The impact of hormonal fluctuations on female vocal folds

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Purpose of review

Sex hormone fluctuations were shown to affect female vocal folds and laryngeal function. Laryngeal changes are evident throughout the span of life, starting at puberty with the arousal of the hormonal system, fluctuating systematically during the reproductive years with the menstrual cycle, and then changing again with the decline of hormonal activity at menopause. This paper reviews recent developments in this field.

Recent findings

Early studies that explored this relation were based merely on subjective impressions of voice quality, recent studies have used more objective tools for examining this relation, including histologic observations, stroboscope, electroglottography (EGG), and computerized acoustic analyses. In these studies, the larynx was shown to be a hormonal target organ and, as such, sex hormones affect its morphology, histology, and function, similar to their effect on the genitals and other organs.

Summary

Examining the relation between sex hormones and the larynx could assist in understanding the mechanisms of voice production, and it could provide the clinician with supplemental diagnostic information on different medical conditions.

Keywords

larynx, vocal folds, voice, hormones, women

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Abbreviation

PMS premenstrual syndrome

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Introduction

The female human larynx, specifically the vocal folds, are affected by various factors, including, for example, age, development, diseases, medications, and hormonal state. Sex hormone fluctuations are one of the factors that influence vocal fold activity and voice production. The impact of sex hormones on laryngeal activity is of interest from both theoretic and clinical perspectives. Initially, better understanding of this relation could enhance our knowledge of the mechanisms underlying voice production. Second, vocal changes might provide information on different medical conditions and could serve as a supplemental diagnostic tool for the physician. This review discusses the effect of sex hormones on the female larynx, with special attention to recent developments in the field.

Female sex hormones

The normal human ovary produces three classes of sex steroidal hormones: progesterone, estrogen, and androgen. These hormones are produced from cholesterol through several enzymatic pathways (progesterone is a precursor of androgens, which in turn are precursors of estrogens). Sex hormones act through specific receptors, located in their target organs, and are responsible for the development and functioning of the genital organs, fertility, bone density, and blood lipids profiles [1].

Estrogen causes hypertrophy and proliferation of the endometrial, vaginal, and urinary tract mucosa. It is responsible for mammary gland development, it increases bone density, and it has a favorable influence on the lipids profile (decreasing cholesterol and triglycerides). In addition, estrogen causes abundant, watery, thin, clear, and stretchable mucus. Moreover, estrogen seems to have a favorable effect on cognition and on blood vessels, yet under specific conditions it could increase coagulation and risk for thromboembolic events. Progesterone attenuates estrogen activity by speeding up its degradation and inactivation, and by decreasing estrogen receptors. It has an antiproliferative effect on mucosa and it decreases glandular activity and mucus secretions that become more thick and opaque. Progesterone decreases blood vessel permeability, thus increasing edema. At the same time it decreases smooth muscle stimulation. Although estrogen and progesterone are active simultaneously, the effect on the endometrium is mainly provided by pro-

gesterone. Several metabolites of progesterone have androgenic effects.

Androgens in women are produced in the adrenals and in the ovaries. Increased androgens in women cause hirsutism, acne, skeletal muscle hypertrophy, aggressiveness, and masculine vocal changes. They also cause thickening of the cervical mucosa and drying of the seromucous glands [2]. Hormonal treatments with androgenic effect, such as Danazol, have been shown to cause irreversible vocal changes, mainly lowering of fundamental frequency [3,4]. On the other hand, androgen deficiency was associated with dysphoric mood, fatigue, and sexual dysfunction, as well as a decrease in mineral bone density and muscle strength [5,6].

Larynx as a target organ for hormones

Voice is one of the secondary sex characteristics, and as such, it varies between men and women, and it changes with sexual maturation. Some age-related vocal changes are attributed to endocrine influence. The correlation between hormonal fluctuations and laryngeal cytologic and functional changes supports this relation. Epithelial smears from the larynx and the vagina show similar changes during a woman's menstrual cycle and menopause [7,8]. Estrogen, progesterone, and androgen receptors were found in the human vocal folds in the epithelial cytoplasm and nucleus, in the glandular cytoplasm and nucleus, and in fibroblasts within the lamina propria [9]. The distribution of the receptors varied significantly with age and gender. Recently, similar receptors were also found in the larynx of other species [10]. The larynx was shown to be a target organ for additional hormones, other than sex hormones. For example, thyroid hormone receptors were found in the human larynx and were clinically associated with vocal changes [11•].

Sex hormones and the larynx throughout the female life span

The female life cycle is strongly related to hormonal changes. Varying dynamics of the three sex hormones unfold at the different life phases: starting at puberty, fluctuating during the reproductive years, and dramatically declining at menopause. These hormonal changes affect the larynx and vocal folds, which in turn affect voice production.

Puberty

During childhood the ovaries are not producing significant amounts of sex hormones as a result of hypothalamic and pituitary suppression. During these years, preceding puberty, the female larynx grows gradually and, with it, the voice profile adjusts with no dramatic changes [12••]. During puberty the ovaries react to the increasing secretions of gonadotropins and initiate production of sex hormones, until a mature menstrual cycle is established. The arousal of the female hormonal system is evident in the larynx as well. Comparisons of prepubertal, pubertal, and adult female larynges indicated an increase in size at puberty, although the general proportion among the laryngeal cartilages remains relatively constant such that the female larynx reaches adult size by puberty [13]. Vocal tract size also increases significantly at puberty [14], although the magnitude of the change is more prominent in boys than in girls. The anatomic and physiologic changes at puberty are manifested in voice characteristics. The primary vocal change is lowering of fundamental frequency by one third, relative to childhood voice [2]. Additional vocal changes include an increase in amplitude as well as an increase in frequency and amplitude perturbation [15].

Reproductive years

During the reproductive years the female body is exposed to cyclic influences of the sex hormones. The endometrial changes during the menstrual cycle are well documented [1]. During the follicular phase (the first phase of the menstrual cycle, until ovulation) the increasing secretions of estrogen induce cellular proliferation and only minimal stromal edema. During the secretory phase (after ovulation), progesterone secretion from the corpus luteum increases, causing significant stromal edema. At this time, glandular secretions increase in response to estrogen and progesterone stimulations, and then 7 to 8 days after ovulation the rates of progesterone and estrogen secretions decline. During menstruation (the phase of estrogen and progesterone withdrawal) there is vasoconstriction of endometrial vessels, endometrial collapse, and epithelial desquamation [1]. Interestingly, histologic (cells and receptors) laryngeal changes during the menstrual cycle were reported to replicate those of the endometrium [2], implying that the larynx is also influenced by cyclic changes.

Menstrual cycle

Several studies have investigated the effect of the menstrual cycle on voice. Most reported voice changes before menses [16,17] or around ovulation [18]. Such vocal changes included vocal fatigue, decreased range and loss of vocal power, and high harmonics. These were reported mainly by vocal performers, whereas among nonprofessional voice users, such complaints were less prevalent [19]. The primary limitation of these studies was that most of them relied on subjective reports of the speaker herself. Although such observations provide important clinical information, it presents an obstacle in evaluation and replication. A more recent study [20] compared 15 classical female vocalists who were reported to abuse their voice with 15 singing students who did not. In both groups, slight subjective vocal problems were reported before menses: slight edema and erythema of the vocal folds, as well as decreased tension of the vocal muscles observed via stroboscope and electroglottography (EGG). Vocal symptoms and instrumental find-

ings were more prevalent in the vocally abusive group. It was suggested that vocally abusive behaviors aggravate the mild vocal changes before menses, thus increasing risk for vocal pathologies.

The prevalence of vocal symptoms associated with premenstrual syndrome (PMS) is estimated to be 33% among nonprofessional voice users [2], and higher among professional singers [16]. These changes are attributed to the observed loss of tone in the striated muscles, edema in Reinke's space, and microvariceal dilatation in the larynx in women with PMS [2]. Chae *et al.* [21] compared acoustic analyses of voice quality among PMS-positive and PMS-negative women. They reported that only jitter values were significantly higher among PMS-positive women, whereas other acoustic measures were not. They did not find, however, a significant menstrual cycle effect for either group, and attributed that to the use of only two recording points along the menstrual cycle. Interestingly, another group of studies that evaluated voice quality during the menstrual cycle using a more comprehensive set of acoustic parameters and multiple recordings during the menstrual cycle reported similar results [22,23••,24,25••]; namely, no changes in voice quality during the menstrual cycle were observed, contradicting earlier findings, which were based on subjective evaluation [18,19]. It is possible, then, that the acoustic parameters used during these studies were not sufficiently sensitive to reveal these differences or, in contrast, subjective vocal changes associated with PMS could be the result of a mechanism other than the vocal folds themselves.

Birth control pills

Birth control pills provide an additional paradigm by which the effect of sex hormones on voice can be examined. In essence, combination pills consist of estrogen and progesterone, which create a stable hormonal balance throughout the menstrual cycle, thus preventing ovulation by inhibiting gonadotropin secretion. The estrogen in the pills prevents follicles from ovulating, whereas the progesterone thickens cervical mucus and creates an endometrial environment that is not receptive to ovum implantation. Older generation pills contained multiphasic formulations with varying doses of estrogen and progesterone, whereas the new-generation monophasic pills, which are commonly used today, have a lower hormonal dose that remains constant throughout the month and produces fewer androgenic derivatives.

Several reports dated in the 1960s and 1970s suggested that birth control pills could induce an adverse effect on the female voice, including virilization, lowered fundamental frequency, and increased harshness (for a review, see Wendler *et al.* [26]). Since then, phoniatricians and voice specialists tend to discourage voice performers from using oral contraceptives, viewing it as a potential risk factor for voice [27,28]. However, with the introduction of the new generation of oral contraceptives, fewer negative vocal symptoms can be expected. In that respect, Wendler *et al.* [26] reported no significant voice changes among women who use new-generation pills. Yet, their results were based primarily on subjective measures.

A series of recent studies addressed this issue using computerized acoustic analyses of voice quality. In the first study of this series [22], a group of young women who use monophasic pills was compared with a control group. Voice quality was assessed using fundamental frequency (F0), jitter, amplitude, shimmer, and harmonic-to-noise ratio. Results did not reveal an adverse effect on voice for the pill group. Moreover, and in contrast with the traditional view of oral contraceptives as a risk factor for voice, jitter and shimmer values were significantly lower in the pill group than in the control group. A follow-up study [23••] reached similar findings, suggesting that voice quality among pill users is more stable and better represents voice of normal quality. Two subsequent studies improved the methodology by including a wider variety of oral contraceptives [24], which enhanced generalization possibilities; and, by expanding the acoustic analyses to include eight measures, refined voice quality evaluation [25••]. Results ascertained that new-generation pills have no adverse effect on voice. In fact, voice quality among pill users was typically better than that of the control subjects. Apparently, because birth control pills eliminate hormonal fluctuations by creating a stable hormonal balance, related vocal changes are reduced or eradicated. To date, it is yet unclear whether sex hormone fluctuations affect only vocal fold mucosa or whether both the mucosa and the deeper layers are affected. Although preliminary acoustic data suggest that hormonal fluctuations modify vocal fold regulation of vibration more than magnitude or efficiency of glottis adduction, a definitive answer to this question is not yet available.

Menopause

During menopause the ovaries lose their ability to produce estrogens and to ovulate. As a result, postmenopausal women are exposed to diminished amounts of estrogens and increased relative amounts of androgens. Among other menopausal symptoms, such as hot flashes and decreased bone density, ovarian dysfunction causes mucosal atrophy that is expressed as vaginal and urogenital dryness. In addition, lack of estrogen causes degradation of connective tissues. Normal voice production depends on the integrity of the connective layers of the vocal folds. The effect of estrogen decrease and androgen increase on these laryngeal layers during menopause has already been demonstrated [29].

Voice changes during menopause have been documented [30]. Early studies noted that professional sing-

ers sometimes complain of loss of brilliance, loss of power, and decreased ability to reach high notes after menopause [31]. These findings, however, consisted merely of anecdotal subjective reports made by the singers themselves. Boulet and Oddens [32] used mailed questionnaires completed by 48 professional female singers. They reported that singers in their sixties often complained of vocal changes associated with menopause. These complaints included loss of vocal flexibility (72%), loss of top notes (69%), change in timbre (44%), reduction in voice stability (36%), and huskiness (25%). Despite the relatively large sample used, it should be noted that this study used only subjective self-reports, and in addition the response rate to the mailed questionnaires was low (19.5%). Thus, the possibility of a biased sample cannot be overruled.

Abitbol *et al.* [2] examined a group of 100 menopausal women using dynamic vocal exploration, stroboscopic examination, and cytologic smears. They reported that, in all women, vocal folds were less supple, had a thinner mucosa, and had reduced vibratory amplitude. Of these women, 17 were diagnosed with dysphonia associated with menopause. In this subgroup, they also noted unilateral or bilateral muscular atrophy of the vocal folds, asymmetric vibratory pattern, and discoloration of the mucosa with appearance of microvarices. Apparently, hormonal changes associated with menopause affect female vocal folds similar to their effect on other organs. The manifestation of these endogenic, histologic, and anatomic changes on voice vary among women and is more likely to be noted by professional voice users, who are more aware of their voice quality but are also more likely to drive their voice to its limits. Further support for this relation was found in the counteracting effect of hormone replacement therapy on vocal change associated with menopause [33], and it was shown that adding specific doses of androgen to hormone replacement therapy during menopause improves libido, well-being, and mood without significant adverse effects [6,34•].

Discussion

A question that was not addressed as of yet is what is the advantage of the larynx being affected by hormonal changes? Although no direct answer for this question is available today, a possible explanation can be found from an evolutional perspective. There are initial clues for the possibility that vocal productions can provide acoustic signaling of mate attraction and time of ovulation. This was demonstrated recently in primates [35], in whom the female voice was shown to contain information on reproductive state, which is perceived by males and affects their reproductive success. It is conceivable, then, that similar mechanisms are present in humans, although possibly to a lesser degree. Further support for this hypothesis was also provided recently using a different paradigm [36•]. This study compared attractiveness ratings of women, made by men, and concluded that women who were rated high on "visual attractiveness" were also rated as more attractive based on their voice. It was suggested that, for example, relatively high-pitch voices might signal higher estrogen levels, which could be perceived by the male listener as a younger and more fertile woman. Whether the relation between these findings and the studies on the direct effect of sex hormone on female voice could be integrated, remains to be answered, yet it presents an intriguing direction for future research.

Conclusion

The relation between voice and sex hormones in the female body is well established. Starting with the subjective reports on vocal changes associated with hormonal changes, through acoustic analysis of voice quality, to finding hormonal receptors in the larynx and in the vocal folds, it is clear that the larynx is affected by sex hormone fluctuations. This line of research provides interesting and valuable information on the mechanisms underlying vocal production, and could improve clinical intervention during different phases in the lives of women. In addition, this body of research demonstrates the importance of studying the larynx and its function not merely in isolation, but as an integral part of the whole body.

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