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The Effects of Hormonal Contraception on the Voice: History of its Evolution in the Literature

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INTRODUCTION: THE MENSTRUAL CYCLE AND THE VOICE

The fluctuation of hormones in the menstrual cycle has significant effects on the voice.[1] Singing teachers should be familiar with the vocal effects of hormones and of hormonal medications such as oral contraceptives (birth control pills), especially in light of recent changes in their chemistry and effects. Vocal symptoms, known as dysphonia premenstrualis, accompany the better known symptoms of premenstrual syndrome (PMS) during the luteal phase of the menstrual cycle.[2] The most common symptoms of dysphonia premenstrualis are difficulty singing high notes, decreased flexibility, huskiness, fuzziness, breathiness, decreased volume, difficulty bridging *passaggios* and intonation problems.[3] Davis and Davis concluded that, on average, singers experience 33 general symptoms of PMS and 3 symptoms of dysphonia premenstrualis.[4] Chae et al. showed that approximately 57% participants met the DSM IV criteria for PMS and also had acoustic evidence of dysphonia premenstrualis, whereas the PMS-negative group did not.[5] The risk of vocal stress and possible damage during the premenstrual period led many European opera houses to offer singers contracts that included "grace days" during their premenstrual period. This accommodation is no longer followed in Europe and was never practiced generally in the United States.[6]

The mechanisms that cause these symptoms lie not just in the actions of the hormones themselves, but also in the cyclic fluctuation of hormone levels. The actions of the hormones on the vocal folds can be correlated with their effects on cervical mucus production. Cervical mucus in the preovulatory or follicular phase is thinner and slippery to aid insemination, while in the premenstrual or luteal phase it is thicker and more viscous.[7] Receptors for estrogen and progesterone have been identified in vocal fold mucosa.[8] Increased estrogen causes increased vocal fold mucus secretions and reduced mucosal viscosity and may increase vocal fold mass or thickness. Estrogen

levels are highest in the follicular phase or preovulatory phase. Increased progesterone causes decreased mucus secretions, dehydration of the mucosa and lamina propria, increased mucous viscosity, associated with decreased mass or thinning of vocal fold mucosa. Progesterone levels are highest during the premenstrual phase or luteal phase.[9] Dehydration and thinning of the vocal folds in the premenstrual phase contributes to the symptoms of dysphonia premenstrualis.

The Physiology of the Menstrual Cycle

The menstrual cycle begins with approximately 5 days of menstrual flow. Both estrogen and progesterone levels are low during the menstruation phase. The follicular phase follows, in which the level of estrogen increases daily until day 14 when ovulation occurs, triggered by a surge in luteinizing hormone (LH). The luteal phase follows in which the estrogen level quickly decreases to mid-level. It plateaus there until the end of the cycle, when it drops quickly prior to menstrual flow. Progesterone remains low after the fifth day of menstrual flow. After ovulation, the progesterone level rises steadily to reach a peak halfway through the luteal phase. Then progesterone starts to decrease and reaches its lowest level prior to menstrual flow.[10]

The Physiology of Oral Contraception

Oral contraceptive pills (OCPs) reduce the overall fluctuation of hormones during the menstrual cycle that results in the depression of ovarian function. They function by feedback inhibition of hypothalamic secretion of gonadotropin releasing hormone (GnRH). The progesterone derivative also suppresses LH secretion from the anterior pituitary, which prevents ovulation. The estrogen derivative suppresses FSH secretion from the anterior pituitary, which inhibits follicle growth prior to ovulation. The major suppression of ovulation is accomplished by the progesterone derivative of the OCP. However, most pills combine estrogen and progesterone derivatives. The estrogen component has a role in the suppression of ovulation, but the progestin component alone would perform this task. The estrogen component stabilizes the endometrium, minimizing breakthrough bleeding. It also potentiates the action of the progestin component, allowing the dose of progestin in the pill to be reduced. The combination pill is generally more popular among women, but the progestin-only method is prudent in women at increased risk for cardiovascular and thromboembolic events.[11]

OCPs are either monophasic or multiphasic. Monophasic pills have the same formulation for 21 days of the cycle, followed by 7 placebo pills. Monophasic pills introduce the lowest levels of estrogen and progesterone needed to inhibit ovulation. Multiphasic (typically triphasic) OCPs attempt to mimic the fluctuation in hormones of the menstrual cycle. Their aim is to lessen the metabolic effects of the drugs and decrease the incidence of breakthrough bleeding and amenorrhea. Given the higher cost, greater complexity of triphasic pills in administration, and lack of evidence of a significant benefit of triphasic pills, monophasic pills are currently recommended as the first choice for initiation of oral contraception, by the Cochrane Database of Systematic Reviews.[12]

HISTORY OF ORAL CONTRACEPTION AND THE VOICE

The first OCP, Enovid® (G. D. Searle Co., Chicago),was tested in 1957 in Japan and Puerto Rico in a formulation containing 75 μg of mestranol and 10 mg of norethynodrel. The dose was lowered to 5 mg norethynodrel prior to being sold in the United States in 1960.[13] Mestranol was found to increase thromboembolism risk. Norethynodrel is a nortestosterone derivative that has androgenic and metabolic effects that include voice virilization.[14] The second generation oral contraceptive developed in the 1970s included a progestin derivative, levonorgestrel (LNG), that allowed inhibition of ovulation at a lower dose. Many of the new, standard, low dose pills contain 100 to 250 μg of LNG combined with 20 to 50 μg of ethinylestradiol. The second generation OCPs began being marketed in the late 1960s and are, to this day, the most popular contraceptive option for women.[15] The 1980s brought the third generation progestins, gestodene and desogestrel. They are less androgenic and thus, result in decreased impact on metabolism, weight gain, acne, and mood changes. Drospirenone, a spironolactone derivative without androgenic effect and with antimineralocorticoid effect, is the progestin component in fourth generation contraceptives released in 2006. Controversy remains as to the safety of third and

fourth generation progestins, as some data have shown an increase in thromboembolism risk. As a result, they are not used as frequently as LNG.[16]

Through the 1980s, the voice community believed strongly that oral contraceptives were damaging to some female voices, resulting in hoarseness, loss of vocal efficiency, lowering of range and loss of high notes. It was said that these permanent effects could occur after only a few months of therapy.[17] Ovosiston (2mg chlormadinone acetate, 0.1 mg mestranol) was shown in 1969 to be associated with a lower mean speaking frequency by 0.8 half-tone as well as an increase in vocal intensity by 5dB in lower third of pitch range.[18] Due to findings such as these, oral contraceptives were recommended only to alter the timing of menstruation to allow for crucial performances and occasionally to lower cyclical recurrent hemorrhage. The voice was to be monitored closely when oral contraceptives were in use.[19]

Studies since have found that first generation contraceptives containing a high dose nortestosterone derivative did cause virilization of the voice. However, second and third generation contraceptives are of a lower dose and do not have a deleterious effect on the voice.[20] First generation progestins are no longer used in the United States and, thus, the long held belief that OCPs are harmful to the voice has been refuted.[21]

THE EVIDENCE

Twenty-four articles were identified that address the effects of oral contraception on the vocal folds. The overall conclusion is that oral contraceptive pills do not affect the voice negatively. In fact, current OCP formulations tend to stabilize the singing voice through dampening of hormonal variation throughout the menstrual cycle.[22] However, the quantity and quality of the evidence are not ideal. There were many inconsistencies between the studies, as well as other shortcomings. Moreover, only combined oral contraceptives have been studied. There are many other forms of hormonal contraception used commonly by women on which there is no literature delineating their effects on the voice. There is also no evidence comparing monophasic to triphasic oral contraceptives.

Most of the literature investigated sustained vowel production. One study evaluated a German lied while others evaluated various vowels or vowel combinations.[23] The formant frequencies of each vowel differ, which theoretically would affect the objective measures used to analyze the voice. No comparison has been made between the various vowels studied in the literature as they relate to hormonal contraception on the voice.

Only five of the studies assessed connected speech,[24] one of which measured both sustained vowels and connected speech.[25] While sustained vowels generally showed a stabilizing affect with OCPs, connected speech did not show a significant difference in most of the literature. However, a study by Meurer et al. using connected speech did show increased frequency variation and intensity in OCP users. The evidence prior to this study had shown the changes in the vocal folds induced by OCPs not to be sufficient to affect connected speech. However, this new evidence suggests that there might be hormone mediated changes in connected speech. The evidence more strongly supports that the sustained vowels in singing are affected by hormonal contraceptives.[26]

The phase of the menstrual cycle that was analyzed was not standardized in the literature. Some of the studies measured acoustic or aerodynamic criteria only during ovulation, while others evaluated hormone levels during one, two, or all three phases of the cycle.[27] The difference between hormone levels of a participant using an OCP versus placebo varies at different time points in the cycle. Ideally, the measurements should be compared during all three phases to compare the differences in hormone levels in OCP versus non-OCP users from phase to phase. The conclusions that have been drawn based on the effects of the hormones have likely been affected by this variable.

Most investigations have assessed nonprofessional voice users. Some did not list the voice experience of the participants, and few included participants who were classically trained singers. The ability of a singer to compensate for changes in the vocal folds and perform well despite being compromised physically is one of the differences between a good singer and a great singer. There may have been hormone induced changes that occurred in the vocal folds in some singers, but their ability to modify the vocal tract to compensate for the change may have obscured the results. A well designed study that compares singers of different calibers on and off of oral contraceptives would distill this possible confounding variable.

The parameters measured vary greatly in the literature. Most investigations used acoustic parameters, including vibrato rate, vibrato extent, signed deviation from pure octave, speaking fundamental frequency, speaking fundamental frequency standard deviation, mean fundamental frequency, jitter (frequency variation), shimmer (amplitude variation), noise-to-harmonic ratio, percentage of irregularity in the frequency of the vocal fold vibration, percentage of irregularity in the amplitude of the vocal fold vibration, dynamic range, mean speaking frequency, amplitude perturbation quotient, signal to noise ratio, sound pressure level, ratio of amplitude of first harmonic to second, ratio of amplitude of first harmonic to first formant, and abruptness of vocal fold closure.[28] Dysphonia severity index used in one study was determined from maximum phonation time, highest frequency, lowest intensity, jitter and shimmer. One study used a rating scale of the quality of the voice judged by speech language pathologists.[29] Only two studies used aerodynamic parameters for analysis including subglottal pressure magnitudes, laryngeal airway resistance, peak flow, minimum flow, and alternating flow.[30] Each parameter varies in its sensitivity to detect changes in the voice as does the particular software program that measures it.[31] The lack of standardization of the parameters used to evaluate the voice, as well as limitations in the sensitivity, validity, and reliability of acoustic and aerodynamic measures, limit the conclusions that can be drawn from the literature.

An example of the significant impact that the parameters measured may have on the conclusions of a study highlights the problem. Two studies by the same author evaluated blood serum concentration of sex hormones including estrogen, progesterone, and testosterone compared to specific acoustic voice parameters. These studies were expected to confirm prior findings that the variation in hormone concentrations should cause increased perturbation in acoustic parameters. However, it was unexpected to find that the variations in hormones were not reflected by pitch variability in participants using placebo. Conversely, those using OCPs had increased variability in intonation compared with placebo users only at the F_5 pitch, the area of the soprano *passaggio*. The vibrato rate was slowed in OCP users as well, but not vibrato extent. Since the other studies measured neither vibrato rate nor vibrato extent, the results may have been a unique effect of OCPs on those parameters. The tenuity of the *passaggio* at F_5 may have rendered it susceptible to disturbance by once the normal flow of hormones, or it might prove idiosyncratic to this investigation; further research is needed to confirm or refute the findings reported in this study. This study suggests that changes in the vocal folds related to OCPs generally do not affect the classically trained voice except for the delicate *passaggio* region in which the slightest hormone variations might affect pitch control.[32] The author also pointed out that it may be the interaction of sex hormones, including testosterone, rather than the hormones individually that contribute to vocal fold changes. The suppression of testosterone by OCPs may play a bigger role in vocal fold fluctuation than was previously thought.[33]

For many years, it was thought that drospirenone, the progestin component in fourth generation OCPs, would avoid the androgenic effects that occur with other progestin derivatives. Drospirenone has been shown to counteract weight gain in opposition to the fluid retention that estrogen induces.[34] Thus, it was theorized that drospirenone-containing oral contraceptive would cause less perturbation in acoustic parameters resulting in an improved voice. Amir was the first to determine that the difference in the type of progestin component of an OCP does not, in fact, have a beneficial affect on the voice compared to other progestin derivatives.[35]

The physical characteristics of the participants have not been given enough consideration in most published research. Abitbol astutely considered fat composition of the patients the effect of exogenous hormones. Estrogen production takes place in adipose cells. Thinner women have less adipose tissue producing estrogen than heavier women.[36] Although the patient weight mean and range were listed in many studies, there was no analysis of weight or BMI compared with the hormonal changes. The contribution of body composition to sensitivity to exogenous hormones remains largely unknown. The ages of the women included in these studies are largely in their early twenties. Davis showed that PMS symptoms were less frequent and severe in women older than 35 years compared with those reported by younger women.[37] One might suspect, therefore, that older singers are either not as sensitive to hormonal changes, or their voices at baseline have deepened, resulting in less noticeable hormonal affect. The hormonal changes that

occur later in life, especially peri- and postmenopausal, likely would affect the results and should be addressed in future research. Because Lã's studies of effects of OCPs included almost exclusively sopranos, conclusions drawn from the studies cannot necessarily be translated to singers of other *Fachs*.[38] There has been no investigation into the nuances of the mezzo soprano voice and the related susceptibility to hormonal changes.

The literature also has not yet included the contribution that auditory feedback plays in vocal acuity and control. A baseline audiogram was not measured in any of the studies; a hearing deficit could affect the ability to control the voice. PMS has been shown to cause sound hypersensitivity, hypersensitivity to a repetitive rhythmic pattern, vertigo, tinnitus, and recurring transient deafness. One study reported that some patients with "perfect pitch" lost that ability during the premenstrual period.[39] Compartmental fluid redistribution may contribute to the auditory symptoms related to PMS.[40] Estrogen receptors have been found in the inner ear, specifically the spiral ganglion type I cells, stria vascularis, and cochlear blood vessels.[41] Progesterone acts indirectly on the inner ear via steroid binding sites on GABA-A receptors in the auditory system.[42] These complex interactions were rarely mentioned and not included in analysis. Further research should include on consideration of the auditory and neurologic contributions to the voice and their hormone-related variations.

Oral contraceptive pills are sometimes prescribed off-label for other indications including polycystic ovarian syndrome (PCOS), endometriosis, and uterine leiomyoma.[43] Danazol, a drug historically used as a treatment for endometriosis, is not standard of care currently due to evidence of androgenic effects including pitch lowering. It is currently used for emergency contraception, but the effects on the voice for this indication have not been studied. Gestrinone, another drug used for emergency contraception, has been shown to cause subjective hoarseness when used for at least 6 months for the indication of endometriosis and uterine leiomyoma.[44] Oral contraceptives used for the purpose of emergency contraception likely would not show a perceptible difference in the voice given the short term use of the drug for this indication. One study showed no subjective voice change in users of the progestin, dienogest, to treat endometriosis.[45] No other investigations have been performed to evaluate the voice after treatment with low dose oral contraceptive therapy in these patient populations. It would be difficult to isolate the effects of oral contraception on the voice in patients with PCOS because the disease process, itself, can cause pitch lowering and instability.[46]

CONCLUSIONS

OCPs currently used today in the United States appear safe to administer to vocalists and likely stabilize the singing voice. The vast majority of the evidence demonstrates decreased pitch and volume variation with increased clarity of the singing voice with OCP use. There is little evidence to show a significant effect of hormonal contraception on speech. Testosterone may play a larger role in hormonally mediated voice changes than previously thought. However, multiple inconsistencies are present that weaken the evidence.

The literature has not addressed the effects of forms of hormonal contraception on the voice other than oral contraception such as intrauterine devices, patches, rings, and implants. Little evidence exists that compares different types of oral contraceptives. Many of the physical attributes of the singers were either not controlled or not factored into the analysis including *Fach*, vocal ability, age, and weight. Hormonal alterations of auditory feedback have not been assessed as they relate to contraception. With these deficiencies in mind, randomized, double blind, controlled trials with adequate statistical power should be encouraged to elucidate the full scope of their effects on the voice.

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Memory, hither come,
And tune your merry notes;
And, while upon the wind,
Your music floats,
I'll pore upon the stream,
Where sighing lovers dream,
And fish for fancies as they pass
Within the watery glass.

I'll drink of the clear stream,
And hear the linnet's song;
And there I'll lie and dream
The day along:
And, when night comes, I'll go
To places fit for woe,
Walking along the darken'd valley,
With silent Melancholy.

"Song: Memory, hither come,"
William Blake