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Altering Hirsutism Through Ovulation Induction in Women With Polycystic Ovary Syndrome

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Abstract

Objective—Many women with polycystic ovary syndrome (PCOS) experience infertility and hirsutism and often seek treatment for both concurrently. We investigated whether women who ovulate in response to treatment with clomiphene citrate, metformin, or both would have greater improvement in hirsutism compared to those who did not ovulate.

Methods—This is a secondary analysis evaluating the change in Ferriman-Gallwey score for the hirsute women (n = 505, 80.7%) from the Pregnancy in Polycystic Ovary Syndrome 1 study. This was a prospective, randomized, doubled-blind trial of 626 women with PCOS and infertility

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recruited from 12 university sites. They were treated with clomiphene citrate, metformin, or both (combination) for up to six cycles, and hirsutism evaluators were blinded to group assignment.

Results—There was a significant decrease in the Ferriman-Gallwey score between baseline and completion of the study in each of the three individual groups (clomiphene citrate, $p=0.024$; metformin, $p=0.005$; combination, $p<0.001$). There was no significant difference in the degree to which the hirsutism score changed when comparing the three groups ($p=0.44$). The change in hirsutism was not associated with the duration of treatment or with the presence or absence of ovulation.

Conclusions—In infertile hirsute women with PCOS, treatment with clomiphene citrate, metformin, or both for up to 6 cycles does not alter hirsutism.

Clinical Trial Registration—ClinicalTrials.gov, www.clinicaltrials.gov, NCT00068861.

INTRODUCTION

Many women with polycystic ovary syndrome (PCOS) seeking treatment for infertility are concurrently seeking treatment for hirsutism (1, 2). Most of the medicines traditionally used to treat hirsutism are contraindicated when trying to conceive and/or when pregnant so this presents a clinical conundrum (3). They are contraindicated because they interfere with ovulation (combined oral contraceptives) and/or because they have potential teratogenic effects as an anti-androgen (spironolactone, finasteride, flutamide) or as an anti-metabolite (eflornithine HCl cream) (4, 5, 6). Additionally, treatment for infertility can often last months or years, raising concerns about the progression of hirsutism during the treatment period. Data to guide counseling of these patients about the effects of various ovulation induction agents on hirsutism are lacking. This secondary analysis offers an excellent opportunity to address this important clinical issue.

The Pregnancy in Polycystic Ovary Syndrome 1 trial, initiated by the Reproductive Medicine Network, was a double-blind, prospective, randomized trial of clomiphene citrate vs. metformin vs. a combination of the two in the treatment of anovulatory, infertile women with PCOS. The primary outcome of the trial was live birth rate (7). All women who were enrolled in this trial met criteria for PCOS, and most had hirsutism. In this secondary analysis, the change in the Ferriman-Gallwey score (F-G) was evaluated in the hirsute subjects. We hypothesized that hirsutism scores would improve with treatment. Previous studies have shown an amelioration of hormonal abnormalities in women with PCOS after ovulation (8), so we further theorized that women who ovulated in response to treatment would also show more improvement in their hirsutism compared to those women who did not.

MATERIALS AND METHODS

Patients in the PPCOS I study were evaluated for hirsutism at baseline and at the end of the study by trained study personnel using the modified Ferriman-Gallwey (F-G) score (9). Women with an F-G value of 8 or greater were considered to be hirsute (4, 10), and comprise the study population reported in this analysis. Sex hormone binding globulin (SHBG) and total testosterone were measured at baseline and completion of the study (7, 11).

The PPCOS I study recruited 626 infertile women with PCOS at 12 sites from November 2002 to December 2004 (7). They were randomized by means of an interactive voice system to blindly receive either standard clomiphene citrate treatment, extended release Metformin XR 1000 mg twice daily, or a combination of the two (7). The institutional review board at each study site approved the protocol and all subjects gave written informed consent.

Patients were monitored with serial progesterone levels, and ovulation was confirmed if progesterone was greater than 5ng/mL. Women were treated for up to six consecutive cycles in the trial. Study participation ended with a pregnancy, drop out, or completion of six cycles of treatment. The post-treatment Ferriman-Gallwey score was performed once at the end of the study and the evaluators were blinded to group assignment.

All samples were blindly analyzed in duplicate by the University of Virginia Center for Research and Reproduction Ligand Assay and Analysis Core Laboratory. Testosterone was measured by RIA (Coat-a-Count Kit; Diagnostic Products Corp., Los Angeles, CA); assay sensitivity (the lowest level an instrument can detect) = 10 ng/dL; intraassay coefficient of variation (CV) = 5.0% and interassay CV = 8.2%. SHBG was measured by chemiluminescent two-site assays (Immulite; Diagnostic Products Corp.; sensitivity = 0.2 nmol/L; intraassay CV = 2.4%; interassay CV = 5.2%). The free androgen index (FAI) was calculated from measurable values for total T and SHBG, as previously described (11), using the following equation:

$$\text{FAI} = \text{total testosterone (nmol/L)} / \text{SHBG (nmol/L)} \times 100.$$

Data analyses were coordinated by the Data Coordinating Center at the Collaborative Center for Statistics in Science at Yale University. Chi-square or Fisher's exact test was used for testing the difference in proportions among the groups for categorical variables. Wilcoxon's signed-rank test was used to evaluate the absolute changes in F-G score and hormone levels between baseline and completion of the study. Wilcoxon rank sum test was used for testing the difference in the changes of F-G score between subjects who ovulated and those who did not. Kruskal-Wallis tests were used for testing differences among three or more groups. Spearman correlation coefficients were used to assess the association between the change in F-G score and the change in total testosterone or SHBG. Bootstrapping method was used to calculate the 95% confidence interval (CI) of the changes in F-G score, total testosterone, SHBG and FAI between baseline and completion of study. All statistical tests were two-sided. The computation was performed using SAS (9.2) and open source software R.

RESULTS

Approximately 81% (505/626) of the subjects had hirsutism at randomization. There were no significant differences in demographic characteristics and baseline hormone profiles among the treatment groups (Table 1). Of those with hirsutism at randomization, 165 (32.7%) were in the clomiphene citrate group, 172 (34.1%) were in the metformin group, and 168 (33.3%) were in the combination group ($p=0.93$).

The baseline F-G score are shown in Table 1. The distribution of the changes in F-G score are shown in Figure 1. The F-G scores significantly decreased from baseline in each of the three individual groups (Table 2). There was no significant difference in the degree to which the hirsutism score changed when comparing the three groups (Table 2). The mean ($\pm$ SD) duration of treatment for clomiphene citrate, metformin and combination groups was 4.4 ± 1.6 , 4.5 ± 1.6 and 4.5 ± 1.6 cycles respectively ($p=0.90$). The change in F-G score between the baseline and completion of the study was not significantly different among subjects with different number of treatment cycles in each of the three groups (Kruskal-Wallis test, clomiphene citrate $p=0.92$, metformin $p=0.57$, combination $p=0.92$). In addition, the presence or absence of ovulation showed no significant effect on the F-G score for any treatment (Table 3).

The absolute changes in total testosterone, SHBG, and FAI from baseline are shown in Table 2. Compared to the levels at baseline, SHBG significantly increased and FAI

significantly decreased for each treatment group (Table 2). Total testosterone also significantly decreased from baseline in metformin and combination groups (Table 2). The changes in total testosterone, SHBG, and FAI are significantly different among the three groups (Table 2), with the largest change in the combination group. In addition, subjects who had more treatment cycles showed a significantly larger change in SHBG in clomiphene citrate (Kruskal-Wallis test, $p<0.001$) and combination ($p=0.002$) groups, and of FAI in clomiphene citrate groups ($p<0.001$). Furthermore, subjects who ovulated showed significantly larger changes in total testosterone and FAI in clomiphene citrate and the combination groups, and significantly larger changes in SHBG in all the three groups when compared to those who did not (Table 4). There was no significant association between the change in SHBG (correlation coefficient = -0.073 ; $p=0.15$) or total testosterone (correlation coefficient = 0.023 ; $p=0.65$) and that of F-G score over the course of the study.

DISCUSSION

Hirsute women in all three treatment groups experienced a statistically significant, though clinically minimal improvement in F-G scores. However, there was no difference in the degree that hirsutism improved between the three groups. The improvement in F-G scores was not correlated with treatment duration or presence or absence of ovulation. Hyperandrogenemia lessened during the study, and serum levels of SHBG increased and FAI decreased significantly for all three groups. Total testosterone decreased significantly in the metformin and combination groups.

Participants completed the study when pregnancy was achieved, with drop out, or after 6 cycles of consecutive treatment so subjects received anywhere from 1 to 6 cycles of medication. Because of the varying lengths of exposure to the medications, it was important to investigate the effect of length of exposure on hirsutism. We expected that the subjects with longer exposure to treatment would have more improvement in hirsutism scores, however this was not seen. This finding may be due to the relatively short duration of treatment; other studies have shown a minimum of 6 months of treatment are needed to see a significant improvement in hirsutism (12, 13, 14). Alternately, the statistically significant change in hirsutism scores may reflect observer bias. Although investigators and coordinators were blinded, they knew that all subjects were on an active drug so they may have looked at hair distribution slightly more favorably knowing that all subjects were on treatment. Other studies of F-G score assessment have noted high variability within and between examiners (13). Although our study coordinators went through extensive training, we did not assess intra-and inter-individual coefficients of variation in hirsutism assessment.

The presence or absence of ovulation did not affect hirsutism scores. Because the hormonal environment in anovulatory women with PCOS normalizes more with ovulation than without ovulation (8), we expected those participants who ovulated more times throughout the study to have a better improvement in hirsutism. It is possible these medications could have effects independent of ovulation.

Testosterone decreased favorably during the study but there was no corresponding change in hirsutism scores. Lowering testosterone may not improve hirsutism in the short term as the transformation to terminal hair is irreversible once complete (11, 12, 15). We noted a negative but not significant association between increase in SHBG during the study and decrease in hirsutism (4). SHBG may cause decreased androgen exposure at the pilosebaceous unit.

Strengths of this study include that it was a large randomized, controlled, double blind trial that investigated the effect of three treatments on hirsutism in women with both anovulatory

infertility and hirsutism. Additionally, we used a generally accepted definition of hirsutism, a modified Ferriman-Gallwey score of 8 or greater, to define hirsutism. The most significant strength of the study is that it provides data describing the effect of typical treatment regimens on hirsutism in PCOS patients and affords the clinician practical information that can be of great help in counseling these anovulatory patients.

Limitations of the study include that change in hirsutism score was a secondary outcome so the design of the study may have prevented us from observing a more clinically important change that could have been identified with a longer protocol. In addition, the women were on the medications for a median of 5 cycles, which is shorter than the traditional 6 months of treatment (12, 13, 14). Although treatment length in this study is a concern, this study addresses a common clinical conundrum; the treatment of hirsutism in infertile women with PCOS undergoing ovulation induction. Additionally, we did not evaluate patient satisfaction with the clinical treatment so it is possible that there may have been subjective patient improvement in their self assessment of hirsutism that was not appreciated by an independent observer (16).

In summary, our results suggest that therapy with oral ovulation induction agents does not worsen hirsutism over a typical treatment duration in this patient population. Many patients with PCOS desire treatment for both infertility and hirsutism. This study provides important information for clinicians counseling these patients.

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Figure 1.

Histogram shows the distribution of F-G score changes between baseline and completion of study in clomiphene citrate, metformin and combination groups.

Table 1**Baseline Clinical Characteristics and Hormonal Profiles of the Study Population**

Characteristics	Clomiphene Citrate (n=165)	Metformin (n=172)	Combination (n=168)	P value*
Age, years	28.2 ± 4.1 [†]	28.0 ± 3.9	28.4 ± 4.0	0.83
Race or ethnic group, n (%)				0.98
Caucasians	114 (69.1)	114 (66.3)	116 (69.1)	
African Americans	29 (17.6)	32 (18.6)	27 (16.1)	
Asians	5 (3.0)	4 (2.3)	4 (2.4)	
Other	17 (10.3)	22 (12.8)	21 (12.5)	
Body mass index, (kg/m²)	36.9 ± 9.0	36.1 ± 8.3	35.0 ± 8.0	0.19
Previous pregnancy- n (%)	62 (37.6)	52 (30.0)	57 (33.9)	0.36
Ferriman-Gallwey score	17.3 ± 7.1	16.4 ± 7.1	16.8 ± 6.1	0.28
Sex hormone – binding globulin (nmol/liter)	29.5 ± 19.3	26.0 ± 13.9	29.4 ± 18.5	0.15
Total testosterone (ng/dl)	64.2 ± 34.2	63.4 ± 26.0	66.1 ± 29.3	0.54
Free androgen index	10.0 ± 7.6	10.6 ± 6.4	10.2 ± 7.0	0.20

Data are mean ± standard deviation unless otherwise specified.

* The chi-square or Fisher's exact test was used for categorical variables. Kruskal-Wallis test was used for continuous variables.

Table 2

Absolute Change in Ferriman-Gallwey Score and Hormone Parameters Between Baseline and Completion of Study

Measure	Clomiphene Citrate Group	Metformin Group	Combination Group	<i>P</i> Value for Comparison Among Three Groups [*]
Ferriman- Gallwey score				0.44
Mean change	-0.6 ± 3.3 (-1.2 to -0.02) [†]	-1.2 ± 4.7 (-2.1 to -0.4)	-1.1 ± 4.0 (-1.8 to -0.4)	
<i>P</i> [‡]	0.024	0.005	<0.001	
T- Testosterone				0.031
Mean change	-2.6 ± 31.7 (-7.5 to 2.4)	-7.4 ± 27.6 (-11.5 to -3.2)	-9.1 ± 33.1 (-14.1 to -3.9)	
<i>P</i>	0.061	<0.001	<0.001	
SHBG				<0.001
Mean change	13.4 ± 16.0 (11.0 to 16.0)	2.7 ± 13.5 (0.9 to 4.9)	15.4 ± 19.5 (12.6 to 18.5)	
<i>P</i>	<0.001	<0.001	<0.001	
FAI				0.002
Mean change	-3.7 ± 5.7 (-4.6 to -2.8)	-1.7 ± 4.7 (-2.4 to -0.9)	-3.9 ± 6.3 (-4.9 to -2.9)	
<i>P</i> value	<0.001	<0.001	<0.001	

Data are mean±standard deviation or mean±standard deviation (95% confidence interval) unless otherwise specified.

^{*} Kruskal-Wallis test was used to compare the difference in changes of F-G score and hormone parameters from baseline among three different groups.

[†] Bootstrap was used to calculate the 95% confidence interval.

[‡] Wilcoxon's signed rank test was used to compare the changes in Ferriman-Gallwey score and hormone parameters from baseline.

Table 3

Changes in Ferriman-Gallwey Score From Baseline for Women Who Ovulated (+) and Those Who Did Not (–)

Treatment	Ovulation	Changes of Ferriman- Gallwey Score From Baseline	<i>P</i> [*]
Metformin	(+)	-1.0 ± 3.8 (–1.9 to –0.1)	0.78
	(–)	-1.5 ± 6.0 (–3.6 to 0.2)	
Clomiphene citrate	(+)	-0.6 ± 3.3 (–1.3 to –0.02)	0.91
	(–)	-0.4 ± 3.5 (–1.6 to 1.0)	
Combination	(+)	-1.1 ± 4.1 (–1.8 to –0.4)	0.49
	(–)	-0.8 ± 2.9 (–2.3 to 0.9)	
All women	(+)	-0.9 ± 3.8 (–1.4 to –0.5)	0.86
	(–)	-1.0 ± 4.8 (–2.2 to –0.03)	

Data are mean $\pm$ standard deviation, (95% confidence interval) unless otherwise specified.

Bootstrap was used to calculate the 95% confidence interval.

^{*} Wilcoxon's rank-sum test was used to compare the difference in the changes of Ferriman-Gallwey score from baseline between subjects who ovulated and those who did not.

Table 4

Changes of Total Testosterone, Sex Hormone–Binding Globulin and Free Androgen Index From Baseline for Women Who Ovulated and Those Who Did Not

Group	Ovulation	Changes in Total Testosterone From Baseline	P*	Changes in SHBG From Baseline	P*	Changes in Free Androgen Index From Baseline	P*
Metformin	(+)	-9.0 ± 29.0 (-14.9 to -2.9) &	0.26	3.8 ± 8.6 (2.2 to 5.7)	0.005	-2.0 ± 4.4 (-2.9 to -1.1)	0.49
	(-)	-5.6 ± 25.9 (-11.2 to 0.5)		1.3 ± 17.5 (-1.9 to 5.8)		-1.6 ± 4.5 (-2.4 to -0.1)	
Clomi phene citrate	(+)	-7.8 ± 29.0 (-13.1 to -2.5)	0.002	15.5 ± 17.5 (12.4 to 18.8)	0.007	-4.5 ± 6.0 (-5.6 to -3.4)	0.001
	(-)	10.6 ± 34.6 (1.0 to 21.3)		8.0 ± 9.5 (5.4 to 11.0)		-1.3 ± 5.1 (-3.0 to -0.4)	
Combi nation	(+)	-12.3 ± 29.7 (-17.3 to -7.4)	0.002	17.5 ± 20.2 (14.3 to 21.1)	<0.001	-4.5 ± 6.6 (-5.6 to -3.4)	<0.001
	(-)	7.9 ± 44.4 (-4.4 to 28.5)		4.4 ± 9.7 (1.3 to 8.6)		-0.5 ± 3.0 (-1.6 to 0.7)	

SHBG, sex hormone–binding globulin.

Data are mean ± standard deviation, (95% confidence interval) unless otherwise specified.

Bootstrap was used to calculate the 95% confidence interval.

* Wilcoxon's rank-sum test was used to compare the difference in the changes of total testosterone, SHBG, and free androgen index from baseline between women who ovulated and those who did not.