

# Influence of Hormonal Changes on Audiologic Examination in Normal Ovarian Cycle Females: An Analytic Study

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## Abstract

**Introduction** There is only limited information from previous studies that suggest that auditory function may be influenced by hormones. Recent advances in the field have exposed the potential role of hormones in modulating the auditory system.

**Objective** This study aims to investigate the relationship between menstrual cycle and outer hair cell function with audiological examination.

**Methods** This is an analytic study with a cross-sectional design. The sampling was a systematic random sampling. We found 49 women with normal menstrual cycle and collected their data through interviews, physical examination, and examination of the ear, with otoscopic and other routine otorhinolaryngology examinations. We evaluated Tympanometry, distortion-product otoacoustic emissions (DPOAE), and pure tone audiometry.

**Results** We found the audiometric threshold worse in the follicular phase than other phases at 4000 Hz of the right ear, and in the ovulation was found best than any other phases at 1000 Hz of the left ear with significant difference. We found significant difference of DPOAE between ovulation time and follicular phase at 3000 Hz and 1000 Hz in the left ear and between ovulation and luteal phase at 2000 Hz, 3000 Hz and 5000 Hz in the right ear and at 1000 Hz in the left ear with  $p < 0.05$ .

**Conclusion** The result of this study showed that only a small part of audiometry threshold had a significant difference between each menstrual phase. In other words, we found no correlation between menstrual and audiometry threshold. Nonetheless, there is a correlation between menstrual cycle phase and DPOAE amplitude.

## Keywords

- ▶ menstrual cycle
- ▶ ovulation
- ▶ luteal phase
- ▶ follicular phase
- ▶ DPOAE

## Introduction

Some researchers have proposed that women with hormonal changes may experience alterations in auditory functions, such as in menopause woman, woman with hormonal contraceptive, or even during the ovarian cycle. Previous studies

suggest that even the physiological fluctuation in reproductive hormones - estrogen and progesterone - during the ovarian cycle may influence auditory function.<sup>1–3</sup> Homeostasis and the biochemical status of inner ear fluid are essential for balance and for hearing. Changes in sodium and water reabsorption that take place during the ovarian cycle may

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affect the functioning of this part of the peripheral auditory system, which could in turn affect homeostasis, causing auditory and labyrinthine symptoms.<sup>4</sup>

The ovarian cycle is divided into three phases:

- The follicular phase begins with menstrual bleeding and lasts, on average, 15 days. It is more variable in length than the other phases. Hormone levels are at their lowest point during this phase, especially during the first five days. Then, estrogen levels begin to rise until about day 13 to 14, when ovulation occurs.
- The ovulatory phase lasts about three days, culminating in ovulation, with the release of an ovule. Estrogen reaches its peak level just before ovulation. Several studies found the estrogen receptor  $\alpha$  (ER $\alpha$ ) and  $\beta$  estrogen  $\beta$  (ER $\beta$ ) in the adult human cochlea (ER $\alpha$  in the spiral ganglion, and ER $\beta$  in the stria vascularis) and animal models with immunohistochemistry.
- The luteal phase lasts ~14 days and ends with the beginning of menstruation, when a new cycle begins. It does not vary much from month to month. In this phase, blood supply to the endometrium continues to increase due to the rising level of progesterone produced by the corpus luteum of the ovary, reaching its highest level around day 7, after ovulation. Progesterone levels peak in the luteal phase as LH/FSH levels decrease even further. High progesterone may increase sodium, chloride, and water reabsorption. Changes in sodium and water reabsorption that take place during the ovarian cycle may affect the function of this part of peripheral auditory system. Most of the changes in women take place in the luteal phase; these changes include fluid retention, weight gain, increased energy demands, changes in glucose uptake, a slower gastrointestinal transit time, and hydrops of the labyrinth (due to sodium retention and the resulting endolymph hypertension).<sup>4-10</sup>

Previous studies have reported on changes in auditory function during the ovarian cycle, focusing on various aspects such as auditory threshold and otoacoustic emission. Nonetheless, there has not been a reliable solution. The aim of this research is to investigate the influence of hormonal variation during the ovarian cycle on auditory threshold and outer hair cell function through the audiometry and distortion product otoacoustic emission (DPOAE) test and the correlation between both examinations, based on a relatively larger sample size.<sup>3,4,11-15</sup>

## Material and Methods

### Subjects

This is an analytic study with a cross-sectional design. We recruited forty-nine patients of reproductive age (20 to 40 years old) by systematic random sampling from the entire population of residents at Adam Malik General Hospital in North Sumatera, Indonesia, with an interval of 10. The Health Research Ethical Committee granted approval for the study. All women reported a regular menstrual cycle ranging between 24 and 35 days. We documented positive LH surge

using a commercial ovulatory kit in all women three months prior to the research, indicating they all had a normal ovulatory cycle. None of the women had been taking hormonal contraceptive or other drug treatment that could alter their auditory function (such as Cisplatin, aminoglycoside, hemodialysis). They had no history of endocrine pathology, hypertension, or otological conditions. All women had normal otoscopy, normal hearing and middle ear function, assessed by pure tone audiometry and tympanometry.

### Clinical Protocol

The subjects underwent tests three times during one ovarian cycle, as follows:

- Follicular phase: Third day after menstruation, indicating the estrogen and progesterone are in the lowest level.
- Ovulation phase: After the ovulation times tested with the ovulatory kit, indicating the estrogen at a high level.
- Luteal phase: Seventh day after the ovulation, indicating the progesterone at a high level.

During each test session, the subjects underwent auditory tests including audiometry, tympanometry, and DPOAE. All auditory tests were held at the same time of the day for each subject, to control for the influence of physiological circadian variation.

### Material

The same audiologist performed each test. For pure tone audiometry, to assess the hearing threshold, the audiologist used Audio Traveler AA222 (Interacoustics, Denmark). The tone pulses were 1–2 seconds in duration to avoid adaptation with ascending sound technique, according to the recommendation from the American Speech-language Hearing Association.<sup>16</sup> The tests were at the frequencies of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz. We excluded patients with conductive hearing loss.

The patients underwent tympanometry to determine the function of middle ear. Using 226-Hz probe tone, the middle ear pressure had to be between –100 Pa and +50 Pa. The peak value of compliance was in the range between 0.3 and 1.6 cm<sup>3</sup>. This indicated good tympanic membrane mobility and normal middle ear pressure, enabling a valid otoacoustic emission recording. For the test, we used the Audio Traveler AA222 tympanometer (Interacoustics, Denmark).

As for the DPOAE, to assess outer hair cell of the cochlea function, the examiner recorded DPOAE via an ear canal probe inserted into the ear canal. The examination was done at the frequencies of 1000 Hz, 2000 Hz, 3000 Hz, 4000 Hz, and 5000 Hz. Signal-to-noise ratio had to be 3 dB or higher at each frequency. The device used in this test was the Elios (Echodia, France).

### Statistical Analysis

We analyzed all of the data with SPSS (Statistical Package for the Social Science), adopting a 0.05 significance level for statistical purposes. Using the paired sample *t*-test, we observed the effect of the menstrual cycle phase on OAE and audiometry.

## Result

The sample consisted of 49 women of reproductive age. Patient's ages ranged from 24 to 36 years, with a mean of 27.35 years. We found a bigger sample size in the age group of 20–30 years old (85.7%) than in the age group of 31–40 years (14.3%).

### Pure Tone Audiometry

The difference between pure tone audiometry threshold of follicular and ovulation phase was found significant at 1000 Hz on the left ear ( $p = 0.005$ ) and at 4000 Hz on the right ear ( $p = 0.008$ ), as shown in ►Table 1. We also found a significant difference between pure tone audiometry threshold of ovulation and luteal phase at 1000 Hz ( $p = 0.003$ ) on the left ear, as shown in ►Table 2, and between follicular and luteal phase at 4000 Hz ( $p = 0.013$ ) on the right ear, as shown in ►Table 3.

Based on this result, we found that right ear pure-tone audiometry at the frequency of 4000 Hz in the follicular phase presents the worst hearing threshold (9.08 dB), in comparison with the ovulation period (7.35 dB) and luteal phase (7.00 dB). Although the hearing threshold was in the normal range, we found significant differences ( $p < 0.05$ ) between follicular phases and between other phases at the frequency of 4000 Hz, showing a slight fluctuation of the hearing function. Furthermore, left ear pure-tone audiometry at the frequency

of 1000 Hz produced the best results (16.33 dB), in comparison with the follicular phase (18.67 dB), and luteal phase (18.57 dB), with significant differences ( $p < 0.005$ ).

### DPOAE

A significant difference was found between DPOAE amplitudes of the follicular phase and ovulation, at 1000 Hz ( $p = 0.022$ ) and 3000 Hz ( $p = 0.000$ ) on the left ear, as shown in ►Table 4. Between the DPOAE amplitudes of ovulation and luteal phase, there were several significantly different frequencies found, including 2000 Hz, 3000 Hz, and 5000 Hz in the right ear ( $p < 0.05$ ) and 1000 Hz, 2000 Hz, and 3000 Hz at the left ear ( $p < 0.05$ ), as shown in ►Table 5. We found no significant differences between DPOAE amplitudes of follicular phase and luteal phase, as shown in ►Table 6.

## Discussion

Several hormones have been known to modulate auditory function. Many studies have found that several different hormone receptors are located in the mammalian cochlea. This condition may cause alteration of auditory function in patient who suffer hormone deficiency, hormone hypersecretion or patient that have hormonal replacement therapy.<sup>17–20</sup> Interestingly, alteration in auditory function also occurs during physiological changes such as the ovarian cycle. Previous data found different hearing sensitivity levels in

**Table 1** Pure-tone audiometry analysis results, considering mean hearing threshold at each frequency and comparison between the follicular phase and ovulation for each ear

| Frequency | Right ear (dB)   |           |                | Left ear (dB)    |           |                |
|-----------|------------------|-----------|----------------|------------------|-----------|----------------|
|           | Follicular Phase | Ovulation | <i>p-value</i> | Follicular Phase | Ovulation | <i>p-value</i> |
| 250 Hz    | 19.90            | 19.08     | 0.315          | 19.59            | 19.39     | 0.808          |
| 500 Hz    | 19.90            | 19.29     | 0.518          | 19.29            | 18.57     | 0.376          |
| 1000 Hz   | 18.00            | 18.39     | 0.593          | 18.67            | 16.33     | 0.005          |
| 2000 Hz   | 11.12            | 11.22     | 0.898          | 11.63            | 10.00     | 0.051          |
| 4000 Hz   | 9.08             | 7.35      | 0.008          | 7.55             | 7.45      | 0.908          |
| 8000 Hz   | 4.59             | 4.29      | 0.764          | 6.22             | 4.59      | 0.125          |

**Table 2** Pure-tone audiometry analysis results, considering mean hearing threshold at each frequency and comparison between ovulation and luteal phase for each ear

| Frequency | Right ear (dB) |              |                | Left ear (dB) |              |                |
|-----------|----------------|--------------|----------------|---------------|--------------|----------------|
|           | Ovulation      | Luteal Phase | <i>p-value</i> | Ovulation     | Luteal Phase | <i>p-value</i> |
| 250 Hz    | 19.08          | 18.47        | 0.508          | 19.39         | 18.00        | 0.521          |
| 500 Hz    | 19.29          | 19.49        | 0.808          | 18.57         | 18.88        | 0.700          |
| 1000 Hz   | 18.39          | 17.14        | 0.114          | 16.33         | 18.57        | 0.003          |
| 2000 Hz   | 11.22          | 10.10        | 0.140          | 10.00         | 10.51        | 0.390          |
| 4000 Hz   | 7.35           | 7.00         | 0.625          | 7.45          | 7.14         | 0.679          |
| 8000 Hz   | 4.29           | 5.82         | 0.104          | 4.59          | 5.71         | 0.242          |

**Table 3** Pure-tone audiometry analysis results, considering mean hearing threshold at each frequency and comparison between follicular and luteal phases for each ear

| Frequency | Right ear (dB)   |              |                | Left ear (dB)    |              |                |
|-----------|------------------|--------------|----------------|------------------|--------------|----------------|
|           | Follicular Phase | Luteal Phase | <i>p-value</i> | Follicular Phase | Luteal Phase | <i>p-value</i> |
| 250 Hz    | 19.90            | 18.47        | 0.142          | 19.59            | 18.00        | 0.442          |
| 500 Hz    | 19.90            | 19.49        | 0.667          | 19.29            | 18.88        | 0.633          |
| 1000 Hz   | 18.00            | 17.14        | 0.052          | 18.67            | 18.57        | 0.904          |
| 2000 Hz   | 11.12            | 10.10        | 0.207          | 11.63            | 10.51        | 0.154          |
| 4000 Hz   | 9.08             | 7.00         | 0.013          | 7.55             | 7.14         | 0.622          |
| 8000 Hz   | 4.59             | 5.82         | 0.248          | 6.22             | 5.71         | 0.694          |

**Table 4** DPOAE analysis, considering mean amplitudes at each frequency and comparison between follicular phase and ovulation for each ear

| Frequency | Right ear (dB)   |           |                | Left ear (dB)    |           |                |
|-----------|------------------|-----------|----------------|------------------|-----------|----------------|
|           | Follicular Phase | Ovulation | <i>p-value</i> | Follicular Phase | Ovulation | <i>p-value</i> |
| 1000 Hz   | 4.55             | 5.35      | 0.181          | 5.02             | 6.61      | 0.022          |
| 2000 Hz   | 7.27             | 7.96      | 0.170          | 6.33             | 7.51      | 0.060          |
| 3000 Hz   | 2.78             | 4.22      | 0.070          | 2.22             | 5.67      | 0.000          |
| 4000 Hz   | 4.59             | 4.20      | 0.690          | 5.08             | 6.57      | 0.263          |
| 5000 Hz   | 5.14             | 7.14      | 0.063          | 5.82             | 7.02      | 0.218          |

**Table 5** DPOAE analysis, considering mean amplitudes at each frequency and comparison between ovulation and luteal phase for each ear

| Frequency | Right ear (dB) |              |                | Right ear (dB) |              |                |
|-----------|----------------|--------------|----------------|----------------|--------------|----------------|
|           | Ovulation      | Luteal Phase | <i>p-value</i> | Ovulation      | Luteal Phase | <i>p-value</i> |
| 1000 Hz   | 5.35           | 4.55         | 0.295          | 6.61           | 5.18         | 0.013          |
| 2000 Hz   | 7.96           | 6.29         | 0.003          | 7.51           | 5.69         | 0.005          |
| 3000 Hz   | 4.22           | 2.16         | 0.003          | 5.67           | 3.71         | 0.014          |
| 4000 Hz   | 4.20           | 3.47         | 0.417          | 6.57           | 4.67         | 0.064          |
| 5000 Hz   | 7.14           | 5.29         | 0.034          | 7.02           | 5.53         | 0.113          |

**Table 6** DPOAE analysis, considering mean amplitudes at each frequency and comparison between follicular phase and luteal phase for each ear

| Frequency | Right ear (dB)   |              |                | Left ear (dB)    |              |                |
|-----------|------------------|--------------|----------------|------------------|--------------|----------------|
|           | Follicular Phase | Luteal Phase | <i>p-value</i> | Follicular Phase | Luteal Phase | <i>p-value</i> |
| 1000 Hz   | 4.55             | 4.55         | 1.000          | 5.02             | 5.18         | 0.782          |
| 2000 Hz   | 7.27             | 6.29         | 0.167          | 6.33             | 5.69         | 0.260          |
| 3000 Hz   | 2.78             | 2.16         | 0.445          | 2.22             | 3.71         | 0.112          |
| 4000 Hz   | 4.59             | 3.47         | 0.249          | 5.08             | 4.67         | 0.713          |
| 5000 Hz   | 5.14             | 5.29         | 0.872          | 5.82             | 5.53         | 0.726          |

each phase of the ovarian cycle with various parameters, from peripheral to the central auditory system.<sup>3,14,21-24</sup> It also has been reported that sensorineural deafness in high frequency can occur with the onset of menstruation.<sup>15</sup>

We found that hearing threshold at the frequency of 4000 Hz of the right ear in the follicular phase was worse than in ovulation and luteal phase. Whereas, hearing threshold at ovulation at the frequency of 1000 Hz of the left ear was better than in the follicular and luteal phases. At follicular phase, we know that estrogen level is at the lowest point. The condition seemed to cause the alteration in auditory function. Previous studies showed a worsening of hearing threshold in the follicular phase or in the early days of menstruation.

Conversely, estrogen during ovulation is high, which may cause a better hearing threshold. Swanson and Dengerink found better hearing thresholds during ovulation at the frequency of 4000 Hz.<sup>12,14</sup> Previous studies have found estrogen receptors in the cochlea by immunohistochemistry. In a study on animals, if severe progressive hearing loss occurred in the inner ear ER $\beta$  knock-out mice. These receptors maintain fluid and electrolyte balance in cochlea. This condition could cause alteration in fluid and electrolyte balance, leading to a disturbance of estrogen level that results in auditory alteration.<sup>17,25-27</sup> In this study, we found that only limited frequencies were disturbed by the hormone fluctuation in ovarian cycle. This shows that the ovarian cycle generally does not influence hearing function. In this research, we also conducted DPOAE examination to evaluate cochlear function. Otoacoustic emissions (OAE) are sounds that arise in the ear canal when the tympanum receives vibration transmitted backward through the middle ear from the cochlea. Distortion product otoacoustic emissions (DPOAE), detected using two stimulus tones from the ear canal, and non-linear intermodulation between the two stimuli, generate several new acoustic frequency components inside the healthy cochlea, which can travel to the ear canal. Therefore, DPOAE can detect abnormalities of the cochlear function.<sup>28</sup>

We found a significant difference between DPOAE amplitudes during ovulation time and the follicular phase at the frequencies of 1000 Hz and 3000 Hz in the left ear ( $p < 0.05$ ). We also found significant differences between ovulation time and the luteal phase at the frequencies of 2000 Hz, 3000 Hz, and 5000 Hz in the right ear, and 1000 Hz, 2000 Hz, and 3000 Hz in the left ear. Our study was similar to Al-Mana's, which found a significant difference between OAE amplitude of early follicular phase and the luteal phase, both early and late.<sup>3</sup>

The result of DPOAE examination was the representation of well-integrated outer hair cells in the cochlea. There were higher DPOAE amplitudes during ovulation in comparison to any other phase. This may be a result of a higher estrogen level at ovulation time, which has a positive effect on auditory function. Estrogen, aside from maintaining the balance of fluid and electrolytes in the cochlea, facilitates auditory information by enhancing glutamatergic neurotransmission, playing a role in neuroprotection. In a recent study, Wang and colleagues reported that estrogen has a protective effect

against noise exposure. Studies have found that estrogen relates to caspase-3 intensity. Caspase-3 are pro-apoptotic agents which become a precursor to the hair cell apoptotic process in the cochlea upon noise exposure.<sup>3,4,13,29</sup>

We found no significant difference of DPOAE amplitude in the luteal phase in comparison to the follicular phase. In the luteal phase, we know that progesterone is at a high level; whereas in the follicular phase, both estrogen and progesterone are low. This fact showed that physiological changes in progesterone did not affect auditory function. Previous research reports that progesterone replacement therapy has a detrimental effect on hearing function, as unnatural levels of progesterone could be detrimental to hearing in females. However, our findings show that the fluctuation of progesterone level in normal ranges has no effect on auditory function.<sup>18,30,31</sup>

## Conclusion

Pure tone audiometry is an examination to evaluate hearing function in general, while DPOAE is a test for evaluating integration of outer hair cell of the cochlea. The result of this study showed that only a small part of audiometry threshold had a significant difference between each phase of ovarian cycle; whereas the DPOAE product shows statistically significant differences at several frequencies between the phases. In other words, we found no correlation between menstrual and auditory threshold. There is, however, a correlation between phases of ovarian cycle and outer hair cell function.

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