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Different oral contraceptives and voice quality — an observational study

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Abstract

The classical literature on endocrine effect on voice considers oral contraceptives (OCs) as a risk factor for voice. However, recent studies revealed no adverse effect of new-generation OCs on voice. It was also suggested that OCs could improve specific voice characteristics via different mechanisms. The aim of the present study was to evaluate the effect of OCs on voices of women who use different formulations containing drospirenone ($n=10$), desogestrel ($n=9$) and gestodene ($n=10$). Acoustic voice measures of the 29 women were evaluated twice during the menstrual cycle. Fundamental frequency, frequency as well as amplitude stability and noise characteristics were measured using a computerized voice analysis program. Results indicated that vocal stability and quality were similar in the three groups tested. Marginal differences were observed between the drospirenone group and the other two groups. This preliminary observational study indicates that although drospirenone was previously shown to reduce water retention, this effect was not found to directly influence voice characteristics of women who use OCs.

Keywords: Oral contraceptives; Drospirenone; Desogestrel; Gestodene; Voice

1. Introduction

Ovarian hormones have been shown to affect the human larynx and, specifically, the vocal folds. This relationship has been established by cytological smears of the vocal fold epithelium in conjunction with cervical smears [1] as well as by discoveries of hormonal receptors in the vocal fold mucosa and epithelium [2,3]. These findings support clinical reports on vocal changes associated with endocrine dysfunction [1,3,4]. In this context, the effect of oral contraceptives (OCs) on voice was previously evaluated among women in their reproductive years. The classical literature on endocrine effect on voice considered OCs as a risk factor. This was attributed to the potential androgenic virilization effect caused by the relatively high dosage of hormones and androgenic metabolites of old-generation progestins [2,4,5]. However, studies conducted more recently have found no evidence for an adverse effect on voice among women who use OCs. This was first demonstrated based on subjective perceptual evaluation of voice [5] and subsequently substantiated based on a series of studies that used acoustic analyses of voice quality [6–8]. Furthermore, it was suggested that specific low-dose formulations might *improve* vocal quality by eliminating abrupt fluctuations in hormonal levels throughout the menstrual cycle, by maintaining lower hormonal levels and due to the lower androgenic influence of the new progestin metabolites [9].

Since new-generation OCs were shown to have no adverse effect on voice, the question remains whether specific formulations might have a more favorable effect on voice. In light of the similarities between the genital tract and the larynx and in order to improve care for OC users, we were interested to learn whether women who use different new-generation OCs would exhibit different voice characteristics. Because new-generation OCs contain similar doses of ethinylestradiol (20–30 μg), OCs were arranged, in the present study, based on their progestin content (drospirenone, desogestrel and gestodene). We assumed that because desogestrel and gestodene are nortestosterone derivatives, their impact on voice would be similar. In contrast, drospirenone, which is a spironolactone derivative, might

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affect voice differently. To test this hypothesis, computerized acoustic analyses of voice were performed. This paradigm was previously demonstrated as sensitive for demonstrating and quantifying fine vocal changes under various conditions [10] and, specifically, in association with hormonal fluctuations [8,11].

2. Materials and methods

Twenty-nine women who use OCs were recruited from a group of 60 women who agreed to participate in this study. After obtaining an approval from our institutional review board and a verbal and written consent from all participants, an initial screening was conducted. Only women who reported using OCs regularly for more than 3 months were selected for inclusion in the study. Exclusion criteria consisted of the following: (a) remarkable medical history; (b) reported illness at the time of the study; (c) history of intubations or surgery; (d) hormonal imbalance; (e) smoking or substance abuse; (f) gastroesophageal reflux; (g) pregnancy or breast-feeding over the preceding 6 months; and (h) neurological problems. All selected women reported regular menses and menstrual cycles in addition to having no history of formal singing or voice training. All women were aware of the content of their pills, and all reported no omission in pill taking during the preceding 3 months.

The selected 29 women were divided into three groups based on the progestin content of their OCs. Ten women used OCs containing 3.0 mg of drospirenone and 30 μg of ethinylestradiol (drospirenone group). Mean age for this group was 25.3 years (range, 20–34), mean weight was 55.7 kg (range, 46–70) and mean height was 162.8 cm (range, 153–169). Nine women used OCs containing 150 μg of desogestrel and 20 or 30 μg of ethinylestradiol (desogestrel group). Mean age for this group was 25.3 years (range, 23–30), mean weight was 56.3 kg (range, 50–66) and mean height was 165.0 cm (range, 158–168). Ten women used OCs containing 75 μg of gestodene and 20 or 30 μg of ethinylestradiol (gestodene group). Mean age for this group was 24.8 years (range, 22–30), mean weight was 55.7 kg (range, 45–70) and mean height was 165.7 cm (range, 158–175). In general, physical characteristics (height, weight and body mass) are not viewed as confounding factors for an individual speaker's voice quality [12]. Nonetheless, to avoid possible bias of the results, which could be attributed to physical characteristics, separate analyses of variance were used to evaluate weight, height and age differences among the three groups. No significant differences were found among the three groups for weight, height or age.

All women were recorded twice over a single menstrual cycle. One recording was performed between the 10th and 17th days of pill intake, when hormonal levels reach a steady state [13]. The other recording was performed during the first 3 days of menses, when no pills are taken and hormonal levels are minimized after withdrawal of hormones, considering their half-life times ($t_{1/2}$) [13]. The decision to perform two recordings instead of multiple recordings was based on the results of previous studies that used acoustic analyses [6–8]. These studies have shown that performing multiple recordings throughout the menstrual cycle did not contribute to revealing group differences when performing computerized acoustic analyses of voice. Prior to each recording session, every woman was asked, again, about changes in her medical status and about pill omission. Only women who reported no illness and no pill omission at the time of the recordings were included in the study.

During each individual session, participants were recorded while producing the Hebrew vowels /a/ (as in "f*a*ther"), /i/ (as in "h*ee*d") and /u/ (as in "b*oo*t") in isolation, twice for 5 seconds, in a random order. The three vowels were selected because they represent distinct articulatory gestures in many languages [14,15] as well as in Hebrew [16] and because they are commonly used for evaluation of vocal quality in clinical and experimental settings. For the recordings, each participant was seated in a quiet room. A Sony (Tokyo, Japan) ECM-T150 headset microphone was attached approximately 6 cm from each participant's mouth. The recorded signal was directed to a Sony TCD-D100 digital audio tape recorder, with a sampling rate of 44.1 kHz, and stored onto TDK (Tokyo, Japan) DC4-90R digital data cartridges. Following recording, each individual vowel was fed independently to a Multi-Dimensional Voice Program (Model 5105, Ver. 2, Kay Elemetrics, Lincoln Park, NJ), with a sampling rate of 50 kHz.

Four acoustic parameters were measured from each vowel: (a) mean fundamental frequency (mF0): (b) jitter; (c) shimmer; and (d) noise-to-harmonic ratio (NHR). These parameters are commonly used for evaluation of acoustic correlates of vocal quality [12,14] and have been described in detail previously [7,14]. In essence, mF0 represents the number of vocal cycles produced by the vocal folds per second (in hertz). Lower mF0 values were found in association with increased androgens [2,4]. Jitter quantifies the amount of *frequency* perturbation (in percent) in the voice signal, shimmer quantifies the amount of *amplitude* perturbation (in percent) in the voice signal and NHR calculates an average ratio of the inharmonic spectral energy in the frequency range 1500–4500 Hz to the harmonic spectral energy in the frequency range 70–4500 Hz. Lower values of jitter, shimmer and NHR are associated with a healthier voice, whereas higher values are clinically associated with a disordered and less stable voice [14,17].

Data were statistically analyzed using SPSS for Windows 11.5.1 (SPSS Inc., Chicago, Ill). After verification of normality of distribution of all variables, separate multivariate analyses of variance with repeated measures, for each acoustic measure, were performed. In these analyses, vowel (/a/, /i/ and /u/) and pill intake phase (on and off)

Table 1
Values of mean fundamental frequency, jitter, shimmer and NHR of the three OC groups for the vowels /a/, /i/ and /u/ at the on and off pill intake phases

Vowel	Parameter	Group					
		Drospirenone		Desogestrel		Gestodene	
		On	Off	On	Off	On	Off
/a/	mF0 (Hz)	212.34±15.66	209.55±16.04	219.83±20.59	219.86±18.45	205.08±20.03	209.61±23.48
	Jitter (%)	1.39±0.48	1.34±0.84	1.14±0.54	0.98±0.44	0.98±0.43	0.91±0.26
	Shimmer (%)	3.57±0.87	3.56±0.99	3.16±0.80	2.90±0.77	3.28±0.88	3.16±1.05
	NHR	0.13±0.02	0.13±0.02	0.12±0.01	0.12±0.01	0.12±0.01	0.12±0.01
/i/	mF0 (Hz)	217.39±17.91	212.39±15.73	225.03±22.23	225.19±19.54	210.57±19.60	214.93±22.74
	Jitter (%)	1.43±0.49	1.50±0.72	1.20±0.58	1.14±0.60	1.14±0.46	1.18±0.62
	Shimmer (%)	2.32±0.66	2.42±0.76	2.24±0.60	2.18±0.44	2.24±0.70	2.12±0.65
	NHR	0.12±0.01	0.12±0.02	0.11±0.02	0.11±0.01	0.12±0.03	0.11±0.01
/u/	mF0 (Hz)	219.99±18.06	215.10±17.17	224.15±23.08	226.85±20.73	209.78±18.44	214.50±21.52
	Jitter (%)	1.33±0.53	1.53±0.75	1.23±0.42	0.98±0.27	1.13±0.36	1.11±0.46
	Shimmer (%)	2.12±0.68	2.50±1.15	2.42±1.03	1.84±0.44	1.92±0.87	1.66±0.44
	NHR	0.11±0.03	0.11±0.02	0.11±0.02	0.10±0.02	0.11±0.02	0.11±0.01

Values are given as mean±SD.

were treated as repeated factors, whereas grouping (drospirenone, desogestrel and gestodene) was treated as the between-subject factor.

3. Results

Group means were obtained for each acoustic measure at different phases and vowels. These data are presented in Table 1.

Statistical analyses revealed no significant differences among the three groups for any of the acoustic measures. Nevertheless, marginal group differences were observed for the jitter parameter ($F_{2,26}$=2.80; p=.08). Specifically, post hoc analysis revealed that women in the drospirenone group exhibited higher frequency perturbation (lower stability) than the other two OC groups (1.39 vs. 1.19 and 1.08 in the on phase and 1.45 vs. 1.03 and 1.07 in the off phase for the drospirenone, desogestrel and gestodene groups, respectively). These grand mean group differences are illustrated in Fig. 1. Furthermore, the Levene test of equality of error variances demonstrated greater variability within the drospirenone group in comparison with the gestodene group for the jitter measure (p<.05).

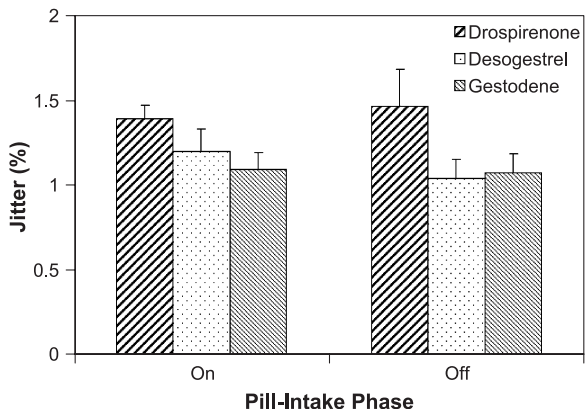

Fig. 1. Mean and SE bars for jitter across the two pill intake phases for the three OC groups.

No significant differences were found between the two pill intake phases (on vs. off) for any of the acoustic measures. As expected, significantly higher values were obtained for the vowel /i/, in comparison with the vowels /a/ and /u/ for mF0 ($F_{1,26}$=26.99; p<.001), shimmer ($F_{1,26}$=101.24; p<.001) and NHR ($F_{1,26}$=33.14; p<.001). These differences are in keeping with established data on Hebrew [16] and other languages [14], thus supporting the validity of the current results. No significant interaction was found between group and vowel or phase for any of the acoustic measures.

4. Discussion

Previous studies have shown that new-generation low-dose OCs, which consist of new progesterones, do not adversely affect voice [5–8]. It was suggested that the new progestins in the combined pills, which were specifically developed to reduce androgenic symptoms [18], also have a favorable effect on the female voice mechanism and, specifically, on the vocal folds [9]. Following this line of research, the present study evaluated voices of women who used different formulations of OCs. The current findings revealed no significant voice differences among users of different new-generation low-dose OCs.

All OCs in the present study contained 20 or 30 μg of ethinylestradiol. These amounts are regarded as low doses and are not expected to manifest any clinical difference. In contrast, the three groups (drospirenone, desogestrel and gestodene) differed in their progesterone content. Most of the progesterones used for OCs (e.g., desogestrel, gestodene) are 19-nortestosterone derivatives, all of which display a residual androgenic effect [19–21]. Clinically, however, this effect is seldom evident since the contraceptive effect requires a low dose. The new progestogens were shown to significantly reduce androgenic side effects through decreas-

ing the levels of total and free androgens, androgen properties and androgen precursors as well as of peripheral androgen activity [19–21]. The new progestin, drospirenone, is derived from 17-alpha-spironolactone instead of from testosterone. Like spironolactone, it has antimineralocorticoid (sodium-excreting) as well as antiandrogenic properties [22,23]. Drospirenone is viewed as more similar to endogenous progesterone because it blocks binding of testosterone to androgen receptors. Clinically, drospirenone was associated with reduced water retention, thus improving weight stability [22–31]. It was also shown to have a favorable effect on facial acne [22] and to reduce incidence and severity of somatic symptoms associated with the menstrual cycle [31–33].

Based on the unique characteristics of drospirenone, we were interested to learn whether these features would be manifested in improved voice characteristics of women who use drospirenone. Our results, however, did not reveal significant group differences in voice measures among the three OC groups. Moreover, the drospirenone group exhibited frequency perturbation values (jitter) that were higher than those of the other two groups. Nonetheless, these group differences were only marginally significant and all values were within normal range, implying no clinical impact on voice quality.

Voice quality is directly affected by water absorption and edema in the vocal fold mucosa [2]. Thus, we assumed that drospirenone would have a favorable effect on voice quality through its contribution to edema reduction. Apparently, however, within the context of the present study, no advantage was found for any of the progestins over the others in relation to their effect on vocal fold tissue and on voice quality. This lack of group difference was consistent despite the fact that the present study increased sample size significantly ($n=29$) in comparison with former studies that demonstrated the effect of OCs on voice ($n=10$–14) [6–8]. It was previously suggested that sex hormones could affect the vocal folds through two alternative mechanisms: (a) modifying water retention in the vocal fold tissue, specifically in the Reinke's space and in the mucosa [2,11] and (b) changing laryngeal neuromotor control through afferent and efferent processes [34]. Our data did not demonstrate improved vocal characteristics for the drospirenone users. Hence, it appears that among OC users, changes in water retention at the level of the vocal folds are not a clinically significant factor in relation to voice. The effects of the different progestins on laryngeal neuromotor control were not tested in the present study, further research is thus warranted before a more definite conclusion can be drawn on the mechanism underlying the effect of sex hormones on the vocal folds. Nevertheless, based on the present findings, no formulation of OCs could be considered superior over the others in relation to voice quality.

The present study did not identify differences in voice quality between the two pill intake phases during the menstrual cycle (on vs. off). This result is in accordance with previous reports. During the menstrual cycle, hormonal influence on the vocal folds is dependent on *fluctuations* of hormonal levels [2,9], at which times vocal changes might be observed. The present study evaluated voice during the hormonal steady states (after 10 days of taking the pill) and after hormonal withdrawal has been completed (during the first days of menses). These periods were selected to maximize differences between the on and off conditions. In addition, this methodological decision was based on previous studies that did not reveal a consistent menstrual cycle effect on acoustic voice parameters among young and healthy women who use OCs [6–8]. Therefore, lack of significant pill intake phase effect on voice could be expected.

This preliminary observational study provides evidence that different new-generation low-dose OCs have similar effects on voices of women. No specific progestin was found to be preferable in its effect on voice. Recent studies have indicated that OCs do not have an adverse effect on voice quality. It was also shown that several acoustic features were even improved among women who use OCs. It seems, then, that although modern OCs should no longer be considered a risk factor for voice, there is no evidence that any of the formulations tested induced a more favorable effect on voice. Although, clinically, this information is relevant to all pill users, it might be specifically pertinent for voice professionals who are more sensitive and aware of their voice quality and performance and who use their voice more intensively. Due to the preliminary nature of this study, our participants had no voice or singing training. Hence, it would be interesting to extend this study to voice professionals and to evaluate laryngeal activity using acoustic as well as direct laryngeal examinations. Finally, this line of research could provide additional information on the effect of menstrual cycle and sex hormones on voice. It would be interesting, then, to extend the present study, using a greater number of participants, to a wider selection of OCs and other hormonal agents in different medical conditions.

References

[1] Abitbol J, de Brux J, Millot G, et al. Does a hormonal vocal cord cycle exist in women? Study of vocal premenstrual syndrome in voice performers by videostroboscopy–glotography and cytology on 38 women. J Voice 1989;2:157–62.

[2] Abitbol J, Abitbol P, Abitbol B. Sex hormones and the female voice. J Voice 1999;13:424–46.

[3] Newman SR, Bulter J, Hammond EH, Gray SD. Preliminary report on hormone receptors in the human vocal fold. J Voice 2000;14:72–81.

[4] Sataloff RT, Emerich KA, Hoover CA. Endocrine dysfunction. In: Sataloff RT, editor. Professional voice: the science and art of clinical care. 2nd ed. San Diego: Singular Publishing Group Inc; 1997. p. 291–7.

[5] Wendler J, Siegert C, Schelhorn P, et al. The influence of Microgunon® and Diane-35®, two sub-fifty ovulation inhibitors on voice function in women. Contraception 1995;52:343–8.

[6] Amir O, Kishon-Rabin L, Muchnik C. The effect of oral-contraceptives on voice: preliminary observations. J Voice 2002;16:267–73.

[7] Amir O, Biron-Shental T, Muchnik C, Kishon-Rabin L. Do oral contraceptives improve vocal quality? Limited trial on low-dose formulations. Obstet Gynecol 2003;101:773–7.
[8] Amir O, Kishon-Rabin L. Association between birth control pills and voice quality. Laryngoscope 2004;114:1021–6.
[9] Amir O, Biron-Shental T. The impact of hormonal fluctuations on female vocal folds. Curr Opin Otolaryngol Head Neck Surg 2004;12: 180–4.
[10] Borden GJ, Harris KS, Raphael LJ. Speech science primer: physiology, acoustics, and perception of speech. 3rd ed. Baltimore: Williams & Wilkins; 1994.
[11] Chae SW, Choi G, Kang HJ, et al. Clinical analysis of voice changes as a parameter of premenstrual syndrome. J Voice 2001;15:278–83.
[12] Campisi P, Tewfik TL, Manoukian JJ, Schloss MD, Peland-Blais E, Sadeghi N. Computer-assisted voice analysis: establishing a pediatric database. Arch Otolaryngol Head Neck Surg 2002;128:156–60.
[13] Kaplan B. Desogestrel, norgestimate, and gestodene: the newer progestins. Ann Pharmacother 1995;29:736–42.
[14] Baken RJ. Clinical measurement of speech and voice. 2nd ed. London (UK): Singular Pub; 1997. p. 95–197.
[15] Ladefoged P. A course in phonetics. 2nd ed. San Diego: Harcourt Brace Jovanovich; 1982. p. 165–96.
[16] Most T, Amir O, Tobin Y. The Hebrew vowel system: raw and normalized data. Lang Speech 2000;43:295–308.
[17] Kay Elemetrics Corp. Multi-Dimensional Voice Program (MDVP) model 5105, ver. 2: software instruction manual. Lincoln Park (NJ): Kay Elemetrics Corp.; 1999.
[18] Apgar BS, Greenberg G. Using progestins in clinical practice. Am Fam Physician 2000;62:1839–46.
[19] Stone SC. Desogestrel. Clin Obstet Gynecol 1995;38:821–8.
[20] Kuhl H, Jung-Hoffmann C, Wiegratz I. Gestodene-containing contraceptives. Clin Obstet Gynecol 1995;38:829–40.
[21] Collins D. Selectivity information on desogestrel. Am J Obstet Gynecol 1993;168:1006–10.
[22] Mansour D. Experiences with Yasmin: the acceptability of a novel oral contraceptive and its effect on well-being. Eur J Contracept Reprod Health Care 2002;7(Suppl 3):35–41.
[23] Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception 2000;62:29–38.
[24] Mansour D. Yasmin — a new oral contraceptive, a new progestogen: the reasons why. Eur J Contracept Reprod Health Care 2000; 5(Suppl 3):9–16.
[25] Parsey KS, Pong A. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. Contraception 2000;61:105–11.
[26] Kaunitz AM. Enhancing oral contraceptive success: the potential of new formulations. Am J Obstet Gynecol 2004;190:S23–9.
[27] Muhn P, Krattenmacher R, Beier S, et al. Drospiridone: a novel progestogen with antimineralocorticoid and antiandrogenic activity. Contraception 1995;51:99–110.
[28] Fuhrmann U, Krattenmacher R, Slater EP, et al. The novel progestin drospirenone and its natural counterpart progesterone: biochemical profile and antiandrogenic potential. Contraception 1996;54:2443–51.
[29] Pollow K, Juchem M, Elger W, et al. Dihydrospirorenone ZK30595: a novel synthetic progesterone-characterization of binding to different receptor proteins. Contraception 1992;46:561–74.
[30] Oelkers W, Berger V, Bolik A, et al. Dihydrospirorenone — a new progestogen with antimineralocorticoid activity: effects on ovulation, electrolyte excretion and the rennin–aldosterone system in normal women. J Clin Endocrinol Metab 1991;73:837–42.
[31] Oelkers W. Antimineralocorticoid activity of a novel oral contraceptive containing drospirenone, a unique progestogen resembling natural progesterone. Eur J Contracept Reprod Health Care 2002; 7(Suppl 3):19–26.
[32] Borenstein J, Yu HT, Wade S, Chiou CF, Rapkin A. Effect of an oral contraceptive containing ethinyl estradiol and drospirenone on premenstrual symptomatology and health-related quality of life. J Reprod Med 2003;48:79–85.
[33] Apter D, Borsos A, Baumgartner W, et al. Effect of an oral contraceptive containing drospirenone and ethinylestradiol on general well-being and fluid-related symptoms. Eur J Contracept Reprod Health Care 2003;8:37–51.
[34] Higgins MB, Saxman JH. Variations in vocal frequency perturbation across the menstrual cycle. J Voice 1989;3:233–43.