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The effect of premature ovarian failure on inner ear function

Isil Karaer^a and Gorkem Tuncay^b

^aMinistry of Health, ENT Clinic, Malatya Training and Research Hospital, Malatya, Turkey; ^bDepartment of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Inonu University Medical School of Medicine, Malatya, Turkey

ABSTRACT

The aim of this study was to test whether hearing function is impaired in women with premature ovarian failure. Thirty (30) women with premature ovarian failure (POF), 30 women in menopause and 30 healthy controls were recruited in this study. Pure tone audiometric (PTA), transiently evoked otoacoustic emissions (TEOAEs) and distortion product otoacoustic emissions (DPOAEs) of the study participants were analysed. At PTA, 6 and 8 kHz were lower in menopause group compared with both women with POF and controls. At TEOAE 3 and 4 kHz and at DPOAE 1, 2, 4 and 6 kHz were lower in menopause group compared with the controls. At DPOAE 6 kHz was lower in the POF group compared with the controls. Women with POF comparing to menopause group at TEOAE 3, 4 kHz and at DPOAE 4 and 6 kHz were lower in the menopause group. Inner ear function of both women in menopause and women with POF was declined compared to the healthy controls. Clinically, evaluation of hearing status may be considered in women with POF.

IMPACT STATEMENT

- **What is already known on this subject:** Premature ovarian failure (POF) affects 1%–2% of women, and it adversely affects on health status (such as cardiovascular, psychological and cognitive disorders). Previous studies suggested that a lack of oestrogen might play a role in hearing disorders in women. However, we do not know POF's adversely effect on cochlea and hearing.
- **What the results of this study add:** The present study demonstrates that lower serum oestrogen has a negative effect hearing in women with POF at DPOAE 6 kHz.
- **What the implications are of these findings for clinical practice and/or further research:** The women with POF must be evaluated for hearing status.

KEYWORDS

Inner ear; menopause; otoacoustic emission; premature ovarian failure

Introduction

Premature ovarian failure (POF) is characterised by amenorrhoea, hypoestrogenism and elevated follicle-stimulating hormone (FSH) levels in women under the age of 40. This condition affects 1%–2% of women in that age group (Shellin 2010). Early menopause is associated with higher risk of cardiovascular disease, psychological distress and depression, cognitive decline, autoimmune disorders, decreased sexual desire and general well-being, osteoporosis and premature deaths (Van Der Voort et al. 2003; Groff et al. 2012; Shuster et al. 2010; Kovanci and Schutt 2015).

Hearing function in men and women differs from birth. Transient evoked otoacoustic emissions (TEOAE) are significantly stronger in newborn girls than in newborn boys (McFadden 1993; Berninger 2007). This advantage continues until the children are older. Studies on aging have shown that hearing declines more rapidly in males than females (Pearson et al. 1995), starting between the ages of 20 and 30 in men and over the age of 50 in women (Gordon-Salant 2005). Hearing level at high frequencies is not impaired in women during their reproductive years, however, after menopause women's hearing levels worsen, especially at high frequencies (Murphy and Gates 1997). A study by Svedbrant

et al. (2015), which followed premenopausal women for 10 years, demonstrated that hearing decline is more rapid after menopause than before. The hormonal effects on hearing function and the decline of circulating oestrogen during menopause may be a possible initiator of the complex actions involved in the onset of hearing decline in women (Hederstierna et al. 2010).

To the best of our knowledge, no previously published studies have investigated the effect of POF on hearing level. Therefore, the aim of the present study is that whether the inner ear is impaired in women with POF.

Materials and methods

A prospective case-control study was conducted in the Department of Otolaryngology at Malatya State Hospital between June 2016 and December 2016. This study was approved by the hospital's ethical review board, and informed consent was obtained from all the patients included in the study.

Ninety (90) patients were enrolled in the study. The patients were divided into three groups: Group 1 (women with POF), Group 2 (women in menopause) and Group 3

(control group). POF was diagnosed as the presence of amenorrhoea for at least 6 months and a serum FSH level greater than 40 mIU/mL on two occasions at least one month apart for women under the age of 40 (Kovanci and Schutt 2015). Menopause was defined as amenorrhoea for at least one year, FSH levels up to 40 mIU/mL, oestradiol (E_2) levels less than 30 pg/mL and age up to 50 years. The control group ($n = 30$) consisted of healthy women that were still menstruating regularly. The controls and the women with POF were matched by age and body mass index (BMI).

Patients who had a previous family history of hearing impairment or a history of noise exposure, any neurological disease or systemic diseases that could affect hearing, and those who had previously used ototoxic drugs or hormone supplements, had smoked cigarettes, or who had consumed alcohol were excluded from the study. To ensure the reliability of the results, all patients underwent an otoscopic examination before the audiology tests were performed. Only patients with a clean external ear channel and a normal eardrum were included in the study. Pure tone audiometric (PTA), transiently evoked otoacoustic emissions (TEOAE) and distortion product otoacoustic emissions (DPOAE) were measured in all three study groups.

PTA testing was conducted using a diagnostic audiometer (Interacoustics AD229e; Interacoustics A/S, Assens, Denmark). PTA was performed at 500 Hz, 1, 2, 4, 6 and 8 kHz frequencies.

TEOAE were performed at 1, 2, 3, 4 and 5 kHz frequencies using Otodynamics ILO 288 Echoport equipment (Otodynamics Ltd., London, UK). TEOAE were recorded using the nonlinear protocol; stimulus levels were kept at the standard default settings with a peak sound pressure level (SPL) ranging from 78 to 82 dB. The recording window was 3–20 ms, and there were 260 subaverages. In the TEOAE analysis, signal-to-noise ratio (S/N -R) was evaluated for the participants' right ears were used for the analyses. The TEOAE measurement method is the standard procedure; a reconstructed reproducibility (correlation) value was accepted only when it was better than 70%.

DPOAE were performed at 1, 2, 4 and 6 kHz frequencies using Otodynamics ILO 288 Echoport equipment (Otodynamics Ltd., London, UK). The sound stimulus for the DPOAE consisted of two simultaneous permanent pure tones at different frequencies. Stimulus parameters, $L1 = 65$, $L2 = 55$ dB SPL with an $f1/f2$ ratio of 1.22, were used, and the amplitude of the DPOAE noise ratio (S/N-R) was recorded. The averages and standard deviations (SD) of the OAE results were calculated.

Statistical analysis

All analyses were conducted using SPSS 15.0 (SPSS® for Windows 15.0, Chicago, IL, USA). The Mann-Whitney U test was used to compare all the parameters. Variables were expressed as mean \pm SD. A two-tailed $p < .05$ was considered to be statistically significant.

Results

The baseline characteristics and hormonal levels of the study participants are shown in Table 1. The ages of the women with POF and controls are similar ($p = .2$). However, the mean age of women with menopause was significantly higher than both the mean age of the women with POF and controls (both p values $< .001$). The mean body mass index (BMI) was 28.1 ± 2.6 kg/m² in women with POF, 29.1 ± 3.4 kg/m² in women with menopause and 27.8 ± 3.0 kg/m² in the controls. There was no statistical significance between the three groups regarding BMI.

FSH level values were 69.13 ± 8.5 mIU/mL in women with POF, 64.29 ± 7.11 mIU/mL in women with menopause and 7.66 ± 1.08 mIU/mL in the controls. The FSH serum level was higher in women with POF than controls ($p < .001$). The serum FSH level was higher in women with menopause than controls ($p < .001$). The FSH serum level was not significantly different between women with POF and women with menopause ($p = .96$). The mean E_2 level was 30.4 ± 6.4 pg/mL in women with POF, 32.5 ± 10.8 pg/mL in women with menopause and 111.3 ± 19.6 pg/mL in controls. The serum E_2 level was lower in both women with POF and women with menopause than controls (both p values $< .001$). There was no statistically significant difference between women with POF and women in menopause regarding serum E_2 levels ($p = .43$).

The PTA results for all groups are shown in Table 2. There were no statistically significant differences for all frequencies when women with POF are compared with the control group (Table 2). Comparing the women with menopause and the

Table 2. PTA responses value (dB) for study participants.

Frequency	Group 1	Group 2	Controls	$p1$	$p2$	$p3$
500 Hz	12.5 ± 8.3	14.6 ± 7.5	12.8 ± 8.0	.33	.42	.44
1 kHz	12.8 ± 8.8	12.9 ± 6.5	12.6 ± 8.0	.94	.96	.92
2 kHz	15.5 ± 8.1	15.9 ± 8.7	15.0 ± 8.2	.86	.88	.82
4 kHz	17.3 ± 8.4	18.0 ± 8.3	16.3 ± 8.1	.44	.82	.31
6 kHz	17.1 ± 9.5	28.5 ± 10.1	17.3 ± 9.3	.34	$<.01^*$.02*
8 kHz	18.0 ± 9.7	29.3 ± 10.2	17.8 ± 9.6	.28	$<.01^*$	$<.01^*$

PTA responses shown as mean dB \pm standard deviation.

$p1$ =Group 1 vs. control; $p2$ =Group 2 vs. controls; $p3$ =Group 1 vs. Group 2.

Significant differences are marked, $*=p<.05$.

Table 1. Clinical characteristics and hormonal profile of study participants.

	Group 1 $n=30$	Group 2 $n=30$	Controls $n=30$	$p1$	$p2$	$p3$
Age(y)	32.5 ± 1.06	54.4 ± 1.1	28.4 ± 1.06	.2	$<.001^*$	$<.001^*$
BMI (kg/m ²)	28.1 ± 2.6	30.1 ± 3.4	27.8 ± 3.0	.54	.27	.49
FSH (mIU/mL)	69.13 ± 8.5	64.29 ± 7.11	7.66 ± 1.08	$<.001^*$	$<.001$	*.96
Oestradiol (pg/mL)	30.4 ± 6.4	32.5 ± 10.8	111.3 ± 19.6	$<.001^*$	$<.001^*$.43
Cigarette smoking	–	–	–			
Alcohol Consumption	–	–	–			

$p1$ = Group 1 vs control; $p2$ = Group 2 vs controls; $p3$ = Group 1 vs Group 2.

Significant differences are marked, $*=p<.05$.

Table 3. TEOAE and DPOAE responses value for study participants.

	Group 1	Group 2	Controls	<i>p</i> 1	<i>p</i> 2	<i>p</i> 3
TEOAE frequencies						
1 kHz	-0.96 ± 0.81	-0.93 ± 0.91	-0.92 ± 0.97	.80	.63	.86
2 kHz	4.1 ± 0.86	2.78 ± 0.8	4.81 ± 0.81	.89	.16	.27
3 kHz	4.81 ± 0.81	3.1 ± 0.94	3.2 ± 0.77	.91	.004*	.028*
4 kHz	0.90 ± 0.82	-1.18 ± 0.98	0.18 ± 0.81	.55	.014*	.044*
5 kHz	-3.2 ± 0.74	-5.03 ± 1.15	-3.96 ± 0.39	.95	.38	.41
DPOAE frequencies						
1 kHz	8.82 ± 1.03	4.86 ± 1.51	11.27 ± 0.92	.07	.001*	.055
2 kHz	14.93 ± 1.24	10.24 ± 1.84	15.9 ± 1.34	.59	.018*	.057
4 kHz	14.84 ± 1.13	11.04 ± 1.26	17.15 ± 1.14	.14	.001*	.042*
6 kHz	9.59 ± 1.62	4.44 ± 1.79	15.19 ± 1.43	.027*	<.001*	.034*

TEOAE responses (S/N-R) shown as mean sound pressure level (SPL) dB ± standard deviation.

DPOAE responses show that S/N-R dB ± standard deviation.

*p*1 = Group 1 vs. control; *p*2 = Group 2 vs. controls; *p*3 = Group 1 vs. Group 2.

Significant differences are marked, * = *p* < .05.

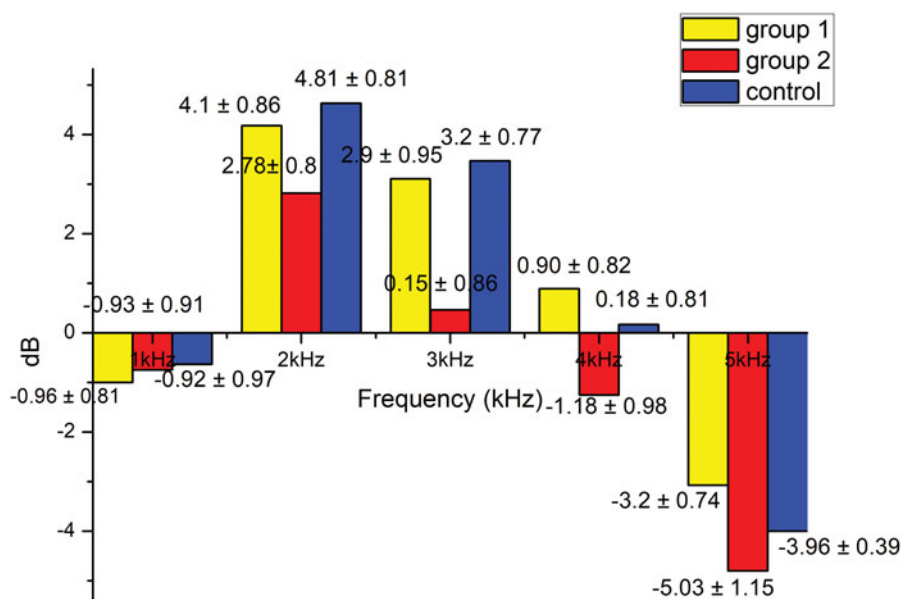


Figure 1. Comparison of the mean TEOAE S/N-R dB SLP thresholds for the three groups at the frequencies tested.

control group, at PTA 6 and 8 kHz responses were identified to be statistically significantly low among the women with menopause (both *p* value < .01). At PTA 6 and 8 kHz responses were identified to be statistically significantly low when the women with menopause are compared to women with POF (*p* = .02, *p* < .01, respectively). The TEOAE results for all groups are shown in Table 3. No statistically significant differences were found in the TEOAE responses for 1, 2, 3, 4 and 5 kHz for women with POF and the control group (Figure 1). The TEOAE responses for 3 and 4 kHz were statistically significantly lower in women with menopause than in women with POF (*p* = .028, *p* = .044, respectively) (Figure 1). The TEOAE responses for 3 and 4 kHz frequencies in women with menopause were significantly lower than in controls (*p* = .004 and *p* = .014) (Figure 1).

The DPOAE results for all groups are shown in Table 3. Women with POF exhibited significantly decreased only at a DPOAE frequency of 6 kHz in comparison with the controls (*p* = .027) (Figure 2). The DPOAE responses for 1, 2, 4 and 6 kHz frequencies in women with menopause were significantly lower than controls (*p* = .001, *p* = .018, *p* = .001,

p < .001, respectively) (Figure 2). The DPOAE responses for 4 and 6 kHz were statistically significantly lower in women with menopause than in women with POF (*p* = .042, *p* = .034, respectively) (Figure 2).

Discussion

In the present study, when the women in the menopause group are compared with controls, there were statistically significant reductions identified for at PTA responses for 6 and 8 kHz, at TEAOE responses for 3 and 4 kHz and at DPOAE responses for 1, 2, 4 and 6 kHz. When the women with POF are compared with the control group, there was a significant decline observed for women in the POF group for only the DPOAE 6 kHz test among the investigated tests.

In the present study, the hearing status was worse in women with menopause than in women with POF and the healthy controls. This finding may result from both age-related hearing loss and low E₂ levels in women with menopause. In agreement with this study, Bertoli and Probst (1997) researched the clinical values of TEOAE measurements

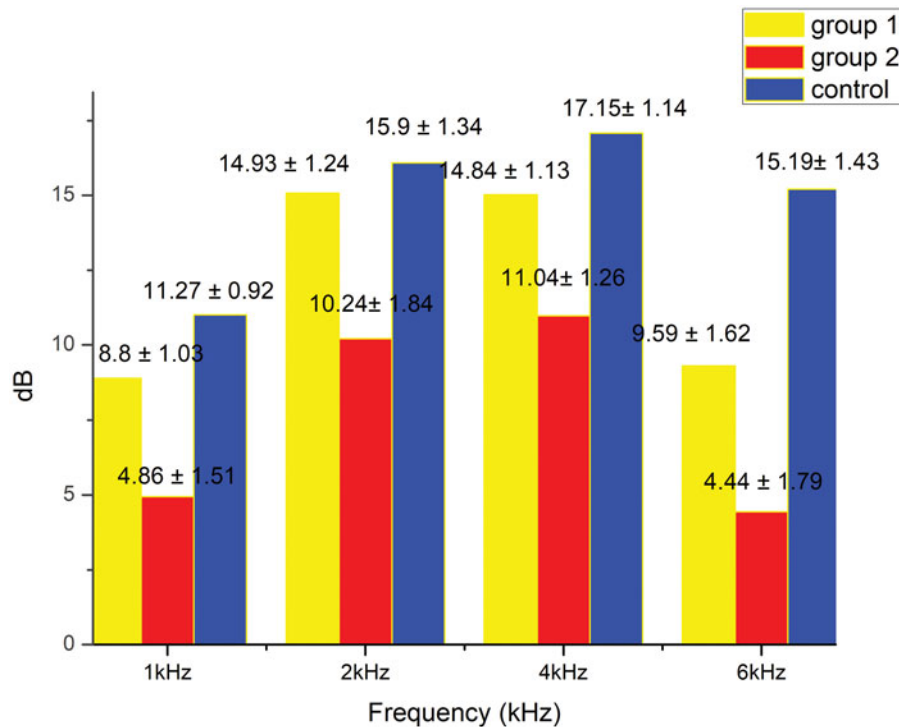


Figure 2. Comparison of the mean DPOAE S/N-R dB thresholds for the three groups at the frequencies tested.

in elderly patients and showed that hearing loss on TEOAE may indicate primary central component age-related hearing loss. In animal models, Guimaraes et al. (2004) demonstrated that DPOAE levels decreased with age for middle-aged and older male mice; however, for female mice those levels did not decline until after menopause. They discovered that the hearing status is better in premenopausal female mice than menopausal mice. Coleman et al. (1994) found that oestrogen therapy in young adult rats shortened the latencies of electric responses in several auditory pathways. That study suggested that a lack of oestrogen might play a role in hearing disorders in postmenopausal women.

There was a significant decreased at DPOAE response at 6 kHz in the women with POF group. This finding may result from low E_2 levels in women with POF. While the literature contained no studies on the effects of POF on the inner ear, a rapid scan of some recent studies revealed that oestrogen is involved in the protection against acoustic trauma (Meltser et al. 2008), while hormone replacement therapy, including progesterone combined with oestrogen, can damage hearing (Guimaraes et al. 2006). These seemingly conflicting data were provided years after case reports of irreversible (Okulicz 1978) or reversible hearing loss (Hanna 1986), tinnitus (Mitre et al. 2006) and vestibular dysfunction (Rybak 1995) following the use of contraceptive pills or hormone replacement therapy. Oestrogen therapy was reported to slow down hearing loss in postmenopausal women (Kilicdag et al. 2004). Better hearing has been reported to be correlated with higher serum E_2 levels in postmenopausal women (Kim et al. 2002). In contrast, the study by Oghan and Coksuer (2012) showed that there was not statistically significant difference between premenopausal women and postmenopausal women. However, study participants of both groups in the study by

Oghan and Coksuer (2012)) had elevated FSH levels, which is an important indicator of poor ovarian reserve. Hultcrantz et al. (2000) created an XO-Turner mouse, which is characterised by low E_2 level model; they found that the absence of oestrogen led to early presbycusis and degradation of the outer hair cell system.

The mechanism by which hormonal changes alter auditory thresholds is unclear (Al-Mana et al. 2008; Horner 2003). However, the physiological and biological effects of sex hormones indicate two possible modes of action: direct effects on the cochlea and various pathways in the central auditory system and modulation of blood flow in the cochlea and brain. Normal inner ear function depends on maintaining hemostasis in the inner ear fluids and on the biochemical integrity of the auditory receptor cells. Altered electrolyte balance in these fluids, caused by decreased oestrogen levels, and the subsequent changes in osmolality might, at least partially, explain the shifts in auditory thresholds in the postmenopausal period (Coleman et al. 1994). When the POF patients are compared with the control group, there was a significant reduction among women in the POF group for only at DPOAE 6 kHz frequency. This situation leads to consideration that oestrogen deficiency negatively affects the inner ear hair cells, and this effect is first shown by DPOAE test. Previous studies have stated that the DPOAE test is more valuable than PTA for identification of cochlear injury (Price et al. 2009; Al-Noury 2011). Similarly, Buckey et al. (2015) stated that the degenerative effects on auditory cells of acoustic trauma and the ototoxic medications may be identified with OAE test results before PTA and that DPOAE is more sensitive than PTA to show degeneration of auditory cells. These findings in the POF group may be due to low E_2 levels.

To the best of our knowledge, this is the first study that has shown the possible POF effects on outer hair cell function. All audiometric measurements were performed by the same audiometrist, who was blinded to the hormonal and medication status of the subjects. They are strengths of this study.

Conclusion

The results of this study demonstrate that POF has a negative effect on hearing function, especially outer hair cell function and E_2 levels in relation to healthy outer hair cell function. However, further studies with a larger series and a longer duration are needed to confirm this POF effect on the inner ear and to determine the exact mechanism through which it acts on hearing. Evaluation of hearing status may be considered in women with POF.

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