Long-Term Response of Hirsutism and Other Hyperandrogenic Symptoms to Combination Therapy in Polycystic Ovary Syndrome

Uche Ezech, MD,¹⁻³ Andy Huang, MD, MBA,⁴ Melanie Landay, MD,⁴ and Ricardo Azziz, MD, MPH, MBA²⁻⁶

Abstract

Background: Polycystic ovary syndrome (PCOS) affects 5%–15% of women and is the most common cause of hirsutism. Data on the time-course of improvement to suppressive therapy and predictors of that response in PCOS are lacking. The objectives of our study are to determine the long-term response and identify predictors of response in PCOS women treated with suppressive therapy, including spironolactone (SPL) + oral contraceptives (OCs).

Materials and Methods: Retrospective cross-sectional analysis of 200 women with PCOS (1990 NIH criteria) treated with suppressive therapy in general, and a subgroup of 138 subjects treated with OCP+SPL who had been prospectively included in a biorepository. Main outcome measure included improvement rate per 100 person-month of follow-up for hirsutism, menstrual irregularity and acne measured qualitatively as “feeling better”, and changes in the severity of hirsutism quantified by modified Ferriman–Gallwey [mF-G] score.

Results: During a mean follow-up of 34.2 months, 85.1%, 82.7%, and 79.3% of patients reported improvement in hirsutism, menstrual dysfunction, and acne, respectively. The modified Ferriman–Gallwey (mF-G) hirsutism score improved by 59.9%. The net reduction in mF-G score and the percent of patients reporting improvement in hirsutism were greater for OC+SPL than for either drug alone, with no difference in the percent of patients free of adverse effects. Among those treated with OC+SPL ($n = 138$), the initial mF-G and sex hormone-binding globulin (SHBG) independently predicted successful therapy for hirsutism.

Conclusion: There is a high rate of patient satisfaction with suppressive therapy in PCOS. The efficacy of suppressive therapy for hirsutism was greater with OC+SPL than with either drug alone. Successful treatment of hirsutism with combination OC+SPL requires at least 6 months of therapy, with the proportion of satisfied patients continuing to increase with treatment duration. The probability of patient satisfaction with OC+SPL treatment for hirsutism can be predicted by her initial mF-G score or SHBG level.

Keywords: PCOS, treatment success, combination oral contraceptive, spironolactone, predictors

Introduction

THE POLYCYSTIC OVARY syndrome (PCOS) affects 5%–15% of reproductive-aged women.¹ Most notably, PCOS patients suffer from signs and symptoms related to hyperandrogenism and ovulatory dysfunction, including hirsutism, acne, androgenic alopecia, polymenorrhea, and oligomenorrhea.^{2,3} Androgen suppression using oral contraceptives (OCs) has traditionally been used for treating hirsutism^{4,5} and acne.⁶ In addition, OCs provide the additional advantages of men-

strual cycle control, effective contraception, and reduced risks of endometrial hyperplasia and cancer. Androgen-receptor antagonists or 5 α -reductase inhibitors are also effective in the treatment of hirsutism,^{4,7-9} although their value is less clear in the treatment of acne^{6,7} and female androgenic alopecia.^{10,11}

The most commonly used antiandrogen in the United States for treating hirsutism is spironolactone (SPL), an aldosterone antagonist and a potassium-sparing diuretic.^{7-9,12} The direct antiandrogenic effect of SPL is primarily mediated through its ability to inhibit the binding of 5 α -dihydrotestosterone to the

¹Department of Obstetrics and Gynecology, Stanford Healthcare-ValleyCare Hospital, Pleasanton, California.

²Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta University, Augusta, Georgia.

³Center for Androgen-Related Disorders, Cedars-Sinai Medical Center, Los Angeles, California.

⁴Department of Obstetrics and Gynecology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California.

⁵Department of Medicine, Medical College of Georgia, Augusta University, Augusta, Georgia.

⁶State University of New York (SUNY) System Administration, Albany, New York.

androgen receptor.¹³ SPL also interferes modestly with testosterone (T) biosynthesis by reducing 17-hydroxylase activity.^{14,15}

Combinations of OC suppression and androgen blockade have been proposed to have greater effect on hirsutism over monotherapy.^{7,9,16} We previously reported on 257 patients with various forms of androgen-related disorders who used combination hormonal therapy, with a mean duration of follow-up of 33.5 months.¹⁷ In these subjects, hirsutism improved in 86%, menstrual dysfunction in 80%, acne in 81%, but hair loss in only 33%. The major side effects noted were irregular vaginal bleeding, nausea, and headaches, with only 36.6% of patients never complaining of side effects. While the prior report noted whether patients reported improvement or not,¹⁷ data that focused on the time-course of that improvement and predictors of response in patients with PCOS are lacking.

The hyperandrogenic signs and symptoms and menstrual dysfunction of PCOS can persist throughout most of a patient's reproductive life (and beyond for hyperandrogenic symptoms).¹⁸ However, few studies have examined the effects of therapy beyond 6 months, and even fewer beyond 12 months. In the present study, we aim to assess the long-term therapeutic response of hirsutism, acne, and menstrual dysfunction to suppressive therapy in general, and to combination OC+SPL in particular. In addition, we aimed to develop predictive models for therapeutic response, which may be used to guide clinical care and patient counseling.

Materials and Methods

Subjects

As previously described,¹⁷ all patients who presented with symptoms potentially related to androgen excess, such as oligomenorrhea, ovulatory dysfunction, excess hair growth, virilization, alopecia, acne, or acanthosis, at the University of Alabama at Birmingham (UAB) between October 1987 and June 2002 were evaluated, and their data collected prospectively and maintained in a computerized database. The study was approved by the Institutional Review Board for Human Use at UAB.

Exclusion and inclusion criteria

In this study, we included 200 initially untreated consecutive nondiabetic women diagnosed with PCOS. Patients were excluded if (i) seeking infertility therapy; (ii) had inadequate duration of follow-up (*i.e.*, follow-up <6 months, or who did not return after their initial visit); or were noncompliant with either treatment or follow-up (*i.e.*, who were noncompliant in taking the medication according to prescribed directions, or who were seen for care at greater than 18-month increments). None of the subjects was premenarcheal or postmenopausal, had undergone prior hysterectomy, oophorectomy, or natural menopause, or had been previously diagnosed or receiving hormonal treatment for at least three months before evaluation.

As previously described, the diagnosis of PCOS was defined by the NIH 1990 criteria,¹⁹ and based on an evaluation that included a medical history and physical examination, focusing on features of menstrual and ovulatory history, and clinical and biochemical hyperandrogenism, including a

modified Ferriman–Gallwey (mF-G) hirsutism score, and a hormonal evaluation.¹⁷ Of note, during the time of this study, ovarian morphology was assessed only intermittently, and consequently is not reported. To minimize the probability of interobserver variability in the assessment of the mF-G scores, all the patients were evaluated by one observer (R.A.). Weight and height were measured in all participants using standardized methods and equipment, and waist and hip circumferences were measured and waist/hip ratio calculated, as previously reported.¹⁷

Treatment protocol

All subjects were treated with suppressive therapy comprising OCs, antiandrogens, or their combinations. The protocol for treatment has been reported previously,¹⁷ as follows:

- All patients with menstrual or ovulatory dysfunction received OCs if no contraindications; the primary OC used consisted of a combination of 35 µg ethinyl estradiol and 1 mg ethynodiol diacetate.
- Patients with unwanted hair growth and evidence of excess facial or body terminal hair growth were treated with SPL (200 mg/day if mF-G ≥8; 100 mg/day if mF-G 3–7) in combination with the OC.
- SPL was used alone, except in the hirsute patient who had previously undergone tubal ligation or used other reliable contraception, who suffered adverse reactions to OC, or those for whom OC was contraindicated.
- Other treatment regimens were occasionally used, including glucocorticoids, insulin sensitizers, GnRH analogs, flutamide, finasteride, and other estrogen–progestin combinations, alone or in combination.

Changes to therapy based on side effects or risks were managed as previously described.¹⁷

Follow-up evaluation

At first visit, subjects were evaluated in a uniform manner and data captured in standardized forms, as previously described.¹⁷ Patients were routinely followed every 4–12 months, questioned about response and side effects of therapy, and periodically assessed mF-G score, usually annually. We did not routinely assess the patients' androgen or sex hormone-binding globulin (SHBG) levels in response to suppressive therapy and hence will not report these data.

We retrospectively reviewed the charts of the patients selected and using a uniform form to extract data related to patients' subjective response to suppressive therapy (reporting whether they were feeling “better,” “same,” or “worse,” or no response), length of follow-up, and mF-G score. Unfortunately, we had too few patients with androgenic alopecia who were followed over time to allow us to arrive at an informed conclusion and therefore have not included these data in this analysis.

Biochemical analysis

At the initial evaluation, blood samples were obtained within the first 8 days of a spontaneous vaginal bleed or, if anovulatory or amenorrheic, after a spontaneous or a progesterone-induced withdrawal bleed induced using oral micronized progesterone,

as previously reported.²⁰ The blood samples were preferably obtained in the morning and fasting, for the measurement of total testosterone (T), dehydroepiandrosterone sulfate (DHEAS), SHBG, and 17-hydroxyprogesterone (17-OHP), and for the calculation of free T as previously described.^{17,20–22}

Statistical analysis

Date of first visit was taken as the start of the treatment, and the date of last follow-up indicated the end of recognized therapy. The therapeutic response was assessed quantitatively by changes in mF-G score (final mF-G minus initial mF-G score), and qualitatively using the patients' perception of feeling better for hirsutism, menstrual irregularity, and acne.

The primary analysis endpoints were (a) change in the severity of hirsutism (by the modified mF-G score), per 100 person-months of follow-up,²³ and (b) overall improvement rates (over survival time) based on the subject's self-assessment of the efficacy of suppressive therapy for hirsutism, irregular menstrual cycle, and acne, calculated as follows:

$$\text{Improvement rate} = \frac{\text{Number reporting improvement or had reduction in mF-G score} \times 100}{\text{Total person-months of follow-up i.e. sum of periods of follow-up}}$$

Logarithmic transformation was performed to achieve a normal distribution for skewed variables (total and free T, DHEAS, 17-OHP and SHBG). Categorical data were analyzed using the χ^2 test or Fisher's exact test, and continuous variables were analyzed using a *t*-test, one-way ANOVA, or Kruskal–Wallis, as appropriate. The improvement rates were compared using Z-test for proportions and presented as events per 100 person-months.

Because the 200 PCOS patients studied had different durations of follow-ups, person-months of follow-up were determined for the outcome variables (*i.e.*, improvement rate per 100 person-months of follow-up). Furthermore, as response to therapy is a time to event outcome, the statistical analysis of treatment results was based on survival instead of only the absolute proportion of patients who improved. Data for patients who were lost to follow-up were censored at the time of the last contact.

The cumulative percent of patients who reported being "better" or had a reduction in mF-G as a function of follow-up time was computed using Kaplan–Meier methods. To simultaneously assess several potential influences on hirsutism improvement rates, the Cox proportional hazard regression model was performed with the (log) of the improvement rate for hirsutism as the outcome (Y), and with adjustments for potential prognostic factors, including age, body mass index (BMI), race, initial mF-G score, total T, free T, SHBG, DHEAS, and 17-OHP levels assessed one at a time and simultaneously.

The log-rank test was used to compare significance differences in improvement rates bivariately, based on initial mF-G score or circulating SHBG levels at presentation. Five-year predicted probabilities of improvement rates were estimated from the Cox model. A graphical representation of the multivariate model was generated for practical use. A two-sided $p < 0.05$ was considered statistically significant. Data analyses were conducted using the StatsDirect statistics software package, version 2.7.8 2010 (Cheshire, England).

Results

General features and duration of follow-up

Of the 200 total PCOS patients assessed, 138 were treated with combination OC+SPL (Group 1), while 62 were treated with OC-alone, SPL-alone, and/or other (Other group) treatment regimens (Group 2). Overall, subjects in Group 1 were slightly younger and had lower total T levels than Group 2, but the two subgroups were similar in terms of their basic demographic and endocrine characteristics (Table 1). About 90% of the subjects in each of the two groups were non-Hispanic white. The overall mean $\pm$ standard error ([SE]; range) follow-up time was 34.2 ± 2.5 (6–155) months, 38.2 ± 3.2 (6–155) months, and 36.0 ± 4.7 (6–139) months for the entire cohort, and Groups 1 and 2, respectively. No significant differences in mean or median follow-up time were found for the 138 PCOS patients treated with OC+SPL compared with that for the 62 treated with other forms of therapy (Table 1).

Since it takes a minimum of 6 months to see a clinical response, it is important to determine the proportion of PCOS

patients who were recruited at the beginning of the study, compared with the ones who completed a descent period of follow-up in each group (OCs, SPL, OCs+SPL, electrolysis, no electrolysis). We found that 73.9% (102 of 138 patients) of PCOS patients treated with OCs+SPL completed at least 12 months of therapy compared with 74.2% (46 of 62 patients) for those treated with other forms of therapy other than OC+SPL, 77.3% (17 of 20 patients) for OC alone, 68.2% (15 of 22 patients) for SPL alone, or 80% (16 of 20 patients) mixed forms of therapy alone ($p = 0.927$). Overall, the proportion of patients who completed at least 12 months of follow-up did not differ in terms of the type of suppressive therapy or electrolysis status.

Overall efficacy of suppressive therapy for hirsutism, menstrual dysfunction, or acne

The success rates (*i.e.*, patients subjectively reporting that they were "better" or had objective decline in the severity of hirsutism quantified by the mF-G score) of suppressive therapy in PCOS are depicted in Table 1. During follow-up, a high proportion of all PCOS patients studied ($n = 200$) reported improvement in hirsutism (85.1%), menstrual dysfunction (82.7%), and acne (79.3%), for improvement rates of 2.5, 2.8, and 2.3 per 100 person-months, respectively (Table 1).

The initial and follow-up mF-G scores were available in 158 subjects of a total of 193 hirsute PCOS patients (*i.e.*, those with mF-G score ≥ 6). The percent of patients with reduction in mF-G score was 87.0% for an improvement rate of 2.3 events per 100 person-months, in 34.2 ± 2.5 months of follow-up. The magnitude of reduction in mF-G score is also shown in Table 1. The mean $\pm$ SE initial mF-G score was 9.1 ± 0.3 and the last recorded mF-G score was 4.1 ± 0.3 , with a mean net decline in mF-G score of 5.2 ± 0.3 and a 55.9% decline in mean mF-G score.

TABLE 1. CHARACTERISTICS OF POLYCYSTIC OVARY SYNDROME WOMEN ACCORDING TO SUPPRESSION THERAPY GROUPS

Characteristics	All PCOS (N=200)	Group 1 vs. Group 2		
		Treated with OC+SPL (Group 1) ^a (N=138)	Treated with other medications (Group 2) ^b (N=62)	p-Value (Group 1 vs. Group 2)
Age (years)	27.3±0.6	26.2±0.7	29.8±1.1	0.0045
BMI (kg/m ²)	32.6±0.7	32.1±0.8	33.7±1.3	0.2778
WHR	0.82±0.01	0.81±0.01	0.84±0.01	0.0731
Race (%)				
Non-Hispanic White	92	92.8	90.3	0.5611
Black	6.5	5.8	8.1	0.5531
Others	1.5	1.5	1.6	0.9012
Overall follow-up (months)				
Median (minimum–maximum)	22.5 (6–155)	24.0 (6–155)	19.5 (6–139)	0.2123
Mean (SE)	34.2±2.5	36.1±2.8	30.0±3.7	0.2796
Subjective improvement in menstrual function				
% (n) Feeling “better”	82.7 (124/150)	85.5 (94/110)	75.0 (30/40)	0.2106
Feeling “better”/100 person-months	2.77 (124/5411)	2.29 (94/4110)	2.31 (30/1301)	0.9685
Subjective improvement in acne				
% (n) Feeling “better”	79.3 (23/29)	79.2 (19/24)	80.0 (4/5)	0.9999
Feeling “better”/100 person-months	2.32 (23/988)	2.32 (19/792)	2.04 (4/196)	0.7659
Subjective improvement in hirsutism ^c				
% (n) Reporting “better”	85.1 (160/188)	89.9 (124/138)	72.0 (36/50)	<0.0001
Reporting “better”/100 person-months	2.45 (160/6776)	2.49 (124/4978)	1.32 (36/1554)	0.7082
Improvement in mF-G score ^c				
% with reduction in mF-G score	86.7 (138/158)	93.0 (107/113)	70.46 (31/45)	0.0002
No reduction in mF-G/100 person-months	2.32 (137/5902)	2.13 (106/4978)	1.72 (31/1798)	0.2849
Improvement in magnitude of mF-G score				
Initial mF-G score (mean±SE)	9.1±0.3	9.9±0.4	7.4±0.5	0.0005
Final mF-G score (mean±SE)	4.1±0.3	4.1±0.3	4.2±0.5	0.834
Reduction in mF-G score (mean±SE) ^d	5.2±0.3	6.0±0.4	3.2±0.5	0.0001
% Reduction in mF-G score	55.9 (5.2/9.1)	60.6 (6.0/9.9)	43.2 (3.2/7.4)	0.0115
Endocrine parameters				
Free T (pg/mL) ^e	0.75(0.13–6.8)	0.72 (0.13–6.8)	0.81 (0.19–2.6)	0.1849
Total T (ng/dL) ^e	75.9 (0.31–635)	71.7 (0.13–203)	86.3 (0.19–635)	0.0346
DHEAS (ug/dL) ^e	1939 (92–6692)	1965 (92–6692)	1881 (323–5648)	0.6864
17-OHP (ng/mL) ^e	1.06 (0.03–8.66)	1.08 (0.11–4.83)	1.01 (0.03–8.66)	0.5715
SHBG (nmol/L) ^f	170 (100–670)	169 (100–670)	171 (100–430)	0.7465

n is the number of patients reporting improvement or who experienced reduction in mF-G score divided by the total who responded, or had both the initial and final mF-G score documented. Mean values are expressed as mean±standard error (SE). Bold *p*-values indicate significant groups.

^aOC + SPL combination therapy.

^bOther medications (suppressive therapy other than OC+SPL regimen).

^cImprovement for hirsutism based on a number of patients' perception of feeling better for hirsutism or patients with net reduction in mF-G score.

^dMagnitude of net reduction in mF-G score.

^eGeometric mean (range), the antilog of the log scale mean, is reported for log-transformed data.

^fNormal mean (±SD) SHBG activity is 29±5 (10⁻⁸ nmol/L) (22).

mF-G, modified Ferriman–Gallwey; OC, oral contraceptive pills; SPL, spironolactone; PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin; WHR, waist/hip ratio; DHEAS, dehydroepiandrosterone sulfate; 17-OHP, 17-hydroxyprogesterone; BMI, body mass index.

Efficacy of suppressive therapy using combination OC+SPL versus all other regimens

The percent of patients who reported improvement for either acne or menstrual dysfunction, and the respective improvement rates per 100 person-months were similar between women being treated with combination OC+SPL (Group 1) versus Other regimens (Group 2) (Table 1). Alternatively, the percent of patients who reported improve-

ment in terms of hirsutism in those using combination OC+SPL was higher than for others (89.9% vs. 72.0%), but the difference in improvement rates per 100 person-months between the two groups did not reach significance (Table 1).

Both the initial and follow-up mF-G scores were available in 81.9% (113 of 138 patients) of those treated with OC+SPL (Group 1) and 72.6% (45 of 62 patients) of those who received other forms of suppressive therapy (Group 2). The OC+SPL resulted in greater net reduction in the magnitude of

mF-G score than other forms of suppressive therapy (6.0 ± 0.4 vs. 3.2 ± 0.5 ; $p = 0.0001$) (Table 1).

The treatment regimens used in all treated Group 2 patients, along with their numbers, duration of follow-up, and efficacy of therapy, are described in Figure 1 and Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/jwh). Of the 62 Group 2 PCOS patients, 20 received OC alone, 22 SPL alone, and 20 other forms of therapy, including dexamethasone ($n = 3$), SPL+metformin ($n = 1$), SPL+dexamethasone ($n = 1$), troglitazone ($n = 1$), OC+others ($n = 12$), and unspecified ($n = 2$). No significant differences in the mean length of follow-up were found between those treated with combination OC+SPL compared with those treated with OC alone, SPL alone, or other forms of therapy (36.1 ± 2.8 vs. 33.5 ± 8.3 , 23.1 ± 3.8 , or 34.4 ± 6.6 , respectively). Similar results were obtained for the median follow-up time.

We then investigated the hypothesis that combination OC+SPL was superior to either medication alone with respect to efficiency in the treatment of hirsutism. The percent of PCOS patients treated with OC+SPL who reported improvement was higher than that found in those who received OC alone, SPL alone, or Other (89.9% or 2.5 events per 100 person-months, vs. 51.0% or 1.7 events per 100 person-months, 68.2% or 2.9 events per 100 person-months, and 50.0% or 1.6 events per 100 person-months, respectively, $p < 0.0117$ to < 0.0001). Alternatively, no significant differences in response were observed between patients treated with OC alone, SPL alone, or Other ($p = 0.4639$).

Similarly, the percent of PCOS patients treated with combination OC+SPL who experienced a net reduction in mF-G score was higher than those who received OC alone or SPL alone (77.5% or 2.2 events per 100 person-months vs. 25% or 0.8 events per 100 person-months, and 54.6% or 2.4 events per 100 person-months, respectively, $p = 0.0422$ to < 0.0001), but similar to the Other group (70.0% or 2.3 events per 100 person-months, $p = 0.5717$). While the percent of patients with a net reduction in mF-G score was lower in the OC alone versus Other ($p = 0.0113$), no difference was found between SPL alone and OC alone ($p = 0.1024$), or between SPL alone and Other ($p = 0.4765$).

As per the treatment regimen described, the mean mF-G score at baseline was greater in the OC+SPL group than in women treated with OC alone or other regimens (9.9 ± 0.4 vs. 5.4 ± 1.1 and 7.7 ± 0.6 , respectively; $p < 0.0479$ to < 0.0001), but comparable with that of the SPL-alone group (9.9 ± 0.4 vs. 9.0 ± 0.9 , respectively; $p < 0.2570$). Nonetheless, therapy with combination OC+SPL resulted in a greater net reduction in mean mF-G score, than either OC or other forms of therapy (6.0 ± 0.4 vs. 1.1 ± 0.8 and 3.7 ± 0.6 , respectively; $p < 0.0023$ to $p < 0.0001$), although the difference did not reach significance when compared with SPL alone (6.0 ± 0.4 vs. 4.2 ± 1.0 , respectively; $p < 0.0636$). The reduction in mean $\pm$ mF-G score in response to OC alone was smaller than that produced by either SPL alone ($p = 0.0070$) or Other ($p = 0.0047$), while it was similar between SPL alone and Other ($p = 0.8395$).

Overall, the magnitude in the reduction in hirsutism measured by the mF-G was greater for those treated with combination OC+SPL compared with those who received OC alone, SPL alone, or Other (66.6% vs. 20.4%, 46.7%, and 48.1%, respectively, $p < 0.01$ to < 0.0001), as was the percent

of patients reporting improvement for hirsutism (Supplementary Table 1).

Efficacy of adjuvant therapy with electrolysis for hirsutism

We compared the efficacy of different regimens among those who received adjuvant electrolysis in terms of changes in mean mF-G score. Sixty patients (53.1%) received OC $\pm$ SPL, 7 (35.0%) OC alone, 8 (36.4%) SPL alone, and 10 mixed forms of therapy (55.6%) ($p = 0.257$). Among these patients, the mean reduction in mF-G score after OC $\pm$ SPL therapy (7.0 ± 0.7) was greater than that observed in those treated with either OC alone (7.0 ± 0.7 vs. 3.7 ± 2.0 , respectively; $p = 0.0221$) or mixed forms of therapy (7.0 ± 0.7 vs. 3.5 ± 0.8 , respectively; $p = 0.0221$), and tended to be greater than those treated with SPL alone (7.0 ± 0.7 vs. 3.7 ± 1.7 , respectively; $p = 0.0582$). Alternatively, no difference was found in magnitude of reduction in mean mF-G score among the groups treated with OC, SPL, and mixed forms of therapy ($p \geq 0.05$).

To remove the confounding effect of differing treatment protocols, we restricted our further analysis of electrolysis status only to the PCOS patients treated with OC $\pm$ SPL. Sixty women with PCOS had electrolysis in addition to suppressive hormonal therapy among the 138 patients treated with combination OC+SPL (Fig. 2). Women who did and did not receive electrolysis were comparable at baseline in terms of age (26.1 ± 1.1 vs. 26.4 ± 1.1 years, respectively; $p = 0.8403$) and BMI (31.04 ± 1.10 vs. 33.02 ± 1.50 kg/m², respectively; $p = 0.2759$). Patients who used electrolysis concomitantly with hormonal suppression had a greater mean duration of follow-up in comparison with those who did not (46.0 ± 4.7 months vs. 29.3 ± 3.9 months, respectively; $p < 0.0048$) (Fig. 2A). They also tended to demonstrate a great net reduction in their mF-G score (7.0 ± 0.7 months vs. 5.0 ± 0.4 , respectively; $p = 0.0781$) (Fig. 2B), a greater percent who reported improvement (95% vs. 83%, respectively; $p = 0.0789$) (Fig. 2C), and a higher improvement rate (2.8 vs. 2.1 per 100 person-months of follow-up, respectively, $p = 0.0761$) (Fig. 2D), although the differences did not reach significance.

The proportion of the PCOS patients who completed at least 12 months of suppression therapy was similar among those treated with OCs $\pm$ SPL suppression therapy plus electrolysis (81.7%; 49 of 60 patients) compared with those who did not receive adjuvant electrolysis therapy (61.3%; 38 of 53 patients) ($p = 0.3018$).

Prediction of response to combination OC+SPL suppressive therapy

To determine prognostic models for response to therapy, we chose to study only the 138 PCOS subjects who had received combination OC+SPL, to analyze subjects who were more homogenous in their therapy. Table 2 depicts the results of the bivariate analysis comparing the improvement rates for hirsutism with suppressive therapy according to the initial mF-G score or SHBG level in the 138 subjects. The improvement rate decreased as the initial modified hirsutism score was greater or the SHBG levels were higher ($p < 0.04$).

Controlling for the initial mF-G score and log SHBG, while using a multivariate Cox model equation, the other variables (age, BMI, race, and 17-HP, total T, free T, and

FIG. 1. Comparison of the efficacy of combination OC+SPL therapy or either drug alone for the treatment of hirsutism. The percent of PCOS patients reporting improvement was higher in the combination OC+SPL group than in the OC-alone or SPL-alone groups (A). The percent of PCOS patients with a net reduction in mF-G score was higher in the combination OC+SPL group than OC or SPL group (B). The magnitude in net reduction for the mF-G score from baseline was greater in the combination OC+SPL group than for OC alone, and tended to be greater than for the SPL-alone group (C). mF-G, modified Ferriman-Gallwey; OC, oral contraceptives; PCOS, polycystic ovary syndrome; SPL, spironolactone.

FIG. 2. Comparison of outcome variables between patients with and without adjuvant therapy with electrolysis for hirsutism. Patients with PCOS who used electrolysis concomitantly with hormonal suppression, in comparison with those who did not use electrolysis, had a greater mean ($\pm$ SE) duration of follow-up (**A**). They also tended to have a greater net change in mF-G score (**B**), a greater percent who reported improvement to suppressive therapy (**C**), and a higher improvement rate per 100 person-months of follow-up (**D**), although the differences did not reach significance.

DHEAS levels) assessed were not associated with response and consequently were not included in the model. The predictive model developed posits that, controlling for log SHBG, for every one unit increase in initial mF-G score, the average rate of hirsutism improvement per 100 person-months decreases by a factor of 0.971. Alternatively, controlling for initial mF-G score, for every one unit increase in log SHBG, the average rate of hirsutism improvement per

100 person-months decreases by a factor of 0.547. The log rate ratio was -0.030 for initial mF-G and -0.603 for log SHBG. The overall chi-square for the model was 7.47 (df=3), $p=0.0238$.

We then attempted to predict the proportion of subjects who reported improvement (*i.e.*, report that they are “better”) for hirsutism as a function of time, SHBG level, and initial mF-G score (Table 3 and Fig. 3). The probability

TABLE 2. BIVALENT DIFFERENCES IN IMPROVEMENT RATE FOR HIRSUTISM USING COMBINATION OC+SPL ($N=138$), BASED ON INITIAL MODIFIED FERRIMAN–GALLWEY SCORE OR SEX HORMONE-BINDING GLOBULIN LEVEL

	Range	F/U (months)	No.	No. “feeling better”	Improvement rate ^a
Initial mF-G score ^b	0–7.0	1293.3	45	40	3.09
	8.0–11.0	1903	54	49	2.57
	12.0–15.0	1008.6	24	20	1.98
	16.0–19.0	428.2	9	9	2.1
	20.0–27.0	321.4	6	6	1.87
log SHBG ^{c,d}	4.61–4.87	1172.2	37	34	2.9
	4.87–5.13	1300.1	36	36	2.77
	5.13–5.30	1263	36	30	2.38
	5.30–6.51	1219.2	29	24	1.97

^aThe improvement rate (feeling better) decreased significantly as the initial mF-G hirsutism score was greater or the plasma SHBG levels were higher.

^bInitial mF-G score subdivided into quartiles.

^cInitial circulating SHBG levels subdivided into quartiles.

^dlog 4.6 (~ 101 nmol/L); log 4.87 (~ 130 nmol/L); log 5.13 (~ 169 nmol/L); log 5.30 (~ 200 nmol/L); log 6.51 (~ 671 nmol/L).

F/U, follow-up.

TABLE 3. COX MODEL PROBABILITY OF HIRSUTISM IMPROVEMENT AS A FUNCTION OF INITIAL MODIFIED FERRIMAN–GALLWEY SCORE AND SEX HORMONE-BINDING GLOBULIN LEVELS

F/U (mos)	Initial mF-G score				Circulating SHBG levels (nmol/L)		
	mF-G=5, %	mF-G=10, %	mF-G=15, %	mF-G=20, %	SHBG=120, %	SHBG=125, %	SHBG=180, %
0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0
6	3	2	2	2	3	2	2
9	13	11	10	8	14	12	11
12	27	23	21	18	28	25	23
18	43	38	34	30	45	40	37
24	51	46	41	37	53	48	45
30	58	52	47	42	60	55	51
36	64	59	53	48	67	62	58
42	70	65	59	54	72	67	63
48	74	69	63	58	76	71	67
54	79	74	68	63	81	76	73
60	83	78	73	68	85	80	77

Bold *p*-values indicate data at 24 months of follow-up.

of any individual patient experiencing improvement in hirsutism at any given point in time was greater, the lower the initial mF-G score and circulating SHBG level at presentation.

Successful treatment of hirsutism with combination OC+SPL requires at least 6 months of treatment, with the

proportion of patients satisfied with the outcome of therapy continuing to increase over subsequent years. Accordingly, the worst response to suppressive therapy is obtained if the follow-up period is less than 6 months and greatest at the 60 months of follow-up, irrespective of baseline hirsutism or SHBG levels.

FIG. 3. Cox plot of the probability of hirsutism improvement as a function of initial mF-G score and SHBG levels. The model depicts the percent of patients with PCOS reporting improvement (reporting that they are “feeling better”) as a function of follow-up time, taking into consideration pretreatment circulating SHBG levels (A) and mF-G score (B). The proportion of PCOS subjects responding to therapy at SHBG levels of 120 nmol/L or those with mF-G score of 5 was higher than that at SHBG levels of 125 or 180 nmol/L, or mF-G scores of 10, 15, or 20. At each level of SHBG or mF-G score, the response to suppression therapy with OC+SPL progressively increases over the subsequent 5 years of therapy. The response was observed beginning at 6 months and increased thereafter for at least 60 months. The duration of follow-up was 6–12 months ($n=41$), 13–24 months ($n=29$), 25–36 months ($n=18$), 37–48 months ($n=11$), 49–60 months ($n=13$), and >60 months ($n=26$). SHBG, sex hormone-binding globulin.

Adverse events

The overall rate of adverse events related to suppressive therapy, regardless of cause, was high at 65% (130 of 200 PCOS patients), although most adverse events were mild to moderate in severity. As previously reported, the most frequent side effects of hormonal suppressive therapy for hirsutism reported include irregular vaginal bleeding, headache, nausea, abdominal pain, and mood changes, similar to our previous study.¹⁷ As expected, weight gain and headaches were more frequent among women using OCs, whether alone or in combination, and irregular bleeding and fatigue among those receiving SPL (17).

Only 37.7% of patients treated with combination OC+SPL did not report any side effects associated with suppressive therapy, compared with 29.0% of all those treated with all other forms of therapy ($p=0.3050$). The percent of patients free of adverse events following treatment with combination OC+SPL was comparable with those treated with OC alone or SPL alone (37.7% vs. 25% and 50% respectively), but higher than that reported in the Other group (37.7% vs. 15%, respectively, $p=0.0466$). The percent of patients who did not experience any side effects in the OC-alone group was similar to that in the SPL alone or Other (25% vs. 45.5% and 15%), while the percent was higher in the SPL-alone group compared with the Other group ($p=0.0330$).

Discussion

In line with other reports,^{3,5,7,9,15,17} the present study indicates that combination suppression therapy induces significant subjective improvement in hirsutism, menstrual dysfunction, and acne in PCOS. It also leads to a significant decline in the severity of hirsutism assessed clinically, with a 59.9% reduction in mF-G score. Improvement was related to time, considering that individual patients respond to suppressive therapy at different rates. Three important novel findings emerge from our study of the long-term outcome of suppressive therapy with OC+SPL in PCOS women with a median follow-up of 27.0 months.

First, the number of patients reporting improvement over time increased with time, at a rate of 2.5, 2.7 and 2.3 cases per 100 person-months for hirsutism, menstrual irregularity, and acne, respectively. Second, the proportion of patients with hirsutism responding to treatment was observed beginning at 6 months and the beneficial effect continued to increase thereafter. The continued increase in the efficacy of suppressive therapy for hirsutism over time beyond 4–6 months may reflect persistent and increasing antiandrogenic activity of SPL and increase in SHBG by OC.

Third, treatment with OC combined with SPL resulted in significantly greater reductions in mF-G score, and a higher percent of patients achieving reduction in their mF-G score, than either drug alone, with no difference in the percent of patients reporting adverse effects. This is in agreement with the few available data from randomized trials suggesting that OC and antiandrogens have additive effects on suppressive therapy for hirsutism.^{9,24,25} Finally, the probability of patient satisfaction with her therapeutic response at any given point can be predicted by her pretreatment mF-G score or circulating SHBG level, thereby providing an important tool for prognostication, therapeutic decision-making, and counseling.

There is relative lack of data on the impact of PCOS-specific treatments on health-related quality of life (HRQOL). Some studies have reported that therapeutic interventions focused at lowering androgens with continuous OC improved overall psychological well-being compromised by obesity, hirsutism, and menstruation in women with PCOS.²⁶ There are reports noting that a 6-month use of OC improved HRQOL scores in lean women with PCOS,²⁷ although antiandrogens did not significantly improve HRQOL.²⁸ Our study also extended the findings of these studies by demonstrating that treatment with combination OC+SPL resulted in a significantly higher proportion of patients satisfied with their care compared with other regimens. While the use of validated survey instruments such as the PCOS Health-Related Quality of Life Questionnaire (PCOSQ)²⁹ or the SF-36 questionnaire,³⁰ which is not specific to PCOS, to assess and model patient satisfaction regarding their response to hirsutism therapy would have been ideal, we instead chose to use a simplified tool to abstract data from the clinical record to assess subjective reports of improvement.

The majority of earlier reports examining the effects of suppressive therapy on hirsutism in PCOS have focused on the efficacy and safety of various treatment regimens, and were limited by their relatively short timeframe, often of less than 12-month duration.^{3,5,7–9,13,15,31} In addition, available data on prognostic factors for hirsutism in PCOS are scarce. In a retrospective study comparing 78 responders and 35 nonresponders among 109 women with hirsutism treated with 75–100 mg/day of SPL,³¹ investigators found that the former had a higher mean baseline mF-G score and tended to have lower DHEAS levels. Although the outcome measures were similar in the present study (self-assessment of hirsutism and mF-G), consideration was given to censored data in our study, reflecting the reality that patients have different durations of follow-up and rates of response.³²

The prognostic model for the response of hirsutism to suppressive therapy was constructed based on the 138 PCOS patients studied who were treated with OC+SPL to analyze subjects who were more homogenous in their therapy. Our data indicate that a lower pretreatment (initial) mF-G score or circulating SHBG level at any given point predicts a higher chance of improvement following therapy for hirsutism. That a worse prognosis was associated with a greater initial mF-G score is not surprising, giving that the mF-G score reflects total terminal hair growth burden. Furthermore, the lower mF-G score as predictor of response likely simply reflects the fact that once facial or body hairs have been fully “terminalized,” they will not respond (*i.e.*, revert to vellus hairs) with androgen suppression/blockade alone. The more severe the hirsutism, the more extensive the number of fully terminalized hairs.

One of the mechanisms by which OCs reduce hirsutism is by increasing circulating SHBG levels, through which free T decreases concurrently with increasing circulating SHBG levels, thereby lowering androgen action at the hair follicle.³³ The decrease in improvement rate in hirsutism with higher initial SHBG levels likely reflects the lesser ability of the OC to reduce free (active) T in these patients and may signal patients whose hair growth is less dependent on circulating androgens.³³ While studies of concurrent assessment of plasma SHBG and T levels in response to OC alone or combination OC+SPL are lacking in PCOS, such studies in response to metformin therapy demonstrated that the greatest decline in

free T occurred in patients with the greatest initial hyperandrogenemia,^{34,35} which is synonymous to a greater response observed among those with initial low plasma SHBG in our study, underscoring the complex interrelationship between androgens, SHBG, insulin, and sebaceous unit.

Electrolysis, although never tested in a randomized controlled setting, has been reported to be an effective means of permanently eliminating unwanted hair growth.³⁶ Of interest is our observation that patients who elected to undergo electrolysis in conjunction with their suppressive therapy seemed to do better than those who did not (Fig. 2), although we recognize the differences did not reach statistical significance. Patients electing to undergo adjuvant electrolysis therapy had a longer mean time to follow-up, suggesting that these individuals may also be more compliant with therapy. Of note, most of the patients who had electrolysis were white (84%), who for cultural and economic reasons may have better access to healthcare in general and to healthcare adjuvants in particular. It is unlikely that the fact that patients undergoing electrolysis had a longer follow-up than those who did not use such an adjuvant therapy influenced the results observed, since electrolysis, if anything, would have accelerated any improvement in hirsutism.

Reliable prognostic factors or models are needed to predict individual response to therapy. Currently, the decision to treat hirsutism is largely based on the recommendation of various professional organizations.^{3,37,38} These recommendations generally note that prolonged medical therapy of at least 6–12 months of duration is necessary for suppression of hirsutism, a recommendation based on the hair follicle growth cycle. Overall, our data extended these recommendations by allowing estimation of 5-year predicted cumulative probabilities of improvement rates, individualized to each patient's needs based on her initial mF-G score and basal levels of SHBG.

The strengths of this study are the large number of subjects included, the significant length of follow-up time, the fact that only one experienced investigator assessed all subjects' mF-G scores, and the uniformity of the subjects' diagnostic criteria. Given that metformin, flutamide, troglitazone, and so on exhibit some significant efficacy in treating hyperandrogenic symptoms, we performed a secondary analysis, excluding these subjects described as mixed or other group. This study is limited by the fact that while the baseline data on the subjects were gathered prospectively, the data on therapeutic outcome were assessed retrospectively. Furthermore, the majority of our study subjects were white or black, who have similar hair distribution,³⁹ such that the findings of this study will need to be confirmed in other racial/ethnic groups. In addition, this study was based on women affected by PCOS as defined by the 1990 NIH criteria (*i.e.*, Phenotypes A and B as currently defined), and therefore, the present data may not be extrapolated to other forms of PCOS. However, it should also be recognized that the only other PCOS phenotype that exhibits hirsutism and is called upon by the broader Rotterdam 2003 criteria is Phenotype C, which includes patients with hyperandrogenism and polycystic ovarian morphology, but normal ovulation (aka "ovulatory PCOS"). Finally, a number of factors, including insulin levels and insulin-like growth factor-1 (IGF-1), that may influence symptoms³⁴ are not assessed in this study.

In conclusion, suppressive therapy in PCOS was associated with significant improvements in menstrual dysfunction,

acne, and hirsutism. The probability of patient satisfaction with her response to hirsutism therapy at any given point can be predicted by her initial mF-G score or circulating SHBG level at presentation, thereby providing an important tool for prognostication, therapeutic decision-making, and counseling. Further studies in other cohorts will be required to validate this predictive model.

Acknowledgments

This work was supported by grants R01-DK073632 and R01-HD29364 from the NIH and an endowment of the Helping Hand of Los Angeles, Inc.

Author Disclosure Statement

R.A. is a consultant to KinDex Pharmaceuticals, Ansh Labs, Medtronic, Spruce Biosciences, and Latitude Capital, and on the advisory board to Global PET Imaging. U.E., A.H., and M.L. have nothing to declare.

References

1. Azziz R, Carmina E, Dewailly D, et al. The androgen excess and PCOS society criteria for the polycystic ovary syndrome: The complete task force report. *Fertil Steril* 2009;91:456–488.
2. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab* 2004;89:2745–2749.
3. Paparodis R, Dunaif A. The hirsute woman: Challenges in evaluation and management. *Endocr Pract* 2011;17:807–818.
4. Escobar-Morreale HF, Carmina E, Dewailly D, et al. Epidemiology, diagnosis and management of hirsutism: A consensus statement by the androgen excess and polycystic ovary syndrome society. *Hum Reprod Update* 2012;18:146–170.
5. Batukan C, Muderris, II. Efficacy of a new oral contraceptive containing drospirenone and ethinyl estradiol in the long-term treatment of hirsutism. *Fertil Steril* 2006;85:436–440.
6. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* 2016;74:945–973.
7. Brown J, Farquhar C, Lee O, Toomath R, Jepson RG. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. *Cochrane Database Syst Rev* 2009;Cd000194.
8. Koulouri O, Conway GS. A systematic review of commonly used medical treatments for hirsutism in women. *Clin Endocrinol (Oxf)* 2008;68:800–805.
9. Swiglo BA, Cosma M, Flynn DN, et al. Clinical review: Antiandrogens for the treatment of hirsutism: A systematic review and metaanalyses of randomized controlled trials. *J Clin Endocrinol Metab* 2008;93:1153–1160.
10. Levy LL, Emer JJ. Female pattern alopecia: Current perspectives. *Int J Womens Health* 2013;5:541–556.
11. Schmidt TH, Shinkai K. Evidence-based approach to cutaneous hyperandrogenism in women. *J Am Acad Dermatol* 2015;73:672–690.
12. Spritzer PM, Lisboa KO, Mattiello S, Lhullier F. Spironolactone as a single agent for long-term therapy of hirsute patients. *Clin Endocrinol (Oxf)* 2000;52:587–594.
13. Tremblay RR. Treatment of hirsutism with spironolactone. *Clin Endocrinol Metab* 1986;15:363–371.

14. Carmina E, Lobo RA. Peripheral androgen blockade versus glandular androgen suppression in the treatment of hirsutism. *Obstet Gynecol* 1991;78(5 Pt 1):845–849.
15. Lobo RA, Shoupe D, Serafini P, Brinton D, Horton R. The effects of two doses of spironolactone on serum androgens and anagen hair in hirsute women. *Fertil Steril* 1985;43:200–205.
16. Tartagni M, Schonauer LM, De Salvia MA, Cicinelli E, De Pergola G, D'Addario V. Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. *Fertil Steril* 2000;73:718–723.
17. Azziz R, Sanchez LA, Knochenhauer ES, et al. Androgen excess in women: Experience with over 1000 consecutive patients. *J Clin Endocrinol Metab* 2004;89:453–462.
18. Hsu MI. Changes in the PCOS phenotype with age. *Steroids* 2013;78:761–766.
19. Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR, (Eds.). *Polycystic ovary syndrome*. Boston, MA: Blackwell Scientific Publications, 1992:377–384.
20. Woods KS, Reyna R, Azziz R. Effect of oral micronized progesterone on androgen levels in women with polycystic ovary syndrome. *Fertil Steril* 2002;77:1125–1127.
21. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: A prospective study. *J Clin Endocrinol Metab* 1998;83:3078–3082.
22. Azziz R, Bradley EL, Jr., Potter HD, Parker CR, Jr., Boots LR. Chronic hyperinsulinemia and the adrenal androgen response to acute corticotropin-(1–24) stimulation in hyperandrogenic women. *Am J Obstet Gynecol* 1995;172:1251–1256.
23. David G, Kleinbaum KMS, Nancy D, Barker. *ActivEpi Companion Textbook: A Supplement for Use with the ActiveEpi CD-ROM*, 2nd ed. New York: Springer, 2013.
24. McCartney CR, Marshall JC. The polycystic ovary syndrome. *N Engl J Med* 2016;375:54–64.
25. Sahin Y, Dilber S, Keleştimur F. Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. *Fertil Steril* 2001;75:496–500.
26. Dokras A, Playford M, Kris-Etherton PM, et al. Impact of hormonal contraception and weight loss on high-density lipoprotein cholesterol efflux and lipoprotein particles in women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2017;86:739–746.
27. Cinar N, Harmanci A, Demir B, Yildiz BO. Effect of an oral contraceptive on emotional distress, anxiety and depression of women with polycystic ovary syndrome: A prospective study. *Hum Reprod* 2012;27:1840–1845.
28. Barnard L, Ferriday D, Guenther N, Strauss B, Balen AH, Dye L. Quality of life and psychological well-being in polycystic ovary syn- drome. *Hum Reprod* 2007;22:2279–2286.
29. Jones GL, Benes K, Clark TL, Denham R, Holder MG, Haynes TJ. The polycystic ovary syndrome health-related quality of life Questionnaire (PCOSQ): A validation. *Hum Reprod* 2004;19:371–377.
30. Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 Health Survey—Manual and Interpretation Guide*. Boston, MA: The Health Institute, New England Medical Center, 1993.
31. Crosby PD, Rittmaster RS. Predictors of clinical response in hirsute women treated with spironolactone. *Fertil Steril* 1991;55:1076–1081.
32. Rosenfield RL. Hirsutism and the variable response of the pilosebaceous unit to androgen. *J Investig Dermatol Symp Proc* 2005;10:205–208.
33. Azziz R, Gay F. The treatment of hyperandrogenism with oral contraceptives. *Sem Reprod Endo* 1989;7:246–254.
34. Landay M, Huang A, Azziz R. The degree of hyperinsulinemia, independent of androgen levels, is an important determinant of the severity of hirsutism in PCOS. *Fertil Steril* 2009;92:643–647.
35. Kolodziejczyk B, Duleba AJ, Spaczynski RZ, Pawelczyk L. Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. *Fertil Steril* 2000;73:1149–1154.
36. Richards RN, Meharg GE. Electrolysis: Observations from 13 years and 140,000 hours of experience. *J Am Acad Dermatol* 1995;33:662–666.
37. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2013;98:4565–4592.
38. Fauser BC, Tarlatzis BC, Rebar RW, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil Steril* 2012;97:28–38.e25.
39. DeUgarte CM, Woods KS, Bartolucci AA, Azziz R. Degree of facial and body terminal hair growth in unselected black and white women: Toward a populational definition of hirsutism. *J Clin Endocrinol Metab* 2006;91:1345–1350.

Address correspondence to:
 Ricardo Azziz, MD, MPH, MBA
 State University of New York (SUNY)
 System Administration
 State University Plaza
 353 Broadway
 Albany, NY 12246

E-mail: ricardo.azziz@suny.edu