THE EFFECTS OF A THIRD GENERATION COMBINED ORAL CONTRACEPTIVE PILL ON THE CLASSICAL SINGING VOICE

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Introduction

Few studies have assessed the effects of oral contraception on voice quality and no research has been carried out specifically concerning the singing voice. Previous reports concerning the effects of oral contraception on the speaking voice have suggested a predominance of adverse effects. Voice virilisation (i.e. changes in the deepness and steadiness of the vocal timbre, and frequent and rapid changes between voice registers) has been associated with the androgen-derived progestogens of some oral contraceptive pills (OCPs). Professional female voice users were advised in the 1980s to avoid the intake of OCPs, and those who were taking

an OCP were advised to have regular phoniatric examinations.[1-5] This was because testosterone and other androgenic substances have adverse effects on the female singing voice, altering the length and extensibility of the connective tissue of the vocal folds and the vocal ligaments that allow the production of different registers during voice production.[6-7]

More recent third generation OCPs have been found not to induce such negative effects on the speaking vocal mechanism of healthy women. Monophasic OCPs with low dosages of synthetic hormones were found to improve the voice quality of a group of healthy female speakers, in comparison with the voice quality of a group of healthy female speakers who were not using an OCP.[8-11] However, these were participants in a non-blinded and non-randomised comparative trial between two groups of different people, and this kind of clinical trial carries unavoidable risk of bias and of type 2 error (i.e. error caused by chance differences between the two groups, for example the possibility that all of the women in the OCP group might have better vocal habits than those in the placebo group). The possibilities of type 2 error can be minimised by a trial design with a cross over between subjects and random allocation to placebo and OCP.[12] Additionally, hormonal concentrations were not measured in this study and correlation with vocal parameters was therefore not assessed. Finally, these findings cannot be extrapolated to the singing voice, because the singing voice involves a much more consciously controlled use of the vocal mechanism than the speaking voice.[13]

The equilibrium within the female registers is delicate, and more demanding compared to the speaking voice.[14] It involves a complicated balance between the two major antagonist muscles: the thyroarytenoid (that increases the tonus and contraction of the vocal folds) and the crycoarytenoid (that causes the stretching of the vocal folds), controlled by aerodynamic forces.[15] Therefore, any alterations in the mass and extensibility of the vocal ligaments involved in voice production that might happen during the menstrual cycle and OCP use may lead to dramatic effects on the singer's performance.

We report the first double blind randomised placebo controlled cross-over trial (RCT) to study the impact of a novel drospirenone containing OCP on the regularity of the pattern of vibration of the vocal folds of semi-professional Western classical singers during the performance of a German classical song (Lied). Measures of reproductive hormones and the patterns of vibration of the vocal folds were carried out during three specified phases of the menstrual cycle: menstrual, follicular and luteal phases.

Methods

Seventeen female singers were recruited to participate in this experiment. Ethics Committee approval was obtained from South Sheffield Ethics Committee. Each volunteer was seen initially by a consultant gynaecologist (W.L.). In these medical consultations, details of the experimental trial were discussed, ensuring that each participant was aware that for the duration of the study, non-hormonal contraception should be used. An individual medical examination was performed to assess each participant's suitability for the use of a combined oral contraceptive pill (OCP). At the end of the meeting, identical, numbered packs of OCP and placebo were given to each singer, with the explanation of how they were to be taken and when the course was to be started. A provisional calendar was made according to each participant's menstrual cycle in order to determine approximately when the first recording should be carried out. All participants reported having regular menstrual cycles.

Only 9 of these singers managed to complete the whole experiment: six withdrew before the first recording session; two only completed half of the experiment because the recording equipment used failed during the second session.

Therefore, we completed data collection for 9 young healthy semi-professional western classical singers (mean age = 23.10 years, SD = 2.183; range = 21 to 27 years old) during the RCT study. They were all final year or post-graduate singing students at several music colleges in the U.K. who had had singing lessons for more than 3 consecutive years, all were

currently having regular singing lessons, and were accepting professional singing engagements. One singer was a mezzo-soprano, and the others were all classified as sopranos. These were all volunteers who had regular menstrual cycles of 20-26 days, were non-smokers and had never been pregnant.

Volunteers were asked to take Yasmin® (a combined monophasic oral contraceptive pill containing 30µg of synthetic oestrogen - ethinylestradiol and 3 mg of synthetic progesterone - drospirenone) and the matched placebo, each during three consecutive menstrual cycles with half of the group randomised to placebo and the other half to Yasmin®. The placebo and Yasmin® were given in randomised order such that neither the researchers nor the participants would know which would come first. Yasmin® and its matched placebo were randomly allocated into identical boxes by the Pharmacy Services Director of the Royal Hallamshire Hospital in Sheffield, for the purposes of this study. Therefore, the researchers were not included in the preparation or dispensing of medication. A total of six blood samples and audio-recordings were collected for each participant during three specific phases of the menstrual cycle: at menstruation and during the follicular and luteal phases of the menstrual cycle. This was done for the third cycle using Yasmin® and for the third cycle using the matched placebo.

Blood samples were taken to measure concentrations of steroid hormones and gonadotropins for all phases of the menstrual cycle. Concentrations of SHBG were measured in the early follicular phase of the menstrual cycle. SHBG concentrations do not vary during the menstrual cycle, thus a single measurement in the earlier follicular phase is sufficient to define SHBG concentration for the placebo and OCP cycles, and to allow calculations of FAI for the studied phases of the menstrual cycle.[16] Blood samples were analysed using: (i) the IMMULITE® analyzer for *in vitro* quantitative measurement of oestradiol, progesterone and sex hormone binding globulin (SHBG) in serum; (ii) the ADVIA Centaur™ System for *in*

vitro quantitative measurement of total testosterone (bound and unbound) in serum, and the quantitative determination of FSH and LH in human serum.

All audio-acoustic-recordings used the same recording equipment: MBNM550E-L microphone; microphone preamplifier Alice MIC•AMP•PAK 1^{TM}; two channel stereo digital audio tape-recorder (DAT) Sony TCD-D7; portable electrolaryngograph which uses two neck electrodes held in place by an elastic neck band. A portable oscilloscope was used to view the output to ensure appropriate electrode placement. The electrolaryngograph was particularly chosen for this study because this is a non-invasive device that allows the study of the vibratory pattern of the vocal folds and can cope with large amounts of data such as those produced during the performance of a Lied.[17]

The electrolaryngograph data were analyzed using the laryngograph PCLX software (Spead and Qanalysis), which enables the display, analysis and printout of the laryngograph waveforms and respective derived percentages of irregularity of frequency (CFx = period-to-period variations in frequency peaks) and amplitude (CAx = period-to-period variations in amplitude peaks) of vibration of the vocal folds. These parameters analyze the crucial phenomenon for voice production, i.e. vocal fold vibration pattern.[18-19]

CFx constitutes a direct method of obtaining a quantitative assessment of pitch variability in a sample of running speech or in a song because it determines the standard deviation of the spread of cycle to cycle differences in regard to periods or frequencies. By plotting successive fundamental frequencies (Fx) and ignoring variations which are part of the normal patterning of vocal fold frequency change in running speech or in a song, a diagram is obtained for which the width of the central core is a measure of vocal fold irregularity, expressed as a percentage. Using a similar measure of irregularity to that employed for CFx, CAx provides a means of assessment of irregularity in the amplitude peaks in the cycle to cycle excitation of the vocal tract; therefore, it is used as a measure of perceived voice hoarseness.[20-24]

Sample size calculations were based on a two sided paired samples t-test. As this was a novel study with no previous data to use as a guide, our sample size calculations were based upon an large anticipated effect size (δ=1.00). This size effect was chosen to be at a level for which changes in vocal quality would be perceived by the singer.

Non parametric paired sample hypothesis tests (Wilcoxon sign rank test, and Sign rank test) were performed to compare the effects of placebo and OCP use on both hormonal and vocal variations for the three phases of the menstrual cycle. The tests were performed at a significance level of α = 5 percent.

Results

We present results of blinded analyses and ELG recordings for the 9 subjects in the menstrual, follicular and luteal phases of the menstrual cycle. After the analysis, it was revealed that five subjects took the placebo during the first arm of the study, and four were taking Yasmin®.

Table 1 shows the means and standard deviations for hormonal concentrations, percentage of irregularity in the frequency of vibration of the vocal folds (CFx) and percentage of irregularity in the amplitude of vibration of the vocal folds (CAx), during the menstrual phase of the menstrual cycle, for both placebo and OCP use, and the results of the non parametric paired sample hypothesis tests.

(Insert Table 1 about here)

Vocal measurements showed no significant differences in CFx percentages between placebo and OCP use for this phase of the menstrual cycle. However, significant differences were found for CAx percentages. Irregularity in the period-to-period amplitude peaks was significantly lower [z = -2.192; p = 0.028] during OCP use for this phase of the menstrual cycle.

Concentrations of oestradiol and progesterone were significantly lower for OCP use when compared with placebo use for this phase of the menstrual cycle, [z = -2.073; p = 0.038] and [z = -2.033; p = 0.042], respectively. A similar result was obtained for concentrations of follicular-stimulating-hormone (FSH) [z = -2.192; p = 0.028], and testosterone [z = -2.429; p = 0.015]. No significant differences were found in concentrations of luteinising hormone (LH). Concentrations of SHBG were significantly higher for OCP use when compared with placebo use, and FAI was significantly lower during OCP use for this phase of the menstrual cycle.

Table 2 shows the means and standard deviations for hormonal concentrations, CFx and CAx during the follicular phase of the menstrual cycle, for both placebo and OCP use, and the results of the non parametric paired sample hypothesis tests.

(Insert Table 2 about here)

For this phase of the menstrual cycle, no significant differences were found between placebo and OCP use for CFx percentages. However, differences were found for CAx [p = 0.039] between placebo and OCP use for this phase of the menstrual cycle; CAx values were significantly lower during OCP use.

Significant differences were found for concentrations of LH [z = -2.073; p = 0.038], FSH [z = -2.312; p = 0.021], testosterone [z = -2.386; p = 0.017] and FAI [p=0.004] in the follicular phase of the menstrual cycle. Concentrations of these hormones and FAI were significantly lower during OCP use. Differences between placebo and OCP use were also found for concentration of progesterone [z = -2.312; p = 0.021], which was significantly higher during OCP use. Significant differences between OCP use and matched placebo could not be found for the concentration of oestradiol.

Table 3 shows the means and standard deviations for hormonal concentrations, CFx and CAx during the luteal phase of the menstrual cycle, for both placebo and OCP use, and the results of the non parametric paired sample hypothesis tests.

(Insert Table 3 about here)

No significant results were found for this phase of the menstrual cycle concerning CFx and CAx percentages.

For this phase of the menstrual cycle, significant differences between placebo and OCP use were found for concentrations of oestradiol [z = -2.547; p = 0.011], progesterone [z = -2.666; p = 0.008], LH [z = -2.666; p = 0.008], FSH [z = -2.666; p = 0.008] and FAI [p=0.039]. Concentrations of these hormones and FAI were significantly lower during OCP use. Significant differences were not found between placebo and OCP use regarding concentrations of total testosterone.

Discussion

In summary, it seems that this study supports previous studies suggesting the existence of vocal problems associated with the menstrual cycle.[25-28] The results of this study show that irregularity in the period-to-period amplitude peaks during vocal fold vibration was significantly higher during placebo use, for both menstrual and follicular phases of the menstrual cycle, and reduced during Yasmin® use.

During the menstrual phase of the menstrual cycle, Yasmin® use showed a significant decrease in concentrations of oestradiol, progesterone, testosterone and FSH. During the follicular phase of the menstrual cycle, Yasmin® use showed a significant decrease in concentrations of testosterone, FSH and LH. During the luteal phase of the menstrual cycle no differences between Yasmin® and placebo use were found concerning the vocal parameters analysed but concentrations of oestradiol, progesterone, LH and FSH were significantly

lower when using Yasmin®. No differences between placebo and Yasmin® use were found for vocal irregularity in period-to-period frequency peaks during the whole menstrual phase.

Irregular cycle-by-cycle amplitude peaks during vocal folds vibration have been related to hoarseness in the speaking voice.[29] Applied to the operatic female voice, higher values of CAx might lead to a 'less focussed voice'. A 'less focussed' voice might be a consequence of two phenomena:

(i) insufficient *appoggio* (i.e. *"a form of breath-management coordination that must be learned if the singer is to unite energy and freedom for successfully meeting the tasks of professional vocalism"*).[30] *Appoggio* is controlled by diaphragmatic, abdominal and intercostal muscles, so it might be jeopardised in a situation such as menstruation, when abdominal cramps are common.[31-] When using an OCP this menstrual symptom is reduced.[32] This might explain the fact that Yasmin® use was associated with lower CAx values during the menstrual phase of the menstrual cycle.

(ii) swelling of the mucosa of the vocal folds. When the vocal folds are swollen, there is asymmetry in their vibration, causing greater irregularity in the amplitude of vibration. [33] This might explain higher CAx values during both menstrual and follicular phases of the menstrual cycle.

Amir & Kishon-Rabin (2004) suggested that concentrations of oestrogens are responsible for a hypertrophic effect on the cells of the vocal mucosa, whereas concentrations of progesterone cause a thickening of the mucosal secretions, and these phenomena account for an increase of vocal irregularity.[11] The highest concentrations of oestradiol and progesterone were found during the luteal phase of the natural menstrual cycle in the current research; however, during this RCT, vocal differences were found between placebo and OCP use only during menstruation and the follicular phase of the menstrual cycle and not during the luteal phase of the cycle. This suggests that vocal changes were unlikely to result from fluctuations in concentrations of oestradiol and progesterone since if this was the case then the pattern of

electrolaryngographic changes would have been different. Rather a new hypothesis emerges: changes in the pattern of vibration of the vocal folds during singing associated with the menstrual cycle might not be related to variations in the concentrations of oestradiol and progesterone, but connected with changes in the concentrations of testosterone.

Comparing measurements of hormonal concentrations between placebo and OCP arms of the study, total testosterone was the only hormone found to show significant differences in concentration for both menstrual and follicular phases, with no differences in the luteal phase. FAI was significantly different between placebo and OCP use for all phases of the menstrual cycle. However, differences in FAI between placebo and OCP use were greater for the menstrual and follicular phases of the menstrual cycle, and smaller for the luteal phase of the menstrual cycle. Therefore, it seems logical to hypothesise that alteration in free testosterone concentration might participate in the mechanism of the observed vocal changes seen between placebo and OCP use during the menstrual cycle. The relatively large differences in concentration of free testosterone (observed by comparing FAI between placebo and OCP use during the menstrual and follicular phases) might be expected to cause significant physiological changes in the vocal folds so that the amplitude of vibration of the vocal folds changes. On the other hand, smaller differences in concentrations of free testosterone (observed by comparing FAI between placebo and OCP use during the luteal phase) seem to have caused less significant changes in the vocal folds, so that vocal measurements were not significantly different between placebo and OCP use. It is likely that the vocal folds are sensitive to large variations in the concentrations of free testosterone, acting in a classical receptor-binding pathway to activate second intracellular messengers and mediate genomic effects on protein and carbohydrate metabolism.[34-35] Women seem to be more susceptible to variations in laryngeal mucosa caused by testosterone than men despite the fact that concentrations of testosterone are much higher in men compared to women, because the percentage of cells that constitute the male laryngeal mucosa tend to remain constant through

the whole month, whereas the cells of the female laryngeal mucosa change during the menstrual cycle.[36]

Elevated concentrations of free testosterone have been associated with an increase in water retention in the mucosa of the vocal folds[6] explaining the higher vocal fold irregularity during menstrual and follicular phases of the menstrual cycle. When using Yasmin®, concentrations of free testosterone were significantly lower in these phases of the cycle. Additionally, Yasmin® has been shown to have antiandrogenic and antimineralocorticoid properties, with a diuretic effect causing small decreases in the sodium and water retention due to the pharmacological properties of its progestogen - drospirenone [37-41]. This effect will have reached a steady state after three months of use, the time at which assessments were made.[42] Antiandrogenic and antimineralocorticoid effects may act synergistically to minimise the fluctuations in body water seen in the natural menstrual cycle, and account for the observed reduction in vocal fold irregularity. Although the mechanism of voice production is never perfect, reduction in the pattern of vibration of the vocal folds can result in a less erratic voice,[43] which seems to occur when using Yasmin®.

Conclusions

These data suggest that Yasmin® can be prescribed to highly trained female singers as a contraceptive method without fearing negative effects on voice production. Due to the antiandrogenic and antimineralocorticoid properties of drospirenone, vocal changes associated with hormonal variations during the menstrual cycle were reduced.

Additionally, by lowering concentrations of testosterone, Yasmin® seems to stabilise the regularity in the pattern of vibration of the vocal folds. The use of Yasmin® seems to create greater regularity in the pattern of vibration of the vocal folds during the highly demanding vocal mechanism of Western classical singing.

In conclusion, this study suggests that highly trained singers might benefit from the use of this OCP, potentially avoiding the complaints of vocal distress associated with the menstrual cycle reported in previous research. The use of Yasmin® decreases vocal irregularity during the menstrual cycle, thus singers might not need to refrain from singing during menstrual phases of the menstrual cycle, as they have been advised to do by phoniatricians and laryngologists.

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