Otoacoustic Emissions in Normal-Cycling Females

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Abstract

The purpose of this study was to determine if the menstrual cycle influences the amplitude of transient (TEOAEs) and distortion-product (DPOAEs) otoacoustic emissions. Thirteen normal-hearing, normal-cycling females were monitored weekly for 12 weeks. TEOAE and DPOAE amplitudes were analyzed to determine if amplitude changes could be detected and correlated to phases of the menstrual cycle. No systematic amplitude changes were observed, demonstrating that evoked OAEs are unaffected by physiologic changes associated with the menstrual cycle.

Key Words: menstrual cycle, otoacoustic emissions

Abbreviations: ABR = auditory brainstem response, DPOAEs = distortion product otoacoustic emissions, OAEs = otoacoustic emissions, RMANOVA = repeated measures analysis of variance, SOAEs = spontaneous otoacoustic emissions, TEOAEs = transient evoked otoacoustic emissions

Otoacoustic emissions (OAEs) have received widespread application in the detection of hearing loss and the identification of auditory neuropathy. Both transient (TEOAEs) and distortion-product (DPOAEs) are reliably elicited in infants with intact cochleas, and neonatal screening programs incorporating OAEs have yielded encouraging results (White et al, 1992, 1993; Norton, 1994). OAE testing appears useful in differentiating cochlear and retrocochlear disorders (Cane et al, 1994; Maurer et al, 1995). OAEs may also prove useful in differentiating hearing loss due to peripheral auditory disorders from those due to central nervous system pathology (Bonfils and Uziel, 1988; Lutman et al, 1989; Robinette and Facer, 1991; Robinette, 1992). Since OAEs are sensitive to interruption of cochlear activity, they may prove effective for monitoring subtle cochlear changes. Finding a sensitive measure to monitor cochlear integrity has eluded clinicians, but studies analyzing changes in OAEs during exposure to ototoxic drugs and to high levels of noise show considerable promise (Anderson and Kemp, 1979; Kemp, 1982, 1986; Zurek et al, 1982; Long and Tubis, 1988; McAlpine and Johnstone, 1990; Frobst et al, 1993; Zorowka et al, 1993; Sutton et al, 1994; Lonsbury-Martin et al, 1995).

The application of OAEs in monitoring subtle shifts in cochlear function requires a thorough understanding of intrinsic functions that may affect the amplitudes of the OAEs response. Since their initial discovery (Kemp, 1978), evoked OAEs have been considered highly reliable. Studies by Johnsen and Elberling (1982), Antonelli and Grandori (1986), Harris et al (1991), Vedantam and Musiek (1991), Franklin et al (1992), and Prieve et al (1993) concluded that TEOAEs are replicable and stable within sessions, across days and weeks, and even over months and years. Studies by Lonsbury-Martin and Martin (1990), Gaskill and Brown (1990), Franklin et al (1992), Roede et al (1993), and Lasky et al (1994) concluded that DPOAEs show high consistency and low variability within and between sessions. The consensus is that OAEs are stable and, therefore, amenable to clinical application.

However, these conclusions have used heterogeneous subject populations. They have not
specifically sought to distinguish male and female responses when evaluating response repeatability, nor have they examined the relationship between evoked OAEs responses and gender-related biological cycles or changes. Other audiologic measures, such as pure-tone thresholds and auditory evoked potentials, were initially considered stable and reliable indices to normal function with no evident male-female distinctions. Yet, on closer examination, significant gender-related response differences were revealed, and variations in response patterns due to a variety of intrinsic factors were uncovered (Cox, 1980; Swanson and Dengerink, 1988; Elkind-Hirsch et al, 1994). Thus, the possible influence of these factors on OAEs warrants further exploration.

The purpose of the present study was to rule out any systematic contribution to response variability of one biological rhythm, the menstrual cycle, on spontaneous OAEs (SOAEs), TEOAEs, and DPOAEs. Two gender-specific cyclical phenomena, menstrual cycle and related shifts in body temperature, were studied. It was assumed that gender-related peripheral auditory effects would be revealed in cyclical amplitude changes in TEOAE or DPOAE measures. SOAEs were measured to determine if the presence or absence of SOAEs followed a cyclical pattern and if SOAEs influenced TEOAE and DPOAE responses.

METHOD

Subjects

Thirteen healthy female volunteers participated in the study (Table 1). They ranged in age from 25 to 49 years. Hearing thresholds were screened at 15 dB HL between 500 and 4000 Hz and demonstrated sensitivity within normal limits for all subjects. None of the women had significant otologic history, based on personal report, for ear infection, noise exposure, or drug ototoxicity. All reported regular menstrual cycles. None were taking oral contraceptives during the study, and none had a history of hormonal contraception use for the 6 months previous to participation in the study.

Procedures

Study participation was initiated within 3 days of menstrual onset. A convenient time was determined at the first session, and subsequent test sessions were held within 2 hours of that time. Attempts were made to test subjects at 7-day intervals over 12 weeks, but schedule conflicts sometimes required altering the number of days between test sessions.

SOAEs, TEOAEs, and DPOAEs were recorded from the right ear of each subject. Acoustic immittance was measured prior to OAE testing to ensure normal middle ear function. At no time during the study did any subject demonstrate significant negative middle ear pressure or decreased tympanic membrane mobility related to otitis media. Body temperature was taken using a B-D oral digital thermometer, which sounded when stable temperature was reached.

Testing was carried out with the subject seated in a double-walled Industrial Acoustics Corporation sound-treated booth using commercially available instruments in combination with a portable computer that stimulated and recorded the emissions. The probe was positioned securely into the ear canal using a Grason-Stadler acoustic immittance tip modified to ensure accurate coupling to the system probe and secure fit in the ear canal. For click evoked SOAEs and TEOAEs, probe fit was assessed by examining the stimulus spectrum in the ear canal and adjusting the probe to produce minimal ringing with a relatively flat spectrum. For DPOAE recordings, probe fit was assessed by measuring external auditory canal volume and adjusting the probe so that volume readings were <6.0 cc. For both conditions, stimulus gain was automatically adjusted by the recording system before testing was initiated.
OAE Recording Parameters

OAE recordings were made using default settings of clinically available OAE equipment. SOAE and TEOAE recordings were obtained using the Otodynamics ILO88 Analyzer. For SOAEs, activity was averaged for a 20-msec silent period following a low-intensity trigger stimulus. For TEOAEs, nonfiltered click stimuli were presented at 80 dB peak SPL at a repetition rate of 50 clicks per second. DPOAE recordings were obtained using the frequency/level function of the Otodynamics ILO92 instrument (DP-gram). The DP-gram was determined using standard test frequencies over the f2 range that extended from 0.7 to 6.5 kHz at 4 points per octave, resulting in 11 test frequencies.

OAE Measurement

SOAEs appear as spectral peaks above the noise floor. The amplitude and frequency of each SOAE was identified by placing a cursor over the peak. TEOAE amplitudes were measured using the full-octave power analysis program provided by the Otodynamics ILO88. The overall intensity, or "echo level," of the TEOAE, as well as energy readings at 0.5, 1, 2, and 4 kHz, was used for analysis. DPOAE amplitudes were measured at +2 standard deviations above the noise floor using the analysis program of the Otodynamics ILO92.

RESULTS

OAE response amplitudes were grouped into weeks of cycle. Sessions 1, 5, and 9 were grouped to reflect responses from week 1 of the cycle; sessions 2, 6, and 10 to reflect responses from week 2 of the cycle; sessions 3, 7, and 11 to reflect responses from week 3 of the cycle; and sessions 4, 8, and 12 to reflect responses from week 4 of the cycle. Data related to specific frequency responses were also examined. TEOAE amplitudes at each response frequency and DPOAE amplitudes at each DP frequency for all subjects were combined for each week.

Repeated measures analysis of variance (RMANOVA) was carried out using the SAS System General Linear Models Procedure. Results from the RMANOVA are as follows.

Statistical analysis was carried out to determine if response amplitudes changed in a regular pattern over the 4 weeks of the menstrual cycle. RMANOVA, comparing responses of weeks 1, 2, 3, and 4, showed no significant difference in response amplitude by week (p > .9), indicating that OAE amplitudes do not follow specific identifiable patterns over the course of the menstrual cycle.

Response amplitudes were compared across frequencies to determine if frequency affected the amplitude of the OAE response. RMANOVA showed a significant frequency effect (p < .01).

The coefficient of variability was calculated at each frequency to determine if OAE response amplitudes within single sessions demonstrated greater variability or stability during different weeks of the cycle. From this calculation, it was apparent that DPOAE amplitudes at DP10 and DP11 and overall TEOAE amplitudes were more stable over the duration of the study. Week of the cycle did not affect the response.

These analyses failed to show a variation across weeks of the menstrual cycle. However, the method of analysis assumed approximately equal cycle duration across subjects and within subjects across the three cycles. Because cycle durations were unequal, periodic OAE changes might have been masked. The data, therefore, were reorganized and reanalyzed.

To determine when in the cycle a session occurred, session day was converted to a “percent of cycle” measure. Percent of cycle was calculated for each subject for each cycle by counting the total number of days in the cycle, counting the day of the test session, with the day of menstrual onset counted as day 1, and dividing the session day into the total number of days of that cycle. For subjects who completed the 12 sessions midcycle, the average number of days in the previous menstrual cycles was used for calculation. To delineate the presence of a cyclical pattern, responses over the three cycles were overlapped and grouped in 10 percent of cycle segments for analysis on a single 0 percent to 100 percent time scale.

To address frequency effects, responses for each DPOAE frequency and for each TEOAE response analysis frequency were analyzed separately.

To address the distinct amplitudes of each subject, raw and normalized amplitude values were used for each subject. To normalize amplitudes, amplitude scores were computer transformed to an equivalent scale of 1 to 10.

Scatter plots were constructed using Minitab Statistical Software to allow visual inspection of all data and document response amplitude changes. All of the following analyses were done using a percent of cycle scale.
Temperature

Body temperature was recorded at each test session to determine whether a correspondence existed between temperature and phase of the menstrual cycle. Temperatures were combined for all subjects and grouped according to percent of cycle. The median temperature for each segment was plotted (Fig. 1). Visual inspection of this plot shows a temperature increase slightly after midcycle. To illustrate the cyclical nature of this temperature change, a sine wave was superimposed over the graph. This pattern was observed in 8 of the 13 subjects.

SOAEs

SOAEs were not included in the initial analysis but were considered when evoked OAEs were re-evaluated. Of the 13 subjects, 11 emitted identifiable SOAEs. Subjects 1, 4, and 11 had robust responses and were classified as the high SOAE group. Subjects 9 and 12 had no identifiable SOAEs and were classified as the zero SOAE group. Subjects 2, 3, 5, 6, 7, 8, and 10 were classified as the intermediate SOAE group. These classifications were used in later analyses to determine if SOAEs influenced the amplitude of evoked OAEs.

To determine if SOAEs follow any pattern over the course of the menstrual cycle, the total number of SOAEs recorded from all subjects was grouped in percent of cycle time segments (Fig. 2). As can be observed, SOAEs are dominant early in the cycle, gradually decrease in number over the course of the cycle, and are least prevalent at the end of the cycle.

TEOAEs and DPOAEs

Although the RMANOVA showed no significant changes in response amplitudes when all data were combined, raw and normalized amplitudes of all TEOAE responses and all DPOAE responses were graphed by percent of cycle to see if patterns could be discerned. Figure 3 presents the combined responses of the raw TEOAE amplitudes and Figure 4 the combined responses of the raw DPOAE amplitudes; Figure 5 depicts the combined responses of the normalized TEOAE amplitudes and Figure 6 the combined responses of the normalized DPOAE amplitudes. No pattern of amplitude change is apparent in any of the plots.

Data were regrouped and reanalyzed in several ways to determine if cyclical patterns were masked due to individual variability in the responses. First, each subject's responses were divided into percent of cycle time segments for each TEOAE and DPOAE frequency, and the median amplitude across subjects for each time segment was calculated and plotted. Second, since inspection of SOAE responses revealed a
distinct pattern over the course of the menstrual cycle, response amplitudes of the three high SOAE subjects were compared to the two zero SOAE subjects to determine if the presence of SOAEs precipitated the formation of cyclical patterns. Third, since some subjects' responses were more variable than other subjects' responses, data were regrouped into highly variable and highly stable response groups and reanalyzed to examine the possibility that response variability masked the presence of cyclical patterns. Finally, response amplitude as a function of frequency was analyzed by comparing TEOAEs and DPOAEs at corresponding frequencies. Even with these new subgroups and new analyses, no consistent cyclical pattern was observed for either raw or normalized TEOAE or DPOAE response amplitudes.

DISCUSSION

The purpose of this study was to monitor evoked OAEs in females to determine whether systematic amplitude changes occur over the course of the menstrual cycle. Several areas were addressed. First, body temperature changes were compared to TEOAE and DPOAE amplitude changes. Second, the relationship of cycle phase to TEOAE and DPOAE response amplitude was analyzed. Finally, the influence of SOAEs on TEOAE and DPOAE amplitudes was explored.

Temperature

Body temperature in fertile women follows a biphasic pattern, with an abrupt temperature increase near midcycle (Marshall, 1968; Lanctot, 1979; Royston and Abrams, 1980). A cyclical effect has also been observed in physiologic measures of the auditory system and has been related to temperature elevation and increased hormone levels (Picton et al, 1981; Dehan and Jerger, 1990; Elkind-Hirsch et al, 1992, 1994).

Figure 1 shows that for the group, an abrupt temperature increase occurs after the 55 percent of the cycle point. This finding is evidence that the study sample exhibited the temperature patterns typical of normal-cycling females. A similar pattern of amplitude shift, however, was not apparent at midcycle for any of the OAE analysis frequencies. The failure to observe significant OAE amplitude cyclical changes indicates that body temperature elevations associated with increased progesterone levels do not affect the evoked OAE response.

SOAEs

SOAEs were recorded from each subject at each session to determine (1) if the presence or absence of SOAEs followed a cyclical pattern and (2) if SOAEs influenced TEOAE and DPOAE responses. Cyclical patterns of SOAEs appeared
when the total number of SOAEs measured in each percent of cycle segment were totaled across subjects (see Fig. 2). SOAEs were most prevalent at menstrual onset, then gradually decreased. This pattern does not resemble the pattern for oral body temperature, which shows a sharp increase midcycle (see Fig. 1), or for SOAE frequency fluctuations, which are higher in frequency at midcycle (Bell, 1992; Haggerty et al, 1993; Penner and Glotzbach, 1994; Penner et al, 1994). O'Brien (1994) has suggested that the inability to correlate temperature and SORE fluctuations in healthy individuals may be because temperature changes are too small to reveal a relationship. Since SOAEs have significant amplitude fluctuations, the cyclical pattern observed in this study may be an artifact of amplitude variability. However, the pattern for SOAEs that was absent in TEOAEs and DPOAEs may also suggest differences in the mechanisms underlying spontaneous and evoked OAEs.

The relationship of SOAEs to TEOAEs and DPOAEs was studied by comparing response patterns of subjects with many SOAEs to subjects who had no SOAEs. In this study, the amplitudes of evoked OAEs were larger in subjects with numerous SOAEs, but neither the strong SOAE group nor the zero SOAE group displayed any consistent, cyclical pattern of response. The presence or absence of SOAEs, therefore, does not cause a cyclical pattern to emerge in TEOAEs and DPOAEs.

**TEOAEs and DPOAEs**

As in other OAE studies of normal-hearing individuals, TEOAEs and DPOAEs could be recorded from all subjects at all sessions. Also typical of TEOAEs and DPOAEs in normal-hearing subjects, response amplitudes varied across individuals and across response frequencies, but remained relatively consistent within a subject (Kemp, 1978, 1982; Antonelli and Grandori, 1986; Gaskill and Brown, 1990; Probst et al, 1991; Nelson and Kimberley, 1992).

Initially, there was concern that the absence of cyclical changes was related to each individual's unique OAE response. Therefore, the data were transformed and reorganized in several ways. First, individual response amplitudes were normalized so that amplitude measures were comparable across subjects. Normalized data still showed no cyclical variation. Second, since SOAE fluctuation has been monitored over the course of the menstrual cycle in some nor-

mal-cycling subjects (Bell, 1992; Haggerty et al, 1993; Penner et al, 1994; Penner, 1995), and the subjects in this study showed SOAE cyclical changes, subjects were grouped based on the presence or absence of SOAEs. Graphic representation for these groups showed no cyclical pattern, demonstrating that cyclical changes in SOAE amplitude among subjects showing strong SOAEs was not paralleled by similar changes in evoked OAEs. Third, since studies have suggested that some subjects show greater variability than others, subjects were regrouped based on variability and stability of response amplitude (Roede et al, 1993). Results, however, showed no significant cyclical changes using raw or normalized data for either the stable or variable group. Finally, OAE amplitudes were grouped based on frequency. This re-examination was carried out for two reasons. First, initial analysis of amplitudes found that certain frequencies were less variable. Second, inspection of amplitude changes of the combined responses of analysis frequencies DP1-DP3 (442, 535, and 636 Hz) appeared to reveal cyclical changes. However, this pattern was not observed at the corresponding 500-Hz TEOAE response analysis frequency or any other frequency. The pattern was, therefore, considered spurious.

The absence of cyclical amplitude changes in evoked OAEs over the course of the menstrual cycle may seem surprising. Studies of pure-tone thresholds, auditory brainstem response (ABR) audiometry, and SOAEs have all demonstrated cyclical fluctuations in normal-cycling females that are absent in males, females using oral contraceptives, amenorrheic females, and/or postmenopausal females (Miller and Gould, 1967; Baker and Weiler, 1977; Picton et al, 1981; Davis and Ahroon, 1982; Dehan and Jerger, 1990; Elkind-Hirsch et al, 1992, 1994; Haggerty et al, 1993; Penner and Glotzbach, 1994; Penner, 1995). The basis of these changes is not known but has been related to changing hormone levels. It was reasonable to assume that OAEs would follow similar patterns.

On closer inspection, however, the absence of cyclical findings may not be surprising, especially when variations in the ABR are analyzed. It is known that the I-V interwave interval is significantly shorter during midcycle in normal-cycling females (Picton et al, 1981; Dehan and Jerger, 1990; Elkind-Hirsch et al, 1992, 1994). When the absolute latency of each of the five waves is individually monitored, a pattern becomes apparent. Waves I and II, which reflect
activity of the distal and brainstem portion of the auditory nerve, remain basically unchanged throughout the cycle. The later waves, which reflect activity of multiple generator sites at progressively higher stages within the auditory brain stem, demonstrate additive latency shifts, with wave V typically demonstrating significant shifts in latency (Dehan and Jerger, 1990; Elkind-Hirsch et al., 1992, 1994). Since changes in the later waves are of central origin, and OAEs reflect outer hair cell activity in the cochlea, peripheral responses may not be affected by these physiologic changes.

Reports of cyclical changes in SOAEs and the SOAE cyclical pattern in this study may seem to contradict this reasoning. Further examination may reveal, however, that SOAEs and evoked OAEs are the result of different cochlear processes or are influenced differently by higher auditory centers. Several response differences give support to this idea. Evoked OAEs are elicited from all normal-hearing ears, but SOAE incidence varies (Martin et al., 1990). SOAEs are more prominent in females, and female SOAEs are more likely to contain multiple peaks (Strickland et al., 1985; Whitehead et al., 1989; Bilger et al., 1990). SOAEs exhibit significant amplitude fluctuations, while evoked OAEs are highly stable (Probst et al., 1986). Spectral analysis of TEOAEs does not always reveal SOAE peaks, and spectral analysis of SOAEs does not always point to areas where TEOAE peaks are observed (Wable and Collet, 1994). McFadden (1993) has suggested that efferent inhibition may influence the SOAE response, and cites gender and ear differences as support for this assumption. Further research differentiating SOAE and evoked OAE activity may reveal that physiologic processes within the central auditory system influence these peripheral responses in different ways and are responsible for their unique characteristics.

Although the TEOAE and DPOAE data were examined in several ways to detect cyclical changes, neither visual inspection nor statistical analysis revealed consistent patterns in the responses. Response amplitudes showed no significant changes at any time in the cycle. Response stability and variability were related to subject and frequency characteristics but not to phases of the menstrual cycle.

CONCLUSIONS

Results confirm that TEOAE and DPOAE amplitudes are stable. Over the course of the study, TEOAE and DPOAE amplitudes showed no systematic changes, suggesting that OAEs are unaffected by physiologic changes known to affect other auditory measures in females.

Further study of normal-cycling females using a younger population may be warranted. Although cycle duration did not appear to be influenced by age, the influence of reduced hormone levels in older subjects was not addressed. Further testing, which included the recording of hormone levels, would determine the influence of cyclical hormone changes on the OAE response.

The clinical potential of OAEs is only beginning to be realized. Studies continue to define optimum stimulus and recording parameters, determine efficient protocols and procedures, and develop methods of interpreting the results. Responses in normal individuals are being clarified and understood, but until norms are established, clinical application of OAEs is limited.

Continued research on both normal and pathological factors influencing OAEs is imperative. Gender differences are one aspect in need of greater definition. This study showed that physiologic events that are gender specific do not cause significant response differences as they do with ABR. Phases of the menstrual cycle, therefore, need not be considered when interpreting OAE results.

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REFERENCES


