Menstrual Cycle, Vocal Performance, and Laryngeal Vascular Appearance: An Observational Study on 17 Subjects

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Summary: Objective. To assess the anatomical and functional features of the vocal folds during different phases of the female menstrual cycle.

Methods. An observational study of 17 healthy fertile female volunteers not using hormonal contraception was carried out. Each volunteer underwent two examinations: first, during the early days of the menstrual cycle when progesterone levels are low (p-depletion), and second, during premenstruation when progesterone levels are high (p-peak). The workup included blood hormone levels, Voice Handicap Index, acoustic analysis, rigid telescopy, stroboscopy, and narrow band imaging. The videos were evaluated by blinded observers.

Results. The participants' mean age was 31.7 ± 5.6 (range 23–43). Progesterone levels were 13- to 45-fold higher in p-peak relative to p-depletion. No significant differences were detected in Voice Handicap Index scores, stroboscopic reports, or acoustic analysis between p-peak and p-depletion examinations. Analyzing the rigid telescopy and narrow band imaging videos, the observers tended to estimate the different laryngeal subsites more vascularized during the p-peak examination. Moreover, this tendency was significantly correlated with blood progesterone levels during the p-depletion examinations; the lower the blood progesterone levels were during p-depletion, the higher the probability for the observers to estimate the p-peak examinations more vascularized (P value = 0.024).

Conclusions. Alterations in laryngeal vascular characteristics are evident throughout the menstrual cycle and may suggest increased congestion during premenstrual days. Variations in progesterone levels during the menstrual cycle correlate with laryngeal vascular changes. Hormone-related alterations in vocal folds' vascularity may have a role in the variability of vocal performance in certain women.

Key Words: Menstrual cycle–Sex hormones–Narrow band imaging–Premenstrual dysphonia–Premenstrual Syndrome.

INTRODUCTION

Voice changes associated with the normal menstrual cycle were reported throughout the years. In 1968, Lacina described "laryngopathia premenstrualis" or premenstrual dysphonia, which affected 40% of female singers of the National Theatre in Prague. This condition was characterized by difficulties in high tone phonation, tone inaccuracy, and tendency to develop vocal fold hemorrhage during the premenstruation period.[1,2] This belief resulted in a practice named "grace days," in which female singers were excused from singing in European opera houses during premenstrual and early menstrual days.[2] Similar descriptions of dysphonia during premenstrual or early menstrual days were reported throughout the years,[3–10] along with descriptions of dysphonia around ovulation.[10–13] Yet, other reports failed to support premenstrual dysphonia, raising doubts about its existence.[14–16]

Furthermore, there has been much debate whether premenstrual dysphonia actually results from direct impact of sex hormones on the vocal folds' tissue. Ovulating women experience a premenstrual phase, and estrogen levels are lowest in the menstrual phase and highest in the late follicular phase. Changes in voice intensity could be indirectly explained by hormonal influence on the vocal folds.[17] Some authors suggested the role of secondary effects; premenstrual syndrome (PMS)-related mood changes and abdominal cramps may result in laryngeal tension or reduction in respiratory effort.[2,5,18,19] A study among 28 nonsinger women found that only subjects who fulfilled the criteria of PMS demonstrated significantly increased frequency perturbation during the premenstrual phase.[20] A more recent study[4] of female singers found that self-perceptual evaluation of vocal performance was lower during days 24 to 4 of the cycle among subjects with premenstrual negative mood changes. Whereas other listeners were unable to detect differences in vocal quality, the affected singers themselves were able to accurately identify the timing of their recordings. The results of these two studies may suggest that women suffering from PMS have higher tendency for premenstrual dysphonia. On the other hand, these results may also imply secondary effects of PMS-related mood changes and pain on vocal performance.

Establishing evidence of direct effect on the vocal folds required histologic investigations. Abitbol et al showed significant similarities between epithelial smears from female larynx and

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vaginal cervix.[3] This has been further supported when the presence of sex hormone receptors (eg, progesterone and estrogen) was demonstrated on human vocal folds by Fergusson et al, Brunings et al, and others.[21–27] These data suggest a link between hormone levels and vocal fold function, which might cause voice changes during premenstruation.

It was hypothesized that the direct effects on the larynx during premenstruation include micro-venous dilatation, edema, and reduced muscle tone.[5] Nevertheless, to date, the results of most previous studies do not provide a definite description of the physiological mechanism in which the menstrual cycle impacts vocal performance, and whether it comprises a direct effect on the vocal fold tissue.

The use of narrow band imaging (NBI) was recently introduced to otolaryngology. NBI applies filters that narrow the frequency range of light into bands of blue (~415 nm) and green (~540 nm). These specific wavelengths enhance visualization of mucosal and submucosal micro-vascularization, based on their depth of penetration and absorption by hemoglobin.[28] Therefore, one can assume that menstrual cycle-related laryngeal vascular chances will be easier to detect by NBI, particularly if these are considered to be overlooked changes. Nevertheless, to date, this application of NBI has never been examined.

Designing this current study, we hypothesized that there is a direct effect that involves subtle vascular changes in the larynx. We therefore aimed to assess both the functional and vascular anatomical features of the vocal folds and the larynx during different phases of the female menstrual cycle by means of subjective self-assessment of voice, acoustic analysis measurements, and imaging of the larynx, including NBI.

METHODS

This was an observational study of healthy fertile female subjects assessing the functional and vascular anatomical features of the larynx during different phases of the female menstrual cycle. The study protocol was reviewed and approved by the institutional ethics committee. All subjects agreed to participate and signed an informed consent form.

Seventeen subjects who met the following inclusion and exclusion criteria were enrolled in the study. Included were female subjects, nonprofessional singers/nonperformers, aged 18–45 who reported regular menstrual cycles with consistent number of cycle days during the recent year. Excluded were subjects with irregular cycles, subjects who were pregnant, breastfeeding, underwent delivery or used any type of hormonal contraception in the preceding 3 months, or intended to use any type of hormonal contraception during the study period. Pregnancy was ruled out with a qualitative urinary hCG test in each visit (Zer Pregnancy Test, Zer Hitech Ltd., Beit Shemesh, Israel). Subjects who had history of laryngeal surgery, pulmonary illness, or neurologic disease were also excluded. Enrolled subjects underwent initial evaluation which involved the collection of the following data: demographic characteristics, previous medical and surgical history, obstetrics and gynecological history, smoking, general social history, vocal use, and habits.

All subjects participating in the study visited our facility twice for examinations. The first examination was during the early days of the menstrual cycle, when both progesterone and estrogen levels are near baseline ("p-depletion" examination). The second examination was after ovulation and before the beginning of the next menstrual cycle (correlating with the premenstrual period), when progesterone serum level reach a peak and its effect is dominant ("p-peak" examination). In each of the two visits, the subjects underwent a thorough workup which included serum progesterone and estradiol levels, Voice Handicap Index (VHI), acoustic analysis, white light (WL), and NBI laryngeal endoscopy and videostroboscopy.

Analysis of serum estradiol and progesterone levels was obtained by immunoassay (Estradiol Reagent and Progesterone Reagent, Access Immunoassay System, Beckman Coulter, Nyon, Switzerland) to establish the menstrual cycle's phase for each examination and to support an event of ovulation between examinations. A Hebrew translation of the VHI[29] was used for subjective self-assessment of voice, as its successful application among Hebrew speakers was previously described.[30] Each recording for acoustic analysis measurements started with calibration for the absolute sound pressure level measurements. A microphone (Shure SM48; Shure Incorporated, Niles, IL) was placed 5 cm from the subjects' mouth. The subjects were asked to phonate and sustain the vowel /a/ at the most comfortable pitch and loudness for approximately 5 seconds. Data were digitally recorded and transferred to a computer at a sampling rate of 50 kHz using computerized speech laboratory system (KayPENTAX Visi-Pitch IV, Model 3950B; Disordered Voice Database, Model 4337, version 3.2.0, PENTAX Medical, Tokyo, Japan). An interval of 3.75 seconds from the mid-portion of each sample was selected for acoustic analysis. Acoustic analysis measurements including fundamental frequency, perturbation measurements (jitter and shimmer), and noise-to-harmonic ratio parameters were calculated. For maximum phonation time calculation, the subjects were instructed to sustain the vowel /a/ as long as they could on one deep breath, at a relatively comfortable pitch and loudness. This was repeated three times, and the longest measurement was entered into the analysis.

WL videolaryngoscopy was recorded by rigid telescopy (Karl Storz, 10-mm, 70° rigid telescope; KARL STORZ GmbH & Co., Tuttlingen, Germany). NBI was used to enhance superficial mucosal and submucosal vascularity. NBI was obtained using ENF-V2 digital video rhinolaryngoscope (Olympus Medical System Corporation, Tokyo, Japan). All subjects in both visits were examined by the exact same conditions, instrumentations, and techniques: similar hour of the day, same examination room, same digital video rhinolaryngoscope and rigid telescope, same light source and intensity, and similar technique for white balance calibration. Videostroboscopy was performed and documented during the rigid telescopic examination, using *EndoSTROB System* and *DiVAS software* (XION GmbH, Berlin, Germany). Evaluation of videostroboscopy was performed by completing the Stroboscopy Evaluation Rating Form.[31]

To assess the laryngeal vascular congestion, the videos were evaluated by two fellowship trained laryngologists (HSH, YL); both are well experienced with the use of NBI as part of their everyday practice. The observers were blinded to the subjects' descriptions and to the menstrual cycle phase in which the