University of Catania, Catania, Italy. All subjects provided their written informed consent before participating in the study, which was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of the research committees of both the Departments approved the study. The study was not advertised, and no remuneration was offered. The study was conducted as a prospective study, the primary objective being to monitor modifications in ABR during oral contraception, and the secondary objective to determine the effects of each type of pill on wave latencies and inter-peak latencies.

Subjects

A total of 118 healthy volunteers (mean age 26.9 ± 5.7 years; range 19–38 years) who were attending the Family Planning Centre and planning to take oral contraceptives, participated in the study. None of the subjects had ever used any oral contraceptive or any other hormonal contraceptive or treatment. Each woman reported not having hearing loss or hearing disorders, nor any nose or throat problems. Subjects with tobacco use and/or drug abuse were excluded from the study. Moreover, the women enrolled in the study did not report any dysendocrinism or metabolic or neoplastic pathologies. Inclusion criteria required a normal gynaecological history and

examination, with normal menstrual cycles (mean cycle length 28.3 ± 3.3 days).

To confirm ovulation, sonography was performed on days 10, 12 and 15 of the cycle, and serum progesterone concentrations were measured on days 21 and 25. Serum hormone concentrations were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Roche, Monza, Italy). The menstrual cycle was defined as ovulatory when the serum progesterone level was >18 IU/ml. Of the 118 women screened, 14 were excluded from the study for medical problems: nine had metabolic problems and five had hearing pathologies. Moreover, during enrolment, 10 women with both sonography aspects of anovulatory cycles, and serum progesterone levels <18 IU/ml were also excluded from the study. Therefore, the sample consisted of 94 women of mean age 27.9 ± 6.1 (range 20–38) years. The mean body mass index (BMI) of the participating women (24.4 ± 1.3 kg/m²) was within the normal range (18.5–25.9 kg/m²).

Clinical testing

Before undergoing the audiometric tests, all women underwent ear, nose and throat checks to identify any inflammation of the upper airways. The audiometric thresholds were then measured for each woman at test frequencies of 250, 500, 1000, 2000 and 4000 Hz in an acoustically shielded room using an Amplaid 311 (Amplifon, Milan, Italy). Compliance of the tympanic cavity was evaluated to identify possible inflammation of the middle ear. Stapedial reflex threshold was then measured to evaluate the correct functioning of the neuronal arc (constituted by the acoustic nerve, reticular formation and facial nerve) using an Amplaid 711 (Amplifon) impedance audiometer. Each woman underwent the auditory brainstem test (with her eyes closed) in an electrically and acoustically shielded dark room. The test was performed using an Amplaid MK 12 (Amplifon). The ABR was recorded with three surface electrodes (impedance <5 K Ω). The first was placed on the forehead (20% of nasion-inion length), the second on the ipsilateral mastoid, and the earth lead on the contralateral mastoid. A differential amplifier and a second-stage amplifier recorded the activity received from these electrodes; filters on both amplifiers were set at 100 and 3000 Hz. The acoustic stimuli were 100 dB peak sound pressure level; these were clicks at 11/s produced by delivering a 100- μ s electrical square wave to a TDH-49 earphone (Amplifon). Each subject received 2000 stimuli to produce each ABR waveform. The positive peak latencies of waves I, III and V were measured using visual overlay cursors, and the inter-waves I–III, I–V and III–V intervals were calculated for each response. Waves II and IV were not evaluated because of their lesser importance in ABR. Graphic visualization of wave latencies and inter-peak intervals is shown in Figure 1. During the menstrual cycle, each woman underwent three ABR tests, the first at the follicular phase (days 5–8), the second at the periovular phase (days 13–16), and the last at the luteal phase (days 18–23). Both ears of each woman were treated as independent samples; thus, ABR waveforms were analysed separately for each ear. The ears were considered as independent samples because the pathways from the two ears are largely separate anatomically and capable of presenting different waveforms in the same individual. An average of latencies extracted from the ABR waveforms collected from both ears was calculated for each woman because the differences were negligible, ranging from 0.01 to 0.02 ms. The duration of a single measuring session was ~45 min.

Oral contraceptives

After confirming that ovulation occurred during the previous menstrual cycle, and after the clinical testing described above, each

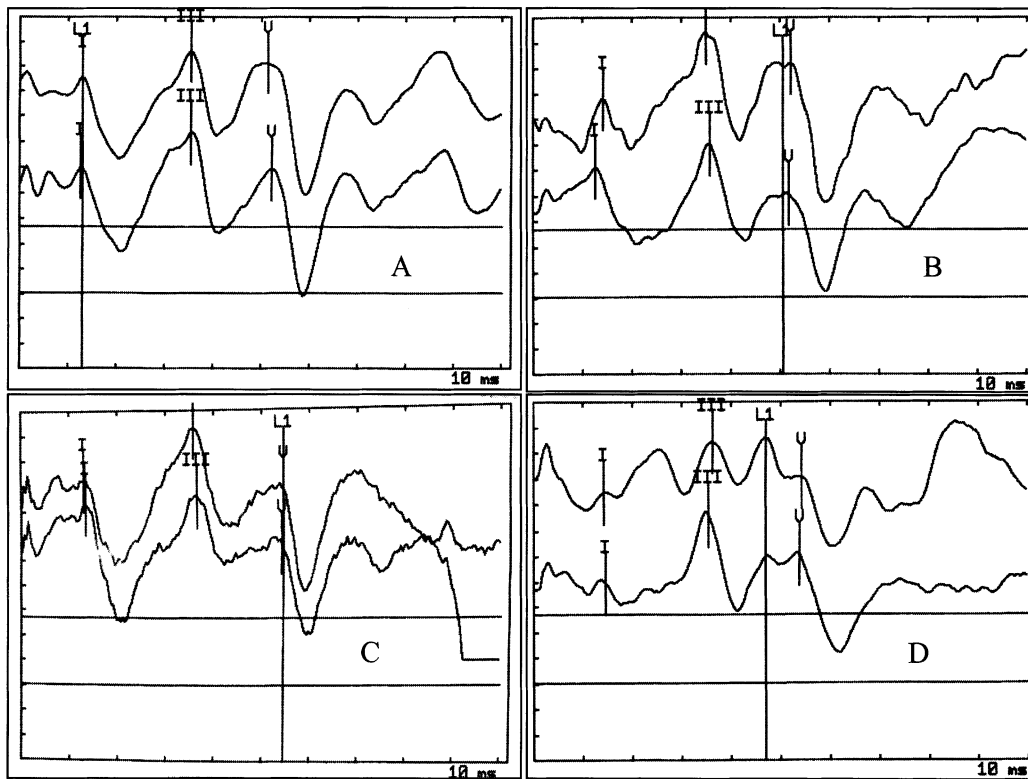


Figure 1. Graphic visualization of wave latencies and inter-peak intervals (in ms) during the follicular phase (A), the periovular phase (B) and the luteal phase (C) of the ovulatory menstrual cycle, and during the third month (21st day) of oral contraceptive intake (D), of a single representative subject. Each of the four graphs shows the values of auditory brainstem response (ABR) for the right ear (upper waveform), and the left ear (lower waveform). I, III and V represent the relative waves. L1 is the cursor, used to determine the distance between waves.

woman received a prescription that allowed her to begin taking oral contraceptives. Twenty-three women were given 20 µg ethinyl estradiol (EE) plus 150 µg desogestrel (Mercilon, Organon Italia, Rome, Italy); 24 women were given 30 µg EE plus 75 µg gestodene (Gynoden, Schering, Milan, Italy; or Minulet, Wyeth-Lederle, Aprilia-Latinia, Italy); and 47 women were given 15 µg EE plus 60 µg gestodene (Arianna, Schering; or Minesse, Wyeth-Lederle). The second set of ABR measurements was collected during the third month of oral contraception use. Each user underwent three tests, at days 7, 14 and 21 of pill intake. At the re-test sessions, each audiometric measurement was repeated.

Statistical analysis

Each statistical analysis was carried out using a software package for Windows 95™ (Glantz, 1997). Using data from previous studies (cited above), the standard deviation was set at 2.2, the mean difference at 0.5 between before and after pill use, and ABR values at $P = 0.05$; therefore the sample size calculation indicated that 77 subjects would be the minimum number required for the study to have 95% power. The analysis of data was based on an intention to treat approach. Consequently, the effects of the oral contraceptive used by each woman were considered, with the last observation carried forward for patients who prematurely discontinued pill use. The primary objective was the outcome of the ABR values obtained during oral contraceptive intake. The ABR values of each phase of the menstrual cycle were compared with the other phases by analysis of variance. A paired data *t*-test was used to compare each phase of the menstrual cycle with the oral contraceptive values, and two-sided *t*-test for independent samples was used to compare the effects of the monophasic oral

contraceptives on ABR aspects. Data were analysed using the Bonferroni method of correction for multiple comparisons. All reported values were reported as mean \pm SD. A P -value ≤ 0.05 was considered statistically significant.

Results

ABRs were obtained from 188 ears with normal pure tone thresholds from 250 Hz through 4 KHz. As noted in Materials and methods, the two-ear wave latency averages were then used for statistical analysis. The statistical comparison analysis of data obtained from each phase of the menstrual cycle compared with the other phases showed shorter wave latencies and inter-peak intervals during the periovular phase than the luteal phase ($P < 0.05$), and than the follicular phase for wave I and inter-peak I–V ($P < 0.05$). Moreover, the values of each wave latency and inter-peak interval obtained during the follicular phase were similar to those of the luteal phase ($P = \text{NS}$). Table I shows the average ABR values during each phase of the menstrual cycle and during the third month of contraceptive use. The means of the measurements made on days 7, 14, and 21 of pill intake were used as it was noted that there were no differences in wave and inter-peak ABR values across the three days. Each value was expressed as mean \pm SD (in ms); hence smaller values indicate more rapid neural transmission. The wave latencies and inter-peak intervals of contraceptive users (in whom the three phases were constant)

Table I. Average wave latencies and inter-peak intervals (in ms) during the three phases of the menstrual cycle and during the third month of contraceptive intake

Wave number	Menstrual cycle phase				<i>P</i> ^a	<i>P</i> ^b	<i>P</i> ^c
	Follicular (<i>n</i> = 94)	Periovular (<i>n</i> = 94)	Luteal (<i>n</i> = 94)	Contraception (<i>n</i> = 94)			
I	1.42 ± 0.9	1.39 ± 0.1	1.45 ± 0.12	1.44 ± 0.14	NS	< 0.005	NS
III	3.58 ± 0.11	3.54 ± 0.12	3.58 ± 0.15	3.58 ± 0.14	NS	< 0.05	NS
V	5.27 ± 0.17	5.22 ± 0.18	5.30 ± 0.19	5.29 ± 0.24	NS	< 0.02	NS
I–III	2.13 ± 0.11	2.12 ± 0.12	2.15 ± 0.11	2.18 ± 0.24	NS	< 0.03	NS
III–V	1.69 ± 0.21	1.67 ± 0.1	1.71 ± 0.9	1.72 ± 0.15	NS	< 0.007	NS
I–V	3.85 ± 0.11	3.82 ± 0.1	3.86 ± 0.9	3.90 ± 0.24	NS	< 0.002	NS

Values are mean ± SD.

^aContraception versus follicular phase.

^bContraception versus periovular phase.

^cContraception versus luteal phase.

NS = not significant.

were: (i) statistically different from those of the periovular phase ($P < 0.05$); and (ii) similar to those of both the follicular phase and the luteal phase ($P = \text{NS}$). Finally, no statistically significant difference was observed among women using different types and formulations of pill on both wave latencies and inter-peak interval surveys ($P = \text{NS}$).

Discussion

The results of this investigation showed that the steroids contained in oral contraceptives might affect changes in auditory neural transmission: ABR surveys emphasized that wave latencies and inter-peak intervals did not show any significant fluctuation with respect to those noted before contraceptive intake, during which time it was possible to observe different values during the three phases of the menstrual cycle. It was also clear the ABR values during pill intake showed linear outlines similar to those of the luteal phase and the follicular phase of the menstrual cycle but statistically different ($P < 0.05$) from the periovular phase in menstruating women. The latter aspect could emphasize the particular feature of monophasic pills, the hormonal activities of which are mainly progestative. Although the present subjects used different monophasic pills, containing different dosages of estrogen and/or type of progestagens, there were no differences between all the monophasic formulations with regard to both wave latencies and inter-peak intervals. This could be due to the direct activity of ovulation inhibition rather than to the effects of the steroids contained in the pill.

There are no recent data demonstrating any changes in inter-peak latency changes during the menstrual cycle. Results from one study (Fagan and Church, 1986) suggested that temperature changes during menses could be responsible for the differences noted in ABRs. Also, others (Bruce and Russel, 1962) have raised the possibility that changes in sodium and potassium metabolism could influence ABRs by changing the axon conduction time and/or the availability of neurotransmitters at synapses. Moreover, these two reports have suggested that there are latency changes of waves related to fluctuating hormone levels, even if the exact mechanism of

the hormonal effects is not clear. It was also suggested that estrogen might influence acetylcholine synthesis (Picton *et al.*, 1981), which was shown recently to be present in the auditory system (Weinberger and Bakin, 1998).

The ABR fluctuations could depend on the action of the different qualitative and quantitative ovarian steroids either during the menstrual ovulatory cycle, or during pill intake. The present study showed that the increased neural conduction time of the ABR coincides with ovulation, in contrast to the data reported by others (Parlee, 1983; Elkind-Hirsch *et al.*, 1992b, 1994) who did not find any statistically significant changes in wave latencies and inter-peak intervals among the three phases of the menstrual cycle, though this discrepancy might be attributable to the failure of previous studies to determine the exact time of ovulation. By comparison, ovulation was verified in all of our subjects by the use of sonography and by monitoring serum levels of progesterone.

During the menstrual cycle there are differences in the androgen concentration, with testosterone or free testosterone peak at mid-cycle (Morris *et al.*, 1987). During the present investigation, ABR were not measured at menses (as was the case for other authors; Swanson and Dengerink, 1988; Elkind-Hirsch *et al.*, 1992b, 1994), mainly because it was considered that the data available from literature were both sufficient and clear. The level in hearing sensitivity at menses, during which gonadal steroids are at a minimum, is similar to that normally found in the male (McFadden, 1998). Naturally, at ovulation both androgen and estrogen levels temporarily rise, and during the periovular phase shorter wave latencies in ABR were noted than during both the follicular and luteal phases. Substantially lower levels of free testosterone have been observed among pill users (Bancroft *et al.*, 1991). Sex hormone-binding globulin levels are increased and, therefore, free testosterone levels appear to be affected by the use of birth control pills (DeCherney, 2000).

Although the present data have confirmed the existence of changes of ABR in oral contraceptive users with respect to non-users, further studies are required to investigate if the variations of wave latencies and inter-peak intervals of ABR

could contribute to variation in the sexual behaviour of the subject, and, if so, in what way.

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