Birth Control Pills and Nonprofessional Voice: Acoustic Analyses

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Purpose: Two studies are presented here. Study 1 was aimed at evaluating whether the voice characteristics of women who use birth control pills that contain different progestins differ from the voice characteristics of a control group. Study 2 presents a meta-analysis that combined the results of Study 1 with those from 3 recent studies that compared voices of women who use and do not use birth control pills.
Method: In Study 1, voice samples from 30 women with no history of voice training, who use pills with different progestins (drospirenone, desogestrel, gestodene), and 10 women who do not use the pill were recorded at specific time points across the menstrual cycle and were analyzed acoustically. In Study 2, results from Study 1 were analyzed jointly with results from three recent studies, which used similar methodologies.
Results: Results of Study 1 did not reveal acoustic differences in sustained phonation of vowels across the pill groups and controls. Results of the meta-analysis performed in Study 2 indicated that pill users exhibited lower jitter and shimmer values on sustained vowels, whereas no difference of fundamental frequency was observed among women who use the pill.
Conclusions: These results support findings from previous studies, which suggested that no adverse effect on voice was detected among nonprofessional speakers who use new-generation monophasic birth control pills, for the measures studied. Furthermore, results of the meta-analysis suggested that some acoustic properties of the voice, which are reflected in perturbation measures in sustained vowels, may be improved among women who use the pill.

KEY WORDS: voice assessment, acoustic measurements, hormones, women, birth control pills

The effects of the two major ovarian hormones, estrogen and progesterone, on the larynx and, specifically, on the vocal folds have been demonstrated previously. Cytological smears of the vocal folds, which were reported to exhibit characteristics similar to those from cervical smears taken simultaneously across the menstrual cycle, have provided histological evidence for the relationship between ovarian hormones and the larynx (Abitbol et al., 1989). Moreover, receptors for these hormones were found in the vocal fold epithelium and mucosa (Abitbol, Abitbol, & Abitbol, 1999; Newman, Butler, Hammond, & Gray, 2000). Behavioral evidence for this relationship between hormones and laryngeal performance has been provided by reports of changes in performance on various behavioral (Hampson & Kimura, 1988; Saucier & Kimura, 1998) and perceptual tests (Sanders & Wenmoth, 1998) across the menstrual cycle. Recently, temporal coordination of the speech mechanism, as reflected by voice onset time (VOT) characteristics, has also been found to be affected

by ovarian hormone fluctuations across the menstrual cycle (Whiteside, Hanson, & Cowell, 2004). Furthermore, it has been suggested that laryngeal neuromotor control could be influenced by fluctuations in ovarian hormonal levels through afferent and efferent processes (Higgins & Saxman, 1989).

The effect of ovarian hormones on the female larynx has also been examined in various studies on menopause and the menstrual cycle (for extensive reviews, see Abitbol et al., 1999; Amir & Biron-Shental, 2004). In essence, estrogen is known to cause mucosal hypertrophy and proliferation, while progesterone has an antiproliferative effect on the mucosa. The progesterone contradicts the estrogen effect on the mucosa; it causes a decrease in glandular activity and mucus secretions and also thickens mucus secretions. In menopause, the hormonal climate is characterized by a constant decrease in estrogen and progesterone secretions. This, in turn, results in ovarian secretions that consist mainly of androgen. Hormonal changes during the menstrual cycle, however, have a cyclic nature. These changes are divided into two major phases: the proliferative phase and the luteal/secretory phase. During the proliferative phase, there is a gradual increase in estrogen levels. After sufficient estrogenic stimulation, ovulation occurs, around the 14th day of the cycle. The luteal/secretory phase begins after ovulation and is characterized by a decrease of estrogen levels, initially, followed by an increase of its levels during the midluteal phase as a result of corpus luteum secretions. Progesterone levels increase after ovulation and can be used as a sign that ovulation has occurred. Both estrogen and progesterone levels remain elevated as long as the corpus luteum functions, and with its demise, about 7 to 10 days after the beginning of the luteal phase, they sharply decrease. This leads to menstruation and the initiation of the following menstrual cycle (Speroff, Glass, & Kase, 1999).

These changes in hormonal levels across the menstrual cycle have been reported to be associated with variations in voice production in women. Voice changes have been perceived in the days close to ovulation (Higgins & Saxman, 1989) or during the days preceding menses (Abitbol & Abitbol, 1998; Davis & Davis, 1993). It has been estimated that approximately one third of all women experience vocal symptoms associated with their menstrual cycle (Abitbol & Abitbol, 1998; Boulet & Oddens, 1996). Among female singers, these estimates are reported to be even higher, and as many as 83% of young female singers may develop symptoms (Lã, Davidson, Ledger, & Howard, 2004). Symptoms may include vocal fatigue, reduced abilities to perform in the high spectrum of the vocal range, a reduction in the intensity range, and a decrease in frequency and amplitude stability (Abitbol et al., 1999; Chae, Choi, Kang, Choi, & Jin, 2001; Higgins & Saxman, 1989) and can be regarded as a vocal premenstrual syndrome (VPMS; Amir, Kishon-Rabin, & Muchnik, 2002). Such vocal changes have been reported mainly among female singers; their prevalence among nonsingers is not clear, although it is generally estimated as markedly lower than that among singers.

Traditionally, studies that have examined the effect of ovarian hormones on the female voice have been conducted on women who do not use birth control pills (e.g., Higgins & Saxman, 1989; Silverman & Zimmer, 1978). The reason for the exclusion of women who use the pill is that the synthetic hormones modify the hormonal balance and, therefore, these women do not experience natural menstrual cycles. Moreover, the classic literature on voice regarded the use of birth control pills as a risk factor for voice problems because of their possible adverse effects, mainly virilization (Sataloff, Hawkshaw, & Rosen, 1997). However, those effects have been associated primarily with the old-generation progesterones previously used in oral contraceptives (Speroff, Glass, & Kase, 1999). Modern birth control pills consist of minimal doses of estrogen and new formulations of progesterones that have fewer androgenic derivates than those used in the 1960s and 1970s, suggesting a lower probability for adverse side effects in general and for changes to the voice in particular. Furthermore, unlike the old-generation formulations, the monophasic birth control pills used in most cases today maintain constant levels of estrogen and progesterone. As a result, the natural cyclic fluctuations that characterize the menstrual cycle are eliminated, and a steady hormonal climate is created. Therefore, it has been suggested that stabilization of the hormonal balance across the menstrual cycle, combined with the reduction or even elimination of androgenic side effects, could reduce VPMS symptoms in women who use birth control pills (Amir & Biron-Shental, 2004). This issue has become particularly relevant, because the number of women who use birth control pills has consistently increased over the past decades (e.g., Spinelli, Talamanca, & Lauria, 2000).

Subsequent to the pharmacological advances in the field of contraception, studies were conducted to reevaluate the effect of birth control pills on the female voice. In contrast to the early reports, these recent studies did not identify any adverse effect on voice among women who have no background in voice training and who use modern monophasic birth control pills (Amir & Biron-Shental, 2003; Amir, Biron-Shental, Muchnik, & Kishon-Rabin, 2003; Amir et al., 2002; Gorham-Rowan, Langford, Corrigan, & Snyder, 2004; Wendler et al., 1995). Moreover, a few studies have suggested that the voices of women who use these birth control pills are more stable, as reflected by acoustic measures of amplitude perturbation alone (Gorham-Rowan, 2004) or by acoustic measures of both frequency and amplitude perturbation (Amir et al., 2002, 2003; Amir & Kishon-Rabin, 2004;

Lã et al., 2004). Although this line of research, which is based on acoustic analyses of voice, examined nonsingers, these observations were also supported by a recent report (Lã et al., 2004) indicating a lower incidence of VPMS among female singers who use birth control pills, in comparison with others who do not use the pill. This favorable effect on voice was attributed to the reduced dosages of hormones and especially to the new-generation progestins used in the pills tested.

It should be noted, though, that the previous studies did not compare different formulations of pills or different progestins. The majority of these studies included in the same experimental group women who use various types of formulations with different progestins (Amir et al., 2003; Amir & Kishon-Rabin, 2004; Amir et al., 2002; Gorham-Rowan, 2004; Gorham-Rowan et al., 2004). The gynecological literature suggests that different formulations of birth control pills, specifically different progestins, could have different side effects (Kuhl, 1997; Ludicke, Gaspard, Demeyer, Scheen, & Lefebvre, 2002; Newton, 1995; Oelkers, 2004; Wilde & Balfour, 1995). In light of this issue, a comparison of voices of women who use birth control pills with different formulations was deemed desirable.

Because of the reported similarities between selected genital and laryngeal tissues in their reaction to hormonal fluctuations, we were interested to learn whether women who use specific formulations of birth control pills would have different voice characteristics in comparison with women who use other formulations and in comparison with a control group of women who do not use the pill. Most new-generation birth control pills contain similar doses of ethinylestradiol (20–30 μg). However, the different brands vary in their progestin content. In a preliminary study, Amir, Biron-Shental, Tzenker, and Barer (2005) compared three groups of women who used birth control pills. The three groups differed in progestin content of their pill: drospirenone, desogestrel, and gestodene. In that study, it was hypothesized that women who use birth control pills that contain drospirenone would exhibit lower perturbation and noise indices values, in comparison with the other two groups. This assumption was based primarily on the fact that drospirenone is a progestin that is a spironolactone derivate. As such, drospirenone is not androgenic and, therefore, differs markedly from previously used progesterones. In contrast, desogestrel and gestodene are progestins that are nortestosterone (androgenic) derivates. Preliminary results obtained in that study, which was based on isolated vowel productions, did not reveal significant group differences in the acoustic measures tested among the three pill groups. The major limitations of the study were that it included no control group and that it evaluated voice production using only a limited set of acoustic measures.

Drospirenone is, essentially, an antimineralocorticoid steroid with no androgenic effect. In fact, it could have a partial antiandrogenic effect (Sitruk-Ware, 2002). Another reported potential advantage of drospirenone over the other progestins stems from the fact that its antimineralocorticoid activity is similar to that of the natural progesterone. In that respect, estrogens are known to increase sodium retention, thus leading to increased edema, and progesterones that are derivates of nortestosterone are unable to counteract this effect. As a consequence, women who use combined oral contraceptives that contain these progesterones often experience side effects of fluid retention, edema, and elevated body weight. Unlike these progestins, drospirenone has been shown to counteract weight gain and other symptoms related to estrogen-induced fluid retention (Thorneycroft, 2002). This advantage was attributed, first, to the fact that drospirenone induces mild natriuresis, second, to its similarity to the natural progesterone, and, third, to the fact that drospirenone does not present a sodium retention effect. These systemic effects were evident in the genital organs and, thus, could be expected to affect the voice mechanism as well (Thorneycroft, 2002). Moreover, preliminary clinical observations on women who use birth control pills that contain drospirenone (Lã et al., 2004) suggested that these women subjectively reported improved voice quality and fewer VPMS symptoms in comparison with women who do not use the pill.

Two studies are reported here. The first study addressed two major research questions. First, does the speaking voice of vocally untrained women who use birth control pills that contain drospirenone differ from that of women who use other formulations? Second, do women who use birth control pills exhibit voice characteristics that are different from those of controls? This second question arose in light of a research design limitation noted among the studies reported earlier. Acoustic measures of frequency and amplitude perturbation were selected as dependent variables because of a previous suggestion that the sources of fluctuation in the voice signal (e.g., as reflected by perturbation) could be related to various mechanisms, including neurological, biomechanical, and aerodynamic sources (Titze, 2000). Because hormonal changes could affect any or all of these mechanisms, it was assumed that measures of perturbation could illustrate these effects, to the extent that they are reliable and valid indicators of fluctuations in vocal fold performance relative to the question at hand. Furthermore, this assumption was supported by studies suggesting that vocal differences between women who do and women who do not use birth control pills could be quantified by acoustic measures of perturbation. Subsequently, the second study utilized a meta-analysis, in which the results obtained in Study 1 were combined with the results of three earlier

studies that evaluated acoustic differences in the voices of women who use and women who do not use birth control pills.

Study 1
Method

Participants

After an initial screening, 40 women were selected from a group of 100 female university students (undergraduate, graduate, and doctoral program) and local hospital staff who agreed to participate in this study, after obtaining approval from our institutional review board and written consent of all participants. Of these women, 30 had been using birth control pills for more than 3 months, and 10 had never used birth control pills or other hormonal contraceptives. All selected women had a regular menstrual cycle and menses, and none had any history of formal voice or singing training. All women reported typical voice use that did not involve straining the voice for long periods of time, and none of them was employed in a vocally demanding profession. Women who reported any of following were excluded from the study: (a) a history of chronic or systemic medical condition, (b) a history of intubations or surgery, (c) neurological problems, (d) illness at the time of the study, (e) known or suspected gastroesophageal reflux, (f) hormonal imbalance, (g) pregnancy or breast-feeding over the preceding 6 months, and (h) smoking or substance abuse. All women who used birth control pills reported no omission in pill intake during the preceding 3 months.

Of the 30 women who used birth control pills, three groups were defined, based on the progestin content of their pills. Ten women who were using pills that contained 3.0 mg drospirenone and 30 µg ethinylestradiol were defined as the drospirenone group. Mean age for this group was 25.3 years (SD = 4.86); mean height was 162.8 cm (SD = 4.9); and mean weight was 55.7 kg (SD = 8.7). Ten women who were using pills that contained 150 µg desogestrel and 20 to 30 µg ethinylestradiol were defined as the desogestrel group. Mean age for this group was 25.1 years (SD = 2.56); mean height was 164.4 cm (SD = 3.4); and mean weight was 55.8 kg (SD = 5.1). Ten women who were using pills that contained 75 µg gestodene and 20 to 30 µg ethinylestradiol were defined as the gestodene group. Mean age for this group was 24.8 years (SD = 2.70); mean height was 165.7 cm (SD = 6.1); and mean weight was 55.7 kg (SD = 6.1). The fourth group consisted of the 10 women who did not use birth control pills and made up the control group. Mean age for this group was 23.5 years (SD = 2.46); mean height was 162.4 cm (SD = 6.3); and mean weight was 50.8 kg (SD = 6.1).

Although physical features are not considered to directly affect voice quality, the four groups were tested for differences in physical characteristics to assess the possibility of a bias effect. To that end, three separate analyses of variance were performed. No significant differences were found among the four groups for age, height, or weight: $F(3, 36) = 0.61$, $p = .617$; $F(3, 36) = 0.85$, $p = .474$; and $F(3, 36) = 1.11$, $p = .360$; respectively.

Recording Procedure and Instrumentation

The 30 women in the pill groups (i.e., drospirenone, desogestrel, and gestodene) produced acoustic records twice over a single menstrual cycle. One recording was performed between the 10th and the 17th days of pill intake, when hormonal levels reach a steady state (Kaplan, 1995). This recording was regarded as the "on" condition. The other recording was performed during the first 3 days of menses, when no pills are taken and hormonal levels are minimized (Kaplan, 1995). This recording condition was regarded as the "off" condition. Because the women in the control group did not use the pill, the "on" condition did not apply to them. Therefore, these women were recorded only once, which was comparable to the "off" condition observed in the pill groups. Whereas previous studies performed by our team used approximately 15 recordings during a single menstrual cycle, the present study used only two recordings. In general, multiple recordings are required to establish valid acoustic measurements (e.g., Titze, 1995). The use of multiple recordings in our earlier studies did not improve identification of group differences in the acoustic measures tested, however, and we decided to use a smaller number of recordings in this study. Prior to conducting a recording session, each participant was asked about pill omission and about her medical condition. Women who reported pill irregularities or illness were excluded from the study.

Recordings were performed individually, with the participant seated in a quiet room. A Sony ECM-T150 headset-microphone was positioned approximately 6 cm from the corner of the participant's mouth at an angle of 80° to 90°. Recorded signals were saved onto TDK DC4-90R digital cartridges, using a Sony TCD-D100 digital audiotape recorder, with a sampling rate of 48 kHz. This digital recorder has a dynamic range of 87 dB and a flat frequency response (20–2000 Hz). Total harmonic distortion is reported to be less than 0.008%, and wow and flutter are below the measurable limit. During each individual recording session, participants were asked to produce the Hebrew vowels /a/ (similar to the vowel in "father"), /i/ (similar to the vowel in "heed"), and /u/ (similar to the vowel in "boot") at a comfortable pitch and loudness. These vowels were selected because they represent three distinct articulatory gestures in Hebrew (Most, Amir, & Tobin, 2000), as well as in many other languages (Baken, 1997; Ladefoged, 1982). In addition, these vowels

are widely used for clinical and experimental evaluation of voice. Each vowel was produced twice in isolation, for 3 to 5 s in a random order that was changed between recordings.

Acoustic Analysis

Each isolated vowel was fed to the Multi Dimensional Voice Program (MDVP, Model 5105, Version 2, Kay Elemetrics), with a sampling rate of 48 kHz. Subsequently, eight acoustic measures were extracted from each vowel production. First measured was the mean fundamental frequency (mF0). Then, three frequency perturbation parameters were obtained: (a) jitter, which presents a relative evaluation of the period-to-period variability of the pitch within the analyzed voice sample; (b) relative average perturbation (RAP), which presents a relative evaluation of the period-to-period pitch variability with a smoothing factor of 3 periods; and (c) pitch period perturbation quotient (PPQ), which presents a relative evaluation of the period-to-period pitch variability with a smoothing factor of 5 cycles. Two amplitude perturbation parameters were obtained: (a) shimmer, which presents a relative evaluation of the period-to-period variability of the peak-to-peak amplitude, and (b) amplitude average perturbation quotient (APQ), which presents a relative evaluation of the period-to-period variability of the peak-to-peak amplitude with smoothing over 11 periods. Finally, two noise indices were obtained: (a) noise to harmonics ratio (NHR), which calculates an average ratio of the inharmonic spectral energy in the frequency range 1500 to 4500 Hz to the harmonic spectral energy in the frequency range 70 to 4500 Hz, and (b) voice turbulence index (VTI), which calculates an average ratio of the inharmonic high-frequency energy in the frequency range 2800 to 5800 Hz to the spectral harmonic energy in the frequency range 70 to 4500 Hz. In essence, for all parameters included in the analysis (with the exception of mF0), lower values typically represent a healthier voice, whereas higher values are generally associated with a less stable and a poorer, lower quality voice (Chae et al., 2001; Kay Elemetrics, 1999).

Statistical Methods

After the individual acoustic files for all sustained vowels produced by each participant were obtained, initial data reduction was performed. Mean acoustic measure values were calculated for every repeated recording of each vowel obtained in a single session for the individual participants. Based on these calculated means, two sets of data analyses were performed, one to address each of the two major research questions. First, a comparison was performed among the three pill groups. To that end, statistical analyses were performed using analyses of variance (ANOVAs) with repeated measures. Data were analyzed separately for each acoustic measure. In these analyses, vowel (i.e., /a/, /i/ and /u/) and pill intake condition (i.e., "on" and "off") were treated as within-subject factors, whereas group (i.e., drospirenone, desogestrel, and gestodene) was treated as the between-subject factor.

Subsequently, a second set of statistical analyses was conducted to compare results among all four groups. This comparison was performed only for the "off" condition, because as noted earlier, no data for the "on" condition were available for the control group. As for the first set of data, separate ANOVAs with repeated measures were conducted for each acoustic measure. In these analyses, vowel (i.e., /a/, /i/, and /u/) was treated as the repeated factor and group (i.e., drospirenone, desogestrel, gestodene, and control) was treated as the between-subject factor. For the two sets of statistical analyses, overall statistical significance level was set at α = 0.05. Nonetheless, because of the similarities among the three frequency perturbation measures (jitter, RAP, and PPQ) and between the two amplitude perturbation measures (shimmer and APQ) and because of the need to account for the multiple analyses, α levels were adjusted accordingly. Thus, statistical significance levels were set at α = 0.016, for the three frequency perturbation measures and at α = 0.025 for the two amplitude perturbation measures. All statistical analyses were performed with SPSS for Windows 11.5.1 (SPSS, Inc.).

Results

Based on the obtained mean individual values, group means were calculated for each acoustic measure in the two recording conditions ("on" and "off"). These data are presented in Tables 1, 2, and 3 for the vowels /a/, /i/, and /u/, respectively. Results will be summarized, first, for the comparison among the three pill groups (drospirenone, desogestrel, and gestodene). Then, results will be presented for the comparison among all four groups (including the control group).

Comparing the Three Pill Groups

In general, all three pill groups exhibited similar values of acoustic measures. Values of mF0 for the desogestrel group were slightly higher than those of the other pill groups. These differences, however, were not statistically significant, $F(2, 27) = 1.91$, $p = .167$. Similarly, for all frequency and amplitude perturbation measures, the drospirenone group demonstrated slightly higher values than the other two pill groups. Statistical analyses, however, indicated that these small differences among the three pill groups were not statistically significant for any of the frequency perturbation measures ($.153 < p < .201$), amplitude perturbation measures ($.470 < p < .599$) or noise indices ($.481 < p < .640$). Further, no significant main effect for pill intake condition ("on"

Table 1. Means and standard deviations (in parentheses) of acoustic measures for the vowel /a/ produced by the four experimental groups.

Measure	Drospirenone		Desogestrel		Gestodene		Control	
	On	Off	On	Off	On	Off	On	Off
mF0 (Hz)	212.34	209.55	221.62	222.61	205.08	209.61	NA	215.68
	(15.66)	(16.04)	(20.22)	(19.44)	(20.03)	(23.48)		(23.79)
Jitter (%)	1.39	1.34	1.44	0.99	0.98	0.91	NA	1.19
	(0.48)	(0.84)	(1.05)	(0.42)	(0.43)	(0.26)		(0.43)
RAP (%)	0.84	0.80	0.89	0.60	0.59	0.54	NA	0.71
	(0.29)	(0.50)	(0.69)	(0.25)	(0.27)	(0.16)		(0.26)
PPQ (%)	0.80	0.78	0.76	0.55	0.56	0.53	NA	0.71
	(0.29)	(0.51)	(0.47)	(0.25)	(0.26)	(0.15)		(0.25)
Shimmer (%)	3.57	3.56	3.57	2.84	3.27	3.16	NA	3.24
	(0.87)	(0.99)	(1.49)	(0.75)	(0.88)	(1.05)		(0.62)
APQ (%)	2.39	2.44	2.31	1.85	2.33	2.25	NA	2.25
	(0.54)	(0.64)	(0.74)	(0.43)	(0.63)	(0.85)		(0.42)
NHR	0.129	0.132	0.134	0.121	0.122	0.119	NA	0.122
	(0.015)	(0.021)	(0.048)	(0.013)	(0.015)	(0.012)		(0.011)
VTI	0.039	0.044	0.035	0.040	0.044	0.042	NA	0.040
	(0.008)	(0.008)	(0.007)	(0.008)	(0.007)	(0.012)		(0.009)

versus "off") was found for any of the acoustic measures analyzed ($.213 < p < .828$).

As expected, significant differences were found among the three vowels for mF0, $F(2, 26) = 14.50$, $p < .001$. Contrast analysis, for all possible pairs of vowels, demonstrated that the vowel /a/ had significantly lower values than the vowels /i/ and /u/ ($p < .05$). Significant vowel differences were also found for the amplitude perturbation measures: $F(2, 26) = 70.29$, $p < .001$ and $F(2, 26) = 76.89$, $p < .001$, for shimmer and APQ, respec-

tively. Contrast analyses revealed that significantly higher amplitude perturbation values were obtained for the vowel /a/, in comparison with the vowels /i/ and /u/ ($p < .05$). Similarly, significant vowel differences were found for the two noise indices: $F(2, 26) = 17.80$, $p < .001$ and $F(2, 26) = 57.73$, $p < .001$ for NHR and VTI, respectively. Contrast analysis revealed that significantly higher noise index values were obtained for the vowel /a/ in comparison with the vowels /i/ and /u/ ($p < .05$). No significant interactions were found between pill intake condition and group

Table 2. Means and standard deviations (in parentheses) of acoustic measures for the vowel /i/ produced by the four experimental groups.

Measure	Drospirenone		Desogestrel		Gestodene		Control	
	On	Off	On	Off	On	Off	On	Off
mF0 (Hz)	217.39	212.39	227.36	228.00	210.57	214.93	NA	219.01
	(17.91)	(15.73)	(22.20)	(20.45)	(19.60)	(22.74)		(23.47)
Jitter (%)	1.43	1.50	1.40	1.10	1.14	1.18	NA	1.36
	(0.49)	(0.72)	(0.81)	(0.59)	(0.46)	(0.62)		(0.73)
RAP (%)	0.86	0.90	0.86	0.66	0.69	0.71	NA	0.83
	(0.29)	(0.44)	(0.52)	(0.65)	(0.28)	(0.37)		(0.47)
PPQ (%)	0.82	0.85	0.77	0.62	0.66	0.68	NA	0.74
	(0.29)	(0.42)	(0.39)	(0.36)	(0.27)	(0.37)		(0.39)
Shimmer (%)	2.32	2.42	2.39	2.15	2.24	2.12	NA	2.73
	(0.66)	(0.76)	(0.75)	(0.42)	(0.70)	(0.65)		(1.71)
APQ (%)	1.54	1.60	1.58	1.41	1.49	1.52	NA	1.77
	(0.43)	(0.48)	(0.42)	(0.23)	(0.49)	(0.43)		(0.89)
NHR	0.120	0.117	0.114	0.111	0.116	0.011	NA	0.114
	(0.013)	(0.019)	(0.024)	(0.011)	(0.026)	(0.015)		(0.023)
VTI	0.039	0.037	0.036	0.039	0.044	0.036	NA	0.039
	(0.008)	(0.008)	(0.007)	(0.009)	(0.008)	(0.008)		(0.008)

Table 3. Means and standard deviations (in parentheses) of acoustic measures for the vowel /u/ produced by the four experimental groups.

| | Group | | | | | | | |
| | Drospirenone | | Desogestrel | | Gestodene | | Control | |
Measure	On	Off	On	Off	On	Off	On	Off
mF0 (Hz)	220.00	215.10	226.74	229.38	209.78	214.50	NA	219.08
	(18.06)	(17.17)	(23.25)	(21.12)	(18.44)	(21.52)		(22.16)
Jitter (%)	1.33	1.53	1.31	1.18	1.13	1.11	NA	1.13
	(0.53)	(0.75)	(0.47)	(0.68)	(0.36)	(0.46)		(0.51)
RAP (%)	0.83	0.92	0.81	0.73	0.68	0.66	NA	0.68
	(0.30)	(0.46)	(0.31)	(0.45)	(0.22)	(0.28)		(0.32)
PPQ (%)	0.77	0.88	0.71	0.61	0.65	0.64	NA	0.63
	(0.25)	(0.43)	(0.22)	(0.28)	(0.22)	(0.27)		(0.27)
Shimmer (%)	2.12	2.50	2.52	1.86	1.92	1.66	NA	1.79
	(0.68)	(1.15)	(1.02)	(0.42)	(0.87)	(0.44)		(0.52)
APQ (%)	1.44	1.65	1.66	1.20	1.36	1.27	NA	1.25
	(0.42)	(0.69)	(0.63)	(0.25)	(0.57)	(0.29)		(0.28)
NHR	0.107	0.114	0.113	0.110	0.109	0.109	NA	0.102
	(0.025)	(0.017)	(0.023)	(0.028)	(0.020)	(0.013)		(0.018)
VTI	0.023	0.029	0.023	0.022	0.025	0.024	NA	0.024
	(0.006)	(0.007)	(0.009)	(0.006)	(0.017)	(0.007)		(0.005)

$(.090 < p < .563)$, vowel and group $(.086 < p < .916)$, pill intake condition and vowel $(.231 < p < .509)$, or pill intake condition and vowel and group $(.167 < p < .640)$, for any of the acoustic measures tested.

Comparison of the Four Groups (Pill Groups and Control)

In the "off" pill intake condition, the control group exhibited acoustic measure values that were similar to those obtained for all three pill groups. Statistical analyses revealed no significant differences among the four groups for mF0, $F(3, 36) = 1.03$, $p = .390$, or for any frequency perturbation measures $(.223 < p < .281)$, amplitude perturbation measures $(.211 < p < .268)$ or noise indices $(.354 < p < .631)$.

As in the analyses performed among the three pill groups, significant differences were found among the three vowels for mF0, $F(2, 35) = 12.08$, $p < .001$. Contrast analysis, for all possible pairs of vowels, demonstrated that the vowel /a/ had significantly lower values than the vowels /i/ and /u/ ($p < .05$). Significant vowel differences were also found for the amplitude perturbation measures, $F(2, 35) = 37.45$, $p < .001$ and $F(2, 35) = 40.94$, $p < .001$, for shimmer and APQ, respectively. Contrast analysis revealed that significantly higher values were obtained for the vowel /a/ in comparison with the vowels /i/ and /u/ ($p < .05$). Similarly, significant vowel differences were found for the two noise indices, $F(2, 35) = 10.97$, $p < .001$ and $F(2, 35) = 44.83$, $p < .001$ for NHR and VTI, respectively. Contrast analysis revealed that for NHR, higher values for the vowel /a/ were obtained in comparison with those for the vowels /i/ and /u/ ($p < .05$). For VTI, however, lower values were obtained for the vowel /u/ in comparison with those for the vowels /a/ and /i/ ($p < .05$). Finally, no significant Vowel × Group interaction was found $(.139 < p < .930)$ for any of the acoustic measures tested.

Discussion

Although early reports from the 1960s and 1970s suggested that birth control pills might alter a woman's voice, more recent studies have not identified any adverse effect of modern birth control pills on the voices of women. Further studies have suggested that several voice measures, which are related to voice quality, could be improved among pill users with no professional voice experience, in comparison with nonusers. None of these studies, however, has compared voices of women who use different formulations of pills. In the present study, we were interested in determining whether the voice characteristics of women who use birth control pills that contain drospirenone differ from those of women who use pills that contain other progestins (namely, desogestrel or gestodene). This question was raised because of the unique characteristics of the drospirenone, which is generally regarded as producing fewer side effects than the other progestins (Sitruk-Ware, 2002; Thorneycroft, 2002) and because of preliminary clinical reports on its beneficial effect on the voice among professional voice users (Lã et al., 2004).

We implemented computerized acoustic analyses of sustained vowels for the evaluation of differences in voice associated with various birth control pill formulations.

This approach was chosen because previous studies have shown that it successfully demonstrated vocal changes associated with the use of birth control pills (e.g., Amir & Kishon-Rabin, 2004; Gorham-Rowan, 2004). However, in contrast to our expectations, the current findings do not demonstrate significant differences between the drospirenone group and the other pill groups.

Two alternative mechanisms have been suggested to explain the effect of estrogen and progesterone on the vocal folds: (a) changes in water retention in the different layers of the vocal folds, especially in the Reinke's space and in the mucosa (Abitbol et al., 1999; Chae et al., 2001), and (b) modification of laryngeal neuromotor control through afferent and efferent processes (Higgins & Saxman, 1989). Changes in water retention can readily explain variations in vocal production associated with hormonal changes. For example, greater amounts of water in the Reinke's space or in the mucosa could increase the vocal folds' vibrating mass, causing a decrease in fundamental frequency. Nonuniform changes in mass could also interfere with the regularity of the mucosal wave vibration, which could increase frequency and amplitude perturbation. In addition, changes in water retention could affect the vocal fold contact area during vibration (Lã, Davidson, Ledger, Howard, & Jones, 2005). Although these possibilities provide plausible hypotheses, the current findings, which are based on voices of women who are not professional voice users, do not support such hypotheses. It appears that although drospirenone, as a spironolactone derivate with antimineralocorticoid characteristics, decreases water retention, it does not necessarily affect the speaking voice as sampled by perturbation measures in discrete vowels. In fact, the drospirenone group in our study exhibited perturbation values that were slightly higher, although not statistically significant, than those of the other pill groups. This result further weakens the likelihood that water retention is the sole factor in changes to voice production among women who use modern birth control pills. Therefore, another hypothesis could be considered.

Although the effect of drospirenone on water retention has been validated, the effect of the different progestins on laryngeal neuromotor control has never been directly examined. Hence, it is possible only to speculate on this effect. Previous studies have suggested that neurological fluctuations can affect frequency and amplitude perturbation measures in a manner similar to that observed in other body extremities, such as the head, jaw, and fingers (Titze, 2000). Furthermore, fluctuations in the acoustic signal were shown to be affected by biomechanical properties of the vocal folds, as well as by irregularities in blood flow or changes in heart rate (Orlikoff & Baken, 1989). Higgins and Saxman (1989) suggested three mechanisms through which hormonal changes could affect laryngeal neuromotor control: (a) a

reduction in the neural inhibition of extrapyramidal motor function, (b) a change in the speed of neural transmission, and (c) a modification of the sensitivity of the laryngeal mechanoreceptors. Recently, it was also suggested that sex hormones may serve as neuroprotectors through antioxidant effects and through activation of different membrane-associated intracellular signaling pathways (Członkowska, Ciesielska, & Joniec, 2003). Although these models have not yet been substantiated in association with the human larynx, they provide an intriguing direction for future exploration on the effect of estrogen and progesterone on the female larynx.

Drospirenone, as well as its derivates, is known to have antiandrogenic effects. However, the other progestins that were included in this study are also considered new-generation progestins with relatively low androgenic influence. Therefore, it is possible that the lack of differences among the pill groups could be attributed to the small differences in androgenic potency among the formulations included in our study. This possibility is reminiscent of the Cochrane review, which concluded that drospirenone is similar to desogestrel in its clinical effects (Maitra, Kulier, Blomenkamp, Helmerhorst, & Gulmezoglu, 2004). To further explore this possibility, a future study would have to compare a wider range of progestins that are in use in different commercial formulations of birth control pills.

The question regarding possible differences between the voice characteristics of women who use birth control pills and those of women who do not use the pill arose because of some reports in the past that specific acoustic measures associated with voice quality improve among women who use the pill, although other studies have failed to reveal such a finding. To that end, a set of acoustic measures were compared in a group of 10 women who had never used birth control pills nor any other hormonal contraception to the acoustic measures obtained in the three pill groups. This comparison was based on recordings made during the first 3 days of menses. Results failed to reveal any differences among the four groups for any of the acoustic measures. This result is in agreement with the results of previous studies suggesting that modern monophasic birth control pills have no adverse effect on voice (Gorham-Rowan et al., 2004; Wendler et al., 1995). However, it contradicts those of other studies, which implied that improved voice quality in pill users can be quantified using acoustic analyses similar to those used here (e.g., Amir & Kishon-Rabin, 2004; Gorham-Rowan, 2004).

The lack of differences between the results of the acoustic analysis obtained among pill users and nonusers in the present study was evident in spite of the relatively large sample size, $N = 40$, in comparison with the former studies, $N = 10$ to 28 (Amir, Kishon-Rabin, & Muchnik, 2002; Gorham-Rowan, 2004) and in spite of the fact that

this study was the first to separate different pill formulations. Therefore, in an attempt to shed more light on this issue, a meta-analysis was performed, to evaluate the relationship between birth control pills and voice by means of acoustic analyses.

Study 2
Method

Meta-Analysis Procedure

Four studies that had been conducted by our research team to evaluate the voices of women who use birth control pills were included in the meta-analysis: Amir, Kishon-Rabin, and Muchnik, 2002; Amir and colleagues, 2003; Amir and Kishon-Rabin, 2004; and the present study. In this section, these studies will be further referred to as the 2002, 2003, 2004, and 2005 studies, respectively. These studies were selected for inclusion in the meta-analysis because they all utilized similar recording procedures and voice analysis protocols. Because the methodologies used in these studies were not identical, however, we made an effort to minimize the differences among the studies, thus increasing comparability. Therefore, this analysis included only measurements that had been obtained from sustained productions of the vowels /a/ and /i/ which were included in all four studies. Further, only the acoustic measures that were analyzed in all four studies were included in the analysis (mF0, jitter, shimmer). Although the mF0 and jitter measures were analyzed similarly in all four studies, the shimmer measure was quantified differently. In the 2002 and 2003 studies, shimmer was measured in decibels, whereas in the 2004 and 2005 studies, it was calculated as a percentage. Hence, all statistical analyses were performed on the calculated effect size for each study, not merely on the raw data.

In addition, the 2005 study included three groups of pill users, whereas the other studies included only women whose pill formulation was comparable with those in the desogestrel and gestodene groups of the 2005 study. Therefore, to increase comparability among the four studies, the drospirenone group was not included in the meta-analysis. Because no significant differences in acoustic measures were found among the pill groups in the 2005 study for any of the acoustic and background variables, the desogestrel and gestodene pill groups were regarded as one group ($n = 20$).

Finally, it was necessary to account for differences in the timing of the recordings in the four studies. The earlier studies (2002, 2003, and 2004) used similar recording procedures, in which every woman was recorded repeatedly over a period of 36 to 45 days. In contrast, the control group in the 2005 study was recorded only during menses ("off" condition). Therefore, inclusion of this study in the meta-analysis governed a comparison that is based on recordings made only during the days of menses. Thus, data were taken from the "off" condition recordings in the 2005 study and from the corresponding recordings of the earlier three studies.

Statistical Methods for the Meta-Analysis

To begin the meta-analysis of the results of the four studies, an estimator of the effect size was calculated, separately for each study, using the standardized mean difference (Glass, 1976). To that end, the mean of a control group (Mc) is subtracted from the mean of an experimental group (Me) and divided by the pooled standard deviation of both groups:

$$g = (M_e - M_c)/SD$$

In this procedure, SD is the square root of the weighted average of the two variances, calculated as the square root of

$$s^2 = [(n_e - 1)(s_e)^2 + (n_c - 1)(s_c)^2)]/(n_e + n_c - 2)$$

Then, the index d, suggested by Hedges and Olkin (1985, p. 80), was calculated to obtain an unbiased estimator:

$$d = [1 - (3/4) * (N - 9)] * g$$

The homogeneity of the four studies was assessed using the Q statistic.

The weighted integration method was applied to evaluate the overall mean effect size and to test for its significance. According to this method, the weighted overall mean effect size is calculated as

$$d+ = \frac{\sum[d_i/\text{est.}s^2(d_i)]}{\sum[1/\text{est.}s^2(d_i)]}$$

where d_i and $s^2(di)$ are the effect size and variance of the ith study, respectively. All calculations were performed using the meta-analysis program (Schwarzer, 1989).

Results of the Meta-Analysis and Conclusions

As shown in Table 4, the results of the meta-analysis indicate that the fundamental frequency values of women who use birth control pills are similar to those of women who do not use the pill ($p > .05$). In two of the studies (2003, 2004), the effect size for the mF0 measure was negative (suggesting that women who use the pill exhibit a higher mF0 than women in the control group), whereas in the other two studies (2002, 2005) the effect size was positive. Based on these studies, there is no evidence that changes in fundamental frequency in isolated vowel productions occurred among women who use new-generation

Table 4. Summary of the meta-analysis performed on the four studies,* comparing mean fundamental frequency (mF0), jitter, and shimmer in the vowels /a/ and /i/ among women who use birth control pills and women who do not.

Measure	Vowel	Study	Group Size Control	Group Size Pill	Effect Size	P Value
mF0	/a/	2002	5	5	0.0514	
		2003	6	6	−0.2295	
		2004	7	7	−0.1365	
		2005	10	20	0.4695	
		Total			0.1296	0.305
	/i/	2002	5	5	0.2989	
		2003	6	6	−0.2502	
		2004	7	7	−0.1208	
		2005	10	20	0.4886	
		Total			0.1728	0.248
Jitter	/a/	2002	5	5	0.8623	
		2003	6	6	1.3054	
		2004	7	7	0.7671	
		2005	10	20	−0.0682	
		Total			0.4395	0.045
	/i/	2002	5	5	0.4865	
		2003	6	6	0.8098	
		2004	7	7	1.1559	
		2005	10	20	−0.1650	
		Total			0.3475	0.089
Shimmer	/a/	2002	5	5	0.6092	
		2003	6	6	0.9791	
		2004	7	7	0.5872	
		2005	10	20	−0.3457	
		Total			0.2165	0.200
	/i/	2002	5	5	1.5053	
		2003	6	6	1.7709	
		2004	7	7	0.9099	
		2005	10	20	0.2029	
		Total			0.7033	0.004

* Studies included in the analysis: Amir, Kishon-Rabin, & Muchnik (2002); Amir, Biron-Shental, Muchnik, & Kishon-Rabin (2003); Amir & Kishon-Rabin (2004); and the present study (2005), respectively.

monophasic birth control pills. This result is of special interest, because the primary reservation of voice professionals about oral contraceptives is the possibility of a virilization effect (e.g., Sataloff et al., 1997). The current analysis, however, indicates that untrained women who use birth control pills experience no lowering of fundamental frequency.

The meta-analysis of measures of frequency and amplitude perturbation demonstrated different results. Jitter values were higher among women who do not use the pill. These differences were found to be statistically significant for the vowel /a/ and marginally significant for the vowel /i/. This result suggests that frequency

stability in sustained vowels is slightly improved among women who use the pill.

Results for the shimmer measure in the meta-analysis were also found to be dependent on the vowel produced. Shimmer values for the vowel /i/ were significantly lower among women who use the pill in comparison with values obtained among women who do not use the pill. This difference was consistent across all studies. However, group differences for shimmer in the vowel /a/ failed to reach statistical significance in the meta-analysis.

Like the results for the jitter measure, the results for the shimmer measure show that amplitude perturbation values were lower among women who use birth control pills. It is not clear, however, why group differences for the shimmer measure were statistically significant in the vowel /i/, but not in the vowel /a/. Measures of perturbation are typically associated with the regulation of vocal fold vibration. Thus, the effect of the vocal tract resonance on these measures is expected to be relatively small. Yet, even the early studies on frequency and amplitude perturbation (e.g., Horii, 1980; Sorensen & Horii, 1983) noted significant differences in perturbation values among different vowels. Numerous later studies also observed these differences. Although a discussion of the mechanism underlying these vowel differences is beyond the scope of the present study, it appears that nonprofessional voice users who use and do not use birth control pills exhibit different perturbation values in sustained vowels. Nonetheless, the extent to which this effect is evident in frequency and amplitude perturbation and the influence of the phonetic context on this effect should be further examined.

Limitations

Several limitations of this study warrant discussion. Of the four studies included in the meta-analysis, three had a relatively small number of participants. Thus, the overall number of women on which this analysis is based is relatively small (n = 38 and 28, for the pill and control groups, respectively). Vocal dynamics vary greatly among speakers, and although the literature provides standards for defining "normal" voice, many studies report significant within-group variability. Future studies with larger sample sizes and possibly with larger numbers of recordings could provide further insight to the relationship between birth control pills and voice.

Another limitation of the meta-analysis performed here stems from the fact that, for reasons that have been described, all recordings for this part of the analysis were made during the days of the menses. Yet, it is conceivable that larger group differences could be found at other times during the menstrual cycle. It was previously suggested that the cause for the improved voice quality and stability among women who use monophasic birth control

pills is the stabilization in the hormonal climate (e.g., Amir & Biron-Shental, 2004). During the days of the menses, the hormonal status among women who use the pill changes and becomes more similar to that of women who do not use the pill. Therefore, it is possible that greater group differences would have been observed, for example, in the middle of the menstrual cycle (i.e., around ovulation). Because the meta-analysis revealed group differences in voice production during menses, it is expected that future studies to examine voice production across the menstrual cycle may reveal additional group differences of greater magnitude.

The fact that the same research team conducted all four studies may be an additional technical limitation of this analysis. On one hand, this feature enhanced comparability among the studies, but on the other hand, it can be argued that it reduced the ability to generalize the results. A review of the literature identified only one additional recent study that could be considered for inclusion in the meta-analysis (i.e., Gorham-Rowan, 2004). We were interested in including this study in the analysis, both because it had similarities to the other studies and because it included a total of 28 women (of which 18 used the pill and 10 did not). Unfortunately, several technical problems prevented the inclusion of this study in the meta-analysis. First, the study included only recordings of the vowel /a/ in isolation. Second, the women in that study were recorded only once during the menstrual cycle, not during menses. Thus, these recordings could not be matched with the 2005 study. Third, that study's results section had several inconsistencies, which barred its inclusion in the meta-analysis. Therefore, in spite of it being a relevant study, the Gorham-Rowen (2004) study could not be included in the meta-analysis.

Finally, although this research is based on the acoustic analysis of sustained vowels, it is possible to question the validity of such measures for the evaluation of voice quality in general and of vocal changes across the menstrual cycle in particular. Voice characteristics that can be identified in connected speech are sometimes unnoticed in sustained vowels. Therefore, it is often suggested that a complete voice evaluation should include various speech and nonspeech productions (e.g., Colton & Casper, 1996). However, our results indicate that the acoustic analysis of sustained vowels demonstrate significant differences in values of perturbation measures between women who use and do not use birth control pills. It was previously suggested that sustained vowels should be used for voice perturbation analysis because they elicit a stationary process in vocal fold vibration (Titze, 1995). Furthermore, these fluctuations in the voice signal are generally regarded as related to various mechanisms, including neurological, biomechanical, and aerodynamic sources (Titze, 2000). Hence, because hormonal fluctuations could affect any of these mechanisms, it was hypothesized that a paradigm of acoustic analysis of sustained vowels could provide valuable information on the relationship between birth control pills and voice.

Further support for the suitability of the sustained vowel paradigm for identifying subtle vocal differences between the voices of women who use and those of women who do not use birth control pills can be found in the report by Gorham-Rowan and colleagues (2004), which failed to identify vocal differences between the two groups of women in continuous speech. In addition, Lã and colleagues (2005) reported on an experimental study that compared voices of women who use birth control pills containing drospirenone to voices of women who do not use birth control pills. In that study, the authors reported that a small group of professional singers who used birth control pills exhibited improved voice quality in comparison with a control group. These differences, however, were evident only in the singing voice, not in the speaking voice. Apparently, voice differences associated with the use of new-generation monophasic birth control pills are relatively small in magnitude and are more readily identified in sustained phonations, which are expected to be more stable than connected speech.

It is also conceivable that singers perceive and report voice differences more commonly, because they use the full range of their voices and are more aware of their vocal abilities and limitations. Such changes are less likely to be identified in the speaking voice of nonprofessional voice users. Nonetheless, recordings of sustained vowels provide a specific condition in which it is possible to identify evidence for these minor irregularities in the voice signal, even in the voice of nonsingers. Further studies that will combine different sets of recorded stimuli (e.g., prolonged vowels, continuous speech, and singing), in association with aerodynamic and perceptual evaluation, could assist in clarifying the answer to the questions posed.

Conclusions

Two major conclusions can be drawn from the present study. First, no evidence for an adverse effect on voice during sustained vowel production was observed among women who are nonprofessional voice users and who use new-generation monophasic birth control pills. Specifically, no lowering of fundamental frequency was evident, and perturbation measures in sustained vowels were shown to be improved among pill users. Second, although drospirenone is not an androgenic progestin and is known to reduce water retention, these advantages over the other progestins were not manifested in the speaking voice of nonsingers. In particular, acoustic analyses of sustained vowels did not reveal significant differences between voice productions made by women who use birth

control pills that contain drospirenone and other women. Further exploration of the mechanisms through which sex hormones could affect the female voice warrants future research.

Acknowledgments

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