Combined Oral Contraception and Bicalutamide in Polycystic Ovary Syndrome and Severe Hirsutism: A Double-Blind Randomized Controlled Trial

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- Common cause of menstrual irregularity, infertility, hyperandrogenism, metabolic dysfunction
- Lifelong implications
  - Increased risk of metabolic syndrome
  - Type 2 diabetes mellitus
  - Cardiovascular disease
  - Endometrial carcinoma
- Rotterdam Criteria
  - Oligo and/or anovulation
  - Clinical and/or biochemical signs of hyperandrogenism
  - Polycystic ovaries
- Menstrual dysfunction
  - Oligomenorrhea – fewer than 9 periods a year
  - Amenorrhea – no periods for 3 or more consecutive months
- Hyperandrogenism
  - Acne, hirsutism, male-pattern hair loss
  - Elevated serum androgen concentrations
- Polycystic ovaries
  - 12 or more measuring 2-9 mm calculated as a mean of both ovaries
  - Volume > 7.0-7.5 mL
Background - Hirsutism

- Excess terminal body hair in male distribution (upper lip, chin, periareolar, midsternum, along the linea alba)
- Affects 5-10% of women
- Associated with significant emotional distress and depression
- Ferriman-Gallwey score (F&G)
  - Score > 8 is abnormal
  - Scores 8-15 are mild
  - Score 16-25 are moderate
  - Score > 25 is severe
- Must include history of medications that may either mask symptoms or cause symptoms
- Must ask whether the patient removes excess hair
Background - Hirsutism
Purpose

- Assess the efficacy and tolerability of a combined treatment with OCP plus BC in a group of women affected with severe hirsutism.
  - Primary outcome – reduction in hirsutism
  - Secondary outcomes – evaluate tolerability of BC, body composition; occurrence of adverse events
- Demonstrate the validity of a simultaneous assessment of hirsutism with videodermoscopy as being confirmative and more objective compared with the F&G score
Methodology

- Reproductive endocrinology
- Four Italian university clinical centers
- Phase 3
- Prospective
- Randomized
- Double-blind
- Placebo-controlled
Study Population

- Hirsute women with familial classic “type A” PCOS
  - F&G score ≥ 20
  - Ovulatory dysfunction (oligomenorrhea and low plasma progesterone)
  - Polycystic ovarian morphology
  - At least one first-degree relative with PCOS

- Inclusion criteria
  - Age ≥ 18
  - Agrees to avoid other treatment of their hirsutism

- Exclusion criteria
  - Other causes of hirsutism
  - Not eligible for oral contraceptive therapy
  - Receiving drugs for systematic treatment of other illness
  - Receiving other treatment of androgen excess
  - Enrolled in experimental trials during the preceding 6 months
  - Pregnant
  - Breastfeeding
  - Severe liver disease
  - Severe hyperinsulinemia requiring steroids or metformin
Group 1 – OCP therapy + BC 50 mg PO Qday
Group 2 – OCP therapy + BC 150 mg PO Qday
Group 3 – Placebo = OCP therapy alone

Group 2 was ended after amendment was approved due to cost and comparable efficacy of the two different doses

Sample size selection

- Considered clinically relevant reduction as 35% decrease in treatment group and 10% decrease in the placebo group
- Using 1:1 randomization, power of 0.9 and significance threshold of $\alpha = 0.05$, sample size was determined to be $n = 54$
- Based on standard deviation of 28%
Study Population

Assessed for eligibility (n=300)
- Not meeting inclusion criteria (n=97)
- Refused to participate (n=110)
- Other reasons (n=23)

First Randomization (n=105)

Randomized (n=88)
- Excluded (n=230)

Group 1
- Allocation to OCP+BCSO (n=35)
  - Received allocated intervention (n=33)
  - Did not receive allocated intervention (n=2)
  - Lost to follow-up (n=3)
  - Discontinued intervention (n=2)
  - Analyzed (n=28)
  - Excluded from analysis (n=0)

Group 2
- Allocation to OCP+BC1SO (n=18)
  - Received allocated intervention (n=18)
  - Did not receive allocated intervention (n=0)
  - Excluded by analysis after protocol amendment (AIFA)

Group 3
- Allocation to OCP+P (n=35)
  - Received allocated intervention (n=34)
  - Did not receive allocated intervention (n=1)
  - Lost to follow-up (n=5)
  - Discontinued intervention (n=5)
  - Analyzed (n=24)
  - Excluded from analysis (n=0)
Methodology

- Screening visit – PMH, FH, labs, TVUS, physical exam, height, weight, BMI, waist circumference, BP, HR, hirsutism score
- Informed consent
- Baseline visit – physical exam, hirsutism score, body composition, abdominal fat evaluation, evaluation of physical activity, CBC, renal, liver, lipid, coag panels
- Every 6 months – physical exam, hirsutism score, body composition, patient’s subjective evaluation, repeat labs
- All patients also underwent nutritional counselling and recommendations for physical aerobic activity
Methodology

- Ultrasound
  - Cycle days 2-5
  - Subjective manual count of antral follicles between 2-10 mm
    - Both ovaries were added together
  - Ovarian volume \( V = x \times y \times z \times 0.5236/1.000 \)
  - PCOS diagnosed if follicle count \( \geq 24 \) or ovarian volume \( \geq 10 \) cm\(^3\)
Methodology

- F&amp;G score
  - Same physician

- Computerized videodermoscopy
  - Picture of 2 x 2 cm³ area
  - Magnification x 10
  - Software counted number of pilosebaceous units

- Most attention – linea alba, intermammary line, chin

- Body composition was also evaluated by DEXA to determine the level of fat and fat-free mass
• Shapiro-Wilk test of normality – confirm normal distribution
• Variables were presented as means (standard deviation) or medians (interquartile range)
• Parametric t test and nonparametric $x^2$ test – compared the treatment and control groups
• ANOVA
• ANCOVA
• Greenhouse-Geisser correction
• Bonferroni correction
• 95% confidence interval
• $P$ value $< 0.05$ was significant
Results - Hirsutism
## Table 2. Evaluation of Hirsutism at the Baseline and During Follow-Up

<table>
<thead>
<tr>
<th>Target Variables</th>
<th>Treatment</th>
<th>T0</th>
<th>T6</th>
<th>T12</th>
<th>6 Months After Treatment</th>
<th>Time</th>
<th>Treatment</th>
<th>Time \times Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDI</td>
<td>OCP + BC</td>
<td>Mean = 16.9</td>
<td>Mean = 5.5</td>
<td>Mean = 3.6</td>
<td>Mean = 4.4</td>
<td>F(2, 100) = 27.416;</td>
<td>F(1, 50) = 0.002;</td>
<td>F(2, 100) = 3.833;</td>
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<td></td>
<td>SD = 43.9</td>
<td>SD = 19.8</td>
<td>SD = 15.2</td>
<td>SD = 34.68</td>
<td>P &lt; 0.001</td>
<td>P = 0.965</td>
<td>P = 0.053;</td>
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<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 10</td>
<td>Mean = 7.1</td>
<td>Mean = 4.5</td>
<td>Mean = 18.6</td>
<td>P = 0.238</td>
<td>P = 0.031</td>
<td>P = 0.055;</td>
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<tr>
<td></td>
<td>SD = 30.9</td>
<td>SD = 20</td>
<td>SD = 18.5</td>
<td>SD = 20.67</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001;</td>
<td></td>
</tr>
<tr>
<td>Thorax/upper abdomen</td>
<td>OCP + BC</td>
<td>Mean = 7</td>
<td>Mean = 15</td>
<td>Mean = 3.7</td>
<td>Mean = 4.5</td>
<td>F(2, 100) = 45.442;</td>
<td>F(1, 50) = 3.68;</td>
<td>F(2, 100) = 12.985;</td>
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<tr>
<td></td>
<td>SD = 7.1</td>
<td>SD = 0.9</td>
<td>SD = 0.4</td>
<td>SD = 5.25</td>
<td>P &lt; 0.001</td>
<td>P = 0.061</td>
<td>P &lt; 0.001;</td>
<td></td>
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<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 5.1</td>
<td>Mean = 3.5</td>
<td>Mean = 2.7</td>
<td>Mean = 5.7</td>
<td>P = 0.104</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001;</td>
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<tr>
<td></td>
<td>SD = 8.3</td>
<td>SD = 7.3</td>
<td>SD = 3.4</td>
<td>SD = 1.84</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001;</td>
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<tr>
<td>Lower abdomen^b</td>
<td>OCP + BC</td>
<td>Mean = 20.5</td>
<td>Mean = 6.4</td>
<td>Mean = 4.7</td>
<td>Mean = 10.5</td>
<td>F(2, 100) = 42.31;</td>
<td>F(1, 50) = 14.82;</td>
<td>F(2, 100) = 14.562;</td>
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<td>SD = 1.6</td>
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<td>SD = 13.4</td>
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<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001;</td>
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<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 21.8</td>
<td>Mean = 16.9</td>
<td>Mean = 12.6</td>
<td>Mean = 3.9</td>
<td>P &lt; 0.001</td>
<td>P = 0.034;</td>
<td>P = 0.001;</td>
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<tr>
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<td>SD = 9.9</td>
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<td>SD = 13.2</td>
<td>SD = 21.77</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001;</td>
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<tr>
<td>mF&amp;G Total</td>
<td>OCP + BC</td>
<td>Mean = 21.8</td>
<td>Mean = 12.9</td>
<td>Mean = 6.4</td>
<td>Mean = 15.4</td>
<td>F(2, 100) = 185.06;</td>
<td>F(1, 50) = 0.026;</td>
<td>F(2, 100) = 0.543;</td>
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<td>SD = 2.3</td>
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<td>SD = 5.2</td>
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<td>P = 0.583;</td>
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<tr>
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<td>EP + P</td>
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<td>Mean = 12.8</td>
<td>Mean = 1.9</td>
<td>P = 0.041</td>
<td>P = 0.544;</td>
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<td></td>
<td>SD = 3.2</td>
<td>SD = 5.3</td>
<td>SD = 4</td>
<td>SD = 5.16</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001;</td>
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<tr>
<td>Chin</td>
<td>OCP + BC</td>
<td>Mean = 2.7</td>
<td>Mean = 1.6</td>
<td>Mean = 2.2</td>
<td>Mean = 3.5</td>
<td>F(2, 100) = 35.914;</td>
<td>F(1, 50) = 0.172;</td>
<td>F(2, 100) = 1.763;</td>
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<tr>
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<td>SD = 1.3</td>
<td>SD = 1.3</td>
<td>SD = 1.3</td>
<td>SD = 1.37</td>
<td>P &lt; 0.001</td>
<td>P = 0.680</td>
<td>P = 0.177;</td>
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<tr>
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<td>EP + P</td>
<td>Mean = 2.6</td>
<td>Mean = 2.1</td>
<td>Mean = 1.9</td>
<td>Mean = 2.9</td>
<td>P = 0.809</td>
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<td>P = 0.194;</td>
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<td>SD = 1.8</td>
<td>P = 0.001</td>
<td>P = 0.492</td>
<td>P = 0.019;</td>
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<td>Thorax/upper abdomen</td>
<td>OCP + BC</td>
<td>Mean = 1.6</td>
<td>Mean = 0.3</td>
<td>Mean = 1.6</td>
<td>Mean = 3.5</td>
<td>F(2, 100) = 35.914;</td>
<td>F(1, 50) = 0.172;</td>
<td>F(2, 100) = 1.763;</td>
</tr>
<tr>
<td></td>
<td>SD = 0.7</td>
<td>SD = 0.5</td>
<td>SD = 0.4</td>
<td>SD = 0.85</td>
<td>P &lt; 0.001</td>
<td>P = 0.492</td>
<td>P = 0.019;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 1.2</td>
<td>Mean = 0.8</td>
<td>Mean = 0.9</td>
<td>Mean = 0.9</td>
<td>P = 0.302</td>
<td>P = 0.048;</td>
<td>P = 0.058;</td>
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<tr>
<td></td>
<td>SD = 0.7</td>
<td>SD = 0.7</td>
<td>SD = 0.7</td>
<td>SD = 0.76</td>
<td>P &lt; 0.001</td>
<td>P = 0.505</td>
<td>P = 0.502;</td>
<td></td>
</tr>
<tr>
<td>Lower abdomen</td>
<td>OCP + BC</td>
<td>Mean = 3.1</td>
<td>Mean = 1.8</td>
<td>Mean = 2.3</td>
<td>Mean = 6.1</td>
<td>F(2, 100) = 61.505;</td>
<td>F(1, 50) = 0.451;</td>
<td>F(2, 100) = 0.694;</td>
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<tr>
<td></td>
<td>SD = 0.8</td>
<td>SD = 0.8</td>
<td>SD = 0.6</td>
<td>SD = 0.99</td>
<td>P &lt; 0.001</td>
<td>P = 0.505</td>
<td>P = 0.502;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 3.1</td>
<td>Mean = 2.1</td>
<td>Mean = 2.2</td>
<td>Mean = 9.3</td>
<td>P = 0.053</td>
<td>P = 0.093;</td>
<td>P = 0.429;</td>
</tr>
</tbody>
</table>

Note: For OCP + BC and EP + P, mean values are given for each variable at baseline (T0), 6 months (T6), and 12 months (T12) of treatment.
Results

- F&G score was reduced in the whole sample
- No significant difference between groups
- VDI changes
  - Chin
    - OCP + BC
    - OCP + P
  - Thorax/Upper Abdomen
    - OCP + BC
    - OCP + P
  - Lower Abdomen
    - OCP + BC
    - OCP + P
Results

- No significant effects on body composition
- Only one patient in the BC group stopped due to weight gain
- Four patients in the P group stopped
  - Headache
  - Dissatisfied with results
  - Nausea
  - “Heaviness of the lower limbs”
- Total cholesterol – statistically significant difference at the follow up time and also between the two groups over time
- LDL – statistically significant difference in the overall mean between the two groups, the overall mean between times and between the two groups over time
- Bilirubin – difference in the two groups at baseline
- Adverse events – rise in the plasma levels of cholesterol or triglycerides and intermenstrual spotting, nausea, mild anemia, hot flashes, libido reduction, dry skin
Discussion -
Bicalutamide

- Androgen receptor antagonist
- Interferes with dihydrotestosterone (DHT)-induced events required for activation of AR gene expression by androgens
- Binds to ligand-binding pocket but fails to induce the correct conformational change in its coactivator-binding platform (competitive inhibitor)
  - Considered pure due to selective affinity for AR
- Used for male prostatic carcinoma
- Previous study – 42 female patients with androgen excess took 25 mg/d and had decreased hirsutism at 3 and 6 months
Discussion

- Androgens modulate important molecular processes leading to hair growth
- OCPs – suppress ovarian androgen production (by increasing SHBG) and reduce their biologic effect
- Antiandrogens – competitive inhibitors
  - Chlormadinone acetate – steroidal progesterone with antiandrogen effects
  - Spironolactone – unpleasant side effects
  - Finasteride – functions at the level of the dermal papilla blocking conversion of testosterone to DHT, hasn’t been shown to be effective
  - Flutamide – when used with OCPs, better than OCP alone, but can cause dry skin and may cause hepatotoxicity
- Not recommended without OCPs due to being teratogenic
Discussion

- OCP vs. OCP+BC – both are effective in reversing severe hirsutism
- OCP+BC is better than OCP alone
- Daily dose of BC 50 mg was well tolerated
- Only important parameter to monitor is cholesterol
- Videodermoscopy proposed as a way to objectively follow treatments
Discussion –
Strengths

- Randomized controlled study
- Double-blinded
- Placebo controlled
Discussion – Weaknesses

- Inability to analyze the steroids using tandem mass spectrometry
- Patient autonomy regarding whether they dieted and exercised as recommended
Discussion

- Will it change how we practice?
- Where to from here?
- What additional questions does the study raise?
Resources

- Aromatase Inhibitors in Gynecologic Practice, CO 663, June 2016
- Polycystic Ovary Syndrome, PB 108, October 2009
- Diagnosis of polycystic ovary syndrome in adults, UpToDate.com
- Treatment of polycystic ovary syndrome in adults, UpToDate.com
- Epidemiology and genetics of the polycystic ovary syndrome in adults, UpToDate.com
Questions?
Combined Oral Contraception and Bicalutamide in Polycystic Ovary Syndrome and Severe Hirsutism: A Double-Blind Randomized Controlled Trial

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Context: Hirsutism often occurs in women with polycystic ovary syndrome (PCOS). The efficacy of oral contraceptive pill (OCP) plus antiandrogens in the treatment of its severe expression is controversial due to the lack of randomized, double-blind, long-term studies.

Objective: The primary outcome was the reduction of hirsutism in PCOS women objectively measured by videodermoscopy on the androgen-sensitive skin areas assessed by the modified Ferriman and Gallwey (mF&G) total score, after 12 months of therapy with OCP + bicalutamide (BC) vs OCP plus placebo (P). The secondary outcomes were to evaluate tolerability of BC and body composition as well as the occurrence of adverse events.

Design: An experimental, phase 3, prospective, multicenter, randomized, double-blind, P-controlled trial. Patients were evaluated at the baseline visit, at 6 and 12 months during treatment, and 6 months’ posttreatment.

Participants: Seventy women with classic PCOS (severe hirsutism, oligoanovulation, and ovarian polycystic ovarian morphology).

Intervention: Patients received OCP + BC (50 mg/d) or OCP + P for 12 months.

Results: The repeated measures analysis of variance showed that both treatments were effective in reducing hirsutism: The OCP + BC group had a higher reduction compared with the OCP + P group. No adverse effects were described during treatment except an increase in total cholesterol and low-density lipoprotein in the OCP + BC group.

Conclusions: The association of OCP + BC is well tolerated and significantly more effective than OCP alone in treating severe hirsutism. We suggest a combined use of the videodermoscopic index and...
P
cyclic ovary syndrome (PCOS) is a dysmetabolic and reproductive disorder associated with androgen excess in women. It is diagnosed through an identification of four separate phenotypes (A to D), according to the presence or absence of three characteristics: clinical or biochemical hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOM) (1, 2). Therefore, hyperandrogenism is the hallmark of the syndrome. It is a disabling condition from both a clinical and psychosocial point of view. Women affected by it are often overweight and have oligoanovulation and cutaneous manifestations of androgen excess (hirsutism, hyperseborrhea, acne, androgenetic alopecia). Some time ago it was suggested that the hyperandrogenic condition is related to increased cardiometabolic risk, even if the molecular mechanisms linking androgen dysregulation to endothelial dysfunction remain almost unknown (3, 4).

Psychosocial wellness is important for the healthy state of an individual, and hirsutism is one of the main complaints of women affected by PCOS who develop severe psychological problems because of androgenization (5). The pharmacological treatment of severe hirsutism is mainly based on the use of the oral contraceptive pill (OCP) in monotherapy or in association with antiandrogens (2, 5). Antiandrogen monotherapy is not recommended because of its teratogenic potential (5–7). However, the treatment of patients suffering from marked hirsutism with combined estradiol pagan (EP) plus antiandrogen therapy is still a subject for debate because of a lack of double-blind, controlled studies designed to establish the required length, effectiveness, and safety of treatment to reduce hirsutism (8).

Bicalutamide (BC) is an androgen receptor (AR) antagonist drug that interferes with the dihydrotestosterone (DHT)-induced events required for activation of AR gene expression by androgens, binding to the ligand-binding pocket of AR but failing to induce the correct conformational change in its coactivator-binding platform (9, 10). It is currently commercially available in Europe, and its tolerability, efficacy, and pharmacokinetic and clinical benefits have been assessed for male patients with advanced prostatic carcinoma (11). Only a few reports exist about its utilization in women, with one open study demonstrating in 42 patients affected by androgen excess syndrome a significant reduction in the hirsutism modified Ferriman and Gallwey (mF&G) score ($P < 0.001$) obtained after 3 and 6 months of therapy using 25 mg/d of BC (12).

To evaluate correctly the efficacy of antiandrogen therapy in hirsutism, all the units involved in this multicenter study confirmed the mF&G evaluation using a unique videodermoscopy technique. We hypothesized that this instrument could be useful in evaluating hair growth in the androgen-dependent areas of the skin at ×10 magnification in women affected by hirsutism, proposing a unique objective scoring system for evaluating this symptom given that the mF&G scoring system is limited by dependence on its operator. In all the university centers involved in this study, an identical computerized videodermoscope was available as a practical and low-cost objective method able to quantify the number and the density of hair follicles in selected androgen-dependent skin areas by establishing a videodermoscopic index (VDI). The VDI in this study was then used simultaneously with the mF&G score, the subjective method commonly applied to establish levels of hirsutism (13).

Furthermore, at the present time, very few objective methods are indicated for an assessment of hirsutism (14) and none of them have been analyzed for their validity in the evaluation of antiandrogen therapy. In the present double-blind study, we assessed the efficacy and tolerability of a combined treatment with OCP plus BC in a group of women affected with severe hirsutism (mF&G score ≥20), with oligoanovulation, and displaying ultrasound PCOM of their ovaries. To evaluate correctly the efficacy of antiandrogen therapy in hirsutism, we used a unique videodermoscopy technique to quantify the number and the density of hair follicles in selected androgen-dependent skin areas by establishing a VDI. The study aimed to demonstrate the validity of a simultaneous assessment of hirsutism with VDI as being confirmative and more objective compared with mF&G alone.

Subjects and Methods

Study design

The reproductive endocrinology sections of four Italian university clinical centers were involved to conduct this experimental, phase 3, prospective, multicenter, randomized, double-blind, placebo (P)-controlled study. Patients with PCOS were randomly allocated in a 1:1:1 ratio to receive P (EP therapy) or BC 50 mg once daily + EP therapy or BC 150 mg once daily + EP therapy. During the trial, an amendment approved by the Italian Agency for Drugs (AIFA) and by ethical committees allowed the ending of the BC 150 mg group. Such approval was obtained given the cost of P and drug preparation assessed by an interim analysis (not planned in advance) and considering data in the literature showing that the results obtained administering the two BC doses (50 and 150 mg) were strictly overlapping (15).
This clinical research involved women affected with classic PCOS “A” phenotype, where there was the presence of hirsutism, ovulatory dysfunction, and PCOM (2). In the original statement of the AIFA, the prerequisite for participating in the call for funding was selecting PCOS women with at least one first-degree relative affected by the syndrome (familial PCOS), probably potentially to aid genome-wide association studies exploring the relationship between phenotype and therapy responses as a function of the genotype and even to characterize personalized diagnosis and treatment options for PCOS (16). Based on clinical screening, we assessed for eligibility more than 300 oligoanovulatory severe hirsute women affected by familial (at least one first-degree relative affected by the syndrome) PCOS. In accord with the original study protocol, we randomized 105 patients allocated as follows: 35 received OCP + BC 50 mg, 35 received OCP + BC 150 mg, and 35 received OCP + P. No adverse events were described. Following an amendment of the protocol proposed by the AIFA, the number of patients was reduced from 105 to 70 (35 received OCP + BC 50 mg, 35 received OCP + P) to ensure that 54 patients completed the follow-up. The length of treatment of patients and controls was 12 months followed by an extended observation stage of 6 months without therapy.

The study group and the eligibility criteria for participants

The study group was made up of hirsute women with familial classic “type A” PCOS affected with hirsutism with an mF&G score ≥20, ovulatory dysfunction identified by the presence of oligomenorrhea and low plasma progesterone (PR) levels in the supposed luteal phase, and PCOM. The other inclusion criteria to take part in the study were: age ≥18 years old and the patient’s agreement to avoid other treatment of their hirsutism condition in the prestudy stage (at least 6 months before starting the double-blind treatment), during treatment and for 6 months after the end of the treatment. Exclusion criteria were any other condition that could cause hirsutism such as idiopathic hirsutism, idiopathic hyperandrogenemia, congenital adrenal hyperplasia, Cushing syndrome, and androgen-secreting tumors. Women not eligible for oral contraceptive therapy, those receiving drugs for the systematic treatment of other illnesses or receiving other treatment of androgen excess and enrolled in experimental trials during the preceding 6 months, and pregnant or breastfeeding women were also excluded from the study. In addition, women affected by or liver disease liver disease or hirsute patients with severe hyperinsulinemia requiring high doses of steroids or metformin and/or association therapies were not included.

During the various stages of the randomized trial (Fig. 1) with the 300 women screened, 48% did not agree to sign the informed consent statement; 9% were excluded because of familial dyslipidemia and/or liver disease; 3% were excluded because of congenital adrenal hyperplasia; 24% were excluded because of thrombophilia gene mutations; 6% were excluded because they were categorized as having a PCOS phenotype without signs of androgen excess; 8% were excluded because of a wish to have a pregnancy; and 2% were excluded because they were planning to move to another city.

Ethical considerations

This was, to our knowledge, the first randomized, double-blind study in which BC was administered to women. All the clinical centers involved had received approvals from local ethical committees following the first authorization given by the ethical committee of the “San Giovanni Calibita” Fatebenefratelli Hospital in Rome (no. 38/2007). All participants

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**Figure 1.** Flow diagram of hirsute patients with PCOS progress through the stages of the OCP + BC or P study.

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**Assessed for eligibility (n=300)**

- **First Randomization (n=105)**
  - **Randomized (n=88)**
    - Allocation to OCP + BC50 (n=15)
      - Received allocated intervention (n=13)
        - Did not receive allocated intervention (n=2)
      - Lost to follow-up (n=3)
      - Discontinued intervention (n=2)
      - Analyzed (n=28)
      - Excluded from analysis (n=0)
    - Allocation to OCP + BC150 (n=18)
      - Received allocated intervention (n=18)
        - Did not receive allocated intervention (n=0)
      - Lost to follow-up (n=5)
      - Discontinued intervention (n=5)
      - Analyzed (n=24)
      - Excluded from analysis (n=0)
    - Allocation to OCP + P (n=35)
      - Received allocated intervention (n=34)
        - Did not receive allocated intervention (n=1)
      - Excluded by analysis after protocol amendment (ADPA)
      - Analyzed (n=24)
      - Excluded from analysis (n=0)

- **Excluded (n=230)**
  - Not meeting inclusion criteria (n=97)
    - Refused to participate (n=110)
    - Other reasons (n=23)
received detailed oral information about the study and were requested to give written informed consent to their participation. The study (EudraCT 2009-009368-30) was conducted in accordance with the Declaration of Helsinki and its amendments.

**Justification of the sample size**

Considering that the main outcome was the reduction in the number of terminal hair follicles (registered by the software in the observational field of 4 cm² in the androgen-sensitive area), the expected, and considered clinically relevant, reduction was 35% in the group treated with OCP + BC 50 mg, assuming a 10% reduction in the P + OCP-treated group. With a 1:1 randomization, a power of 0.9, and a significance threshold at α = 0.05 (two-sided), the sample size was calculated to be n = 54 patients (27 + 27). Such a calculation was based on a common standard deviation (SD) of 28%, estimated on preliminary observations of patients who were treated with OCP and then followed up in our department. To take into account an attrition rate of about 20% to ensure that 54 patients completed the follow-up, 70 patients affected by hirsutism caused by familial PCOS were randomized between oral 50 mg/d BC + OCP and P + OCP treatment.

**Randomization**

Randomization was conducted in a double-blind experiment, and the list of codes of randomization was prepared and retained by the monitor of the study. During the first stage of the study, randomization was carried out in unbalanced blocks (the number of individuals taking the P or BC 50 or 150 mg was different in the three groups) by using a table of random numbers. After the AIFA amendment, in which the treatment with BC 150 mg was eliminated and the number of experimental samples was reduced from 105 to 70 patients, a method of competitive enlistment of new patients was adopted (Fig. 1). All the centers involved were supplied with drugs that were already packed and equipped only with the label containing the patient code and a list of codes without decoding. Seventy labeled envelopes were created, one for each patient, containing the codes for decoding. These envelopes were kept in a reserved place at the Department of Pharmacy of the “San Giovanni Calibita” Fatebenefratelli Hospital and duly signed. They were opened only at the end of the study. Only in the case of a premature rupture of the double-blind, for justified reasons, could the envelopes be opened.

**The clinical experimental protocol**

The main outcome was to investigate if BC induces a significant reduction in the hirsutism score, measured by means of a computerized videodermoscopy analysis of the terminal pilosebaceous unit number, with the establishment of an VDI analyzed by a software on the basis of the number of terminal pilosebaceous units in the examined 4-cm², androgen-sensitive skin area identified by the mF&G score. Secondary outcome was to detect eventual higher incidence in the experimental group of possible adverse effects.

Patients were randomly allocated to receive, in association with OCP, P, or BC 50 mg tablets, one daily tablet taken orally for 12 months. BC tablets and P were indistinguishable and were prepared by the Department of Pharmacology of the “San Giovanni Calibita” Fatebenefratelli Hospital in Rome, which performed the clinical trial monitoring functions. The BC dose was decided on the basis of doses applied as antiandrogen monotherapy in early and advanced stages of prostate cancer. Different therapeutic third-generation OCP regimens were used, all containing the same dosage of ethinylestradiol (0.030 mg) and a progestogen with the same antiandrogen activity (chloromadinone acetate 2 mg, drospirenone 3 mg, or dinogest 2.5 mg), avoiding ciproterone acetate because of its strongest antiandrogen activity (Supplemental Table 1). This decision was taken in accord with the evidence of comparative studies that demonstrate that these progestogens have similar effects in the treatment of PCOS (17) and taking into account for each patient the tolerability to previously used OCP, tolerance, and side effects. BC and P were started together with OCP on the first day of the menstrual cycle and, in the case of women in amenorrhea, after a pelvic/transvaginal ultrasound observation that demonstrated an endometrial thickness less than 5 mm. We recommended patients to take OCP every day at the same hour, and BC/P after breakfast, to facilitate their compliance. All patients were carefully evaluated baseline at 6 and 12 months during the therapy and 6 months after the end of the treatment.

At the screening visit, the patients were assessed as regards their systemic and family history to include those having direct relatives affected with hyperandrogenism and PCOS. Each patient underwent during the early follicular phase (days 3 to 7 of the menstrual cycle), or anytime if amenorrhoic, morning blood samples (between 8 and 9 AM) after an overnight fast to assess prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), 17β-estradiol (E2), total testosterone, sex hormone-binding globulin (SHBG), 17α-hydroxyprogesterone (17αOHP), PR, dehydroepiandrosterone (DHEA), Δ-4-androstenedione (Δ4AD), DHT, 3αdiolglucuronide (3αDG), thyrotropin-secreting hormone (TSH), insulin and homeostasis model assessment test results, complete blood count results, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol, glucose, and coagulation test results (prothrombin time, partial thromboplastin time, antithrombin III, fibrinogen, protein C, protein S, and homocysteine). To establish the presence of an active luteal function, PR levels were assayed during the supposed luteal phase calculated by the subjective intermenstrual period in each menstruating women, anytime in amenorrhoic patients. In addition, the following were engaged in: a transvaginal or pelvic ultrasound; a complete physical examination, with the registration of anthropometric measurements, height, weight, body mass index (BMI), and waist circumference; an evaluation of blood pressure (recorded on the left arm after a 5-minute rest with the woman supine, using a manual sphygmomanometer) and heart beats; and an establishment of the hirsutism score using the mF&G score and videodermoscopy software (as described later). If they were eligible to enter the study (that is to say all inclusion and exclusion criteria were met), the patients, after giving their informed consent in written form, had a baseline visit: They were assessed through a physical examination, with the detection of vital signs, hirsutism score, body composition, and abdominal fat evaluation, using dual-energy X-ray absorptiometry, as described later, and an evaluation of physical exercise activity (type, how many times and hours each week). A complete blood count, renal, liver, lipid, and coagulation tests, a complete
physical examination, in particular breast and abdomen inspection, the detection of vital signs, hirsutism score, and body composition evaluation were repeated every 6 months to evaluate the efficacy of the therapy and tolerability to it. Every 6 months, patients underwent assessment for any symptoms and signs possibly related to the therapy’s side effects, and all patients were requested to give a subjective evaluation of the efficacy of the therapy and their related comfort levels. All patients underwent nutritional counseling with precise instructions about a calorie restriction regimen as indicated. All patients were instructed to perform constant physical aerobic activity (30 minutes of fast walking or similar activity at least 5 days a week).

Ultrasound screening
At the time of inclusion in the study, transvaginal high-resolution ultrasonography, conducted by experienced professionals, was used with all the patients to ascertain the PCOS phenotype according to the criteria currently available from scientific societies (2). This was performed on days 2 through 5 of the menstrual cycle, and women in amenorrhea were scanned at any time. All the women screened underwent two-dimensional (2D) transvaginal sonography scan of both ovaries with a subjective manual count of antral follicles. All the reproductive units involved in the study evaluated ovarian volume by measuring three diameters in two different sections (longitudinal, transverse, and anterior-posterior diameters) and calculating the volume by means of the formula for a prolate ellipsoid (\( V = \pi \times r \times s \times z \times 0.5236/1.000 \)). The antral follicle count (AFC) was performed by a systematic counting of all follicles between 2 and 10 mm in the preferred (longitudinal and/or transverse) section of the ovary (18, 19). Follicles >10 mm were excluded. Counts from both ovaries were added together to obtain the total AFC. Performing two-dimensional transvaginal sonography scan of both ovaries, PCOS was assessed in the presence of \( \geq 24 \) follicles within the ovaries with a diameter less than 10 mm and an ovarian volume \( \geq 10 \text{ cm}^3 \) (20, 21). The PCOS women selected showed a mean AFC of 16 ± 3 follicles per ovary with a diameter of 6.2 ± 2.1 mm and a mean ovarian volume of 14.5 ± 4.3 cm³. The ovarian stromal echogenicity was found to have increased in all the patients included in the study. No statistically significant differences in PCOM were seen with ultrasound observations performed after the end of treatment (data not shown).

Hirsutism evaluation
Hirsutism was evaluated by the mF&G score (13, 22) performed by the same physician in every clinical center and simultaneously by computerized videodermoscopy. Videodermoscopy is a technique validated to evaluate areas of reduced hair density at the level of the scalp at \( \times 20 \) to \( \times 160 \) magnification (23). The instrument consisted of a video camera (video PICO-I-Scope; Pico Technology Limited, Cambridge, United Kingdom) with polarized light used to take pictures of a \( 2 \times 2 \text{ cm}^2 \) area at \( \times 10 \) magnification. The use of anatomical landmarks allowed us to analyze the same area at each visit. The camera was connected to a laptop in which the software Alphadoc (Medical Hi-Teck, Rome, Italy), developed specifically for the calculation of the number of pilosebaceous units within the photographed area, had been previously installed. The operator involved in the study could clearly distinguish, inside the androgen-sensitive area of the skin (corresponding to the critical areas examined to calculate the mF&G score), the terminal pilosebaceous units from the vellous units, putting a hallmark on each terminal unit. The software then calculated the total number of pilosebaceous units in each area indicated by the mF&G scoring system (14). In agreement with Cook et al. (22), who proposed a simplified Ferriman and Gallwey hair growth scoring system, we decided to pay most attention to the efficacy of the treatment on the following androgen-dependent areas: the linea alba 4 cm below the umbilicus (indicated as lower abdomen), the intermammary line at the height of the breast line and stomach (indicated as thorax/upper abdomen), and the chin. These were, moreover, the areas where the group of women with PCOS studied had the major complaints (Fig. 2).

Body composition
A secondary outcome of this study was to explore if the treatment administered could alter the body composition. All the patients enrolled were then followed through an evaluation at each visit of weight and height, BMI, and waist-to-hip circumference ratio calculated from measurements taken with the patients in a standing position during normal respiration (Table 1). The body composition was evaluated performing whole-body scans using a dual-energy X-ray absorptiometry and determining the level of fat and fat-free mass (24–27). We used the Hologic QDR Discovery A densitometer (Hologic Inc., Zaventem, Belgium), performing whole-body scans and determining the bone and soft tissue composition of the whole body and subregions such as arms, legs, and trunk (28). The instrument was calibrated by using a spine phantom daily and a step phantom weekly. All scans were performed at least 4 to 5 hours after the last meal. All patients wore loose, comfortable clothing, avoiding garments that had zippers, belts, or buttons made of metal. During the evaluation, we asked them to remove all clothes, jewelry, spectacles, and any metal objects or clothing that could have interfered with the X-ray images.

Laboratory measurements
Each reproductive unit involved in the study developed the assays and agreed to make the measurement methods for the hematological, coagulative, hormone, and metabolite assays uniform. Fasting blood samples were taken between 8 and 9 AM during the early follicular phase of the menstrual period. Serum measurements included urea, creatinine, ALT, AST, bilirubin, ALP, GGT, triglycerides, HDL, LDL, total cholesterol, and glucose, which were determined using spectrophotometric analyzers (Cobas 6000 Hitachi Module; Roche Diagnostics, Monza, Italy). TSH, PRL, FSH, LH, insulin, E2, total testosterone, PR, and 17αOHP were analyzed in duplicate by electrochemiluminescence using commercially available kits [Cobas 6000 Elecsys Module for Electrochemiluminescence (ECLIA); Roche Diagnostics, Monza, Italy]. The intra-assay coefficients of variation (CVs) were: TSH 0.8%, FSH 2.4%, LH 2.6%, insulin 0.9%, PRL 2.3%, E2 6.4%, total testosterone 8.6%, P 6.8%, and 17αOHP 7%. The interassay CVs were TSH 1.8%, LH 2.3%, FSH 2.3%, insulin 2.1%, E2 3.4%, total testosterone 9.6%, PR 7.6%, and 17αOHP 10%. Serum DHT, DHEA, Δ4AD, and 3αDG were measured by radioimmunoassay. The intra-assay CVs were DHT 12%, DHEA 4.8%, Δ4AD 3.4%, and 3αDG 7.6%. The interassay CVs were DHT 9.6%, DHEA
5.2%, Δ4AD 6.4%, and 3αoDG 7%. SHBG was measured by immunoradiometric assay. The intra-assay CV was 2.8%. The interassay CV was 3.2%. The free androgen index was calculated according to the formula total testosterone \( \times 100/\text{SHBG blood levels} \) (29). Androgen assays were performed at the time of inclusion in the study to ascertain the PCOS phenotype according to the criteria currently available from scientific societies (2). Biochemical data related to pituitary and steroid hormones in the population of PCOS women included in the study, at baseline and 6 months after the end of the treatment, are shown in Supplemental Table 2. To investigate insulin sensitivity, the homeostasis model assessment for insulin resistance was calculated (30).

Statistical analyses

The normal distribution of continuous data was tested employing the Shapiro-Wilk test. Continuous variables are presented as mean (SD) or as median [interquartile range (IQR) = 25th to 75th percentile]; if necessary, a log-transformation was applied to achieve a satisfying fit to Gaussian distribution. Dichotomous data were characterized by counts (percentages). Parametric (\( t \) test) or nonparametric (Mann-Whitney \( U \) or \( \chi^2 \)) tests were applied to verify differences between the treatment (OCP + BC 50 mg) and control (OCP + P) groups. Parametric Pearson (if appropriate) or nonparametric Spearman correlation coefficients were calculated to evaluate the association between the mF&G score and the VDI. To evaluate the efficacy of the treatment in terms of score reduction, an analysis of variance (ANOVA) for repeated measures was applied with the VDI (log-scale) or mF&G as dependent variables, with time as within-subjects factor and treatment group (therapy OCP + BC 50 mg; therapy OCP + P) as between-subjects factor. To take into account the difference between groups at the baseline, we also performed an analysis of covariance (ANCOVA) model for repeated measurements, adjusting for VDI baseline values. Greenhouse-Geisser correction was applied if the assumption of sphericity was not met. For multiple comparisons post-ANOVA or post-ANCOVA, Bonferroni correction was applied.

The results were presented as a mean or geometric mean, after the back transformation of logarithmic values, and its relative SD. In addition, the percentage reduction and its corresponding 95% confidence interval (CI) were reported. A \( P \) value <0.05 was considered significant.

Results

The demographic, anthropometric, and clinical characteristics of all patients enrolled in the study are summarized in Table 1. No evidence of difference between the two groups was found at the baseline or during follow-up [repeated measures ANOVA (RM-ANOVA), consistently \( P > 0.10 \)]. All of the women studied had a history of menstrual dysfunction, and none had morphological uterine abnormalities.

Evaluation of hirsutism

Aim of this study was to obtain data on the efficacy and tolerability of oral treatment with the association
of OCP plus BC in controlling hirsutism and seborrhea in women with androgen excess due to PCOS. All the clinical objective parameters were carefully recorded overall during the study period and demonstrated no differences between the group of women treated with OCP + BC and the OCP-treated control group (Table 1). The severity of hyperandrogenism was evaluated using a scale from 0 to 4 in each androgen-sensitive region of the body, and a total score was calculated using the mF&G. Particularly relevant changes were observed at the level of chin, thorax/upper abdomen, and lower abdomen (Table 2; Fig. 2): the RM-ANOVA analyses showed a clear time × treatment interaction effect (consistently, \( P < 0.01 \)) in the VDI, confirming that the changes over time were not similar after OCP + BC and after OCP + P.

At the level of the chin area, we observed a significant time effect. The overall mean reduction in the VDI during follow-up time was statistically significant \( (P < 0.001) \), but the time course for the two treatment groups was borderline significantly different (treatment × time effect, \( P = 0.053 \)). In the OCP + BC group, the reduction in the VDI between the baseline and T6 was significant: The percentage of reduction was equal to 67% \((95\% \text{ CI from } 60\% \text{ to } 90\% ; P = 0.053)\). In the OCP + P group, the reduction in the VDI between the baseline and T6 was not significant (percentage reduction = 34%, 95% CI from −10% to 60%; \( P = 0.073 \)). In the OCP + P group, the reduction in the VDI between the baseline and T6 was not significant (percentage reduction = 29%, 95% CI from −20% to 60%; \( P = 0.325 \)), whereas it was significant at T12, with a

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**Table 1. Clinical Characteristics at the Baseline of 28 Patients Analyzed Under Combined Contraceptive Pill and BC 50 mg/d (OCP + BC Group) and 24 Patients Analyzed Under Contraceptive Pill and P (OCP + P Group)**

<table>
<thead>
<tr>
<th>Body composition</th>
<th>T0</th>
<th>T6</th>
<th>T12</th>
<th>Time</th>
<th>Treatment</th>
<th>Time × Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>OCP + BC</td>
<td>Mean = 70.2; SD = 16.43</td>
<td>Mean = 70.2; SD = 16.39</td>
<td>( F(2, 100) = 0.224; )</td>
<td>( F(1, 50) = 0.406; )</td>
<td>( F(2, 100) = 1.049; )</td>
</tr>
<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 68.2; SD = 13.56</td>
<td>Mean = 67.7; SD = 12.43</td>
<td>( P = 0.800 )</td>
<td>( P = 0.527 )</td>
<td>( P = 0.354 )</td>
</tr>
<tr>
<td>Fat mass</td>
<td>OCP + BC</td>
<td>Mean = 26.6; SD = 9.61</td>
<td>Mean = 25.3; SD = 8.68</td>
<td>( F(2, 100) = 1.117; )</td>
<td>( F(1, 50) = 0.669; )</td>
<td>( F(2, 100) = 0.463; )</td>
</tr>
<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 27.7; SD = 7.90</td>
<td>Mean = 27.4; SD = 7.65</td>
<td>( P = 0.331 )</td>
<td>( P = 0.417 )</td>
<td>( P = 0.631 )</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>OCP + BC</td>
<td>Mean = 26.4; SD = 6.2</td>
<td>Mean = 26.3; SD = 6.4</td>
<td>( F(2, 100) = 0.269; )</td>
<td>( F(1, 50) = 0.708; )</td>
<td>( F(2, 100) = 1.079; )</td>
</tr>
<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 25.3; SD = 4.4</td>
<td>Mean = 25.2; SD = 4.1</td>
<td>( P = 0.765 )</td>
<td>( P = 0.404 )</td>
<td>( P = 0.344 )</td>
</tr>
<tr>
<td>Absorptiometry, trunk fat %</td>
<td>OCP + BC</td>
<td>Mean = 32.3; SD = 5.2</td>
<td>Mean = 34.5; SD = 4.1</td>
<td>( F(2, 100) = 0.619; )</td>
<td>( F(1, 50) = 0.106; )</td>
<td>( F(2, 100) = 0.959; )</td>
</tr>
<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 34.7; SD = 6.2</td>
<td>Mean = 34.4; SD = 7.5</td>
<td>( P = 0.541 )</td>
<td>( P = 0.746 )</td>
<td>( P = 0.387 )</td>
</tr>
</tbody>
</table>

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*Nonparametric Mann-Whitney test.

Repeated measures ANOVA analyses were performed considering, for each target variable, only values on T0, T6, and T12. Statistical analyses were applied on logarithmic transformation of the values, and results were reported after back transformation. No statistical differences were found between the two study groups at the baseline and during the whole study time (consistently \( P > 0.10 \)).
percentage reduction of 55% (95% CI from 20% to 70%; \( P = 0.045 \)). These changes remained significant after the adjustment by the VDI chin baseline values (logarithmic scale) in ANCOVA analyses (see \( P \)-adjusted in Table 2).

At the level of the thorax and upper abdomen, the overall mean modification of the VDI was borderline statistically different between women under OCP + BC and controls (\( P = 0.061 \)). In addition, in this area, the changes over time in the two groups were different. At the chin level, we observed in the OCP + BC group a significant reduction in the VDI at T6 compared with the baseline, with a percentage of reduction of 79% (95% CI from 70% to 80%; \( P < 0.001 \)), as well as at T12, with a percentage of reduction of 84% (95% CI from 80% to 90%; \( P < 0.001 \)), but not between the two follow-up times (percentage reduction = 27%, 95% CI from 0% to 50%; \( P = 0.484 \)). In the OCP + P group, only the change between the baseline and T12 was significant: The percentage of reduction was 36% (95% CI from 10% to 50%; \( P = 0.029 \)). Adjusting for baseline VDI thorax values (on a logarithmic scale), the differences in change between the two groups and over time remained statistically significant (see \( P \)-adjusted in Table 2).

At the level of the lower abdomen, significant differences were observed from T0 to T6 in patients under OCP + BC combined therapy (percentage reduction = 69%, 95% CI from 60% to 80%; \( P < 0.001 \)), but not in patients under OCP + P therapy (percentage reduction = 17%, 95% CI from 0% to 30%; \( P = 0.517 \)). Considering the time from the baseline to T12, the reductions in the VDI score were statistically significant both in the OCP + BC combined therapy group (percentage reduction of 77%, 95% CI from 70% to 80%; \( P < 0.001 \)) and in the OCP + P therapy group (percentage reduction of 36%, 95% CI from 10% to 50%; \( P = 0.038 \)). The observed differences in the VDI at the level of lower abdomen remained statistically significant adjusting for the baseline VDI values (logarithmic scale).

### Evaluation of body composition
As a secondary outcome, we evaluated a possible effect over time of treatment on body composition in terms of BMI and trunk fat. RM-ANOVA was applied, and the results showed a nonsignificant effect of treatment. In fact, no changes in terms of BMI were observed either in the OCP + BC combined therapy group or in the OCP + P therapy group (time effect, \( P = 0.765 \); treatment group effect, \( P = 0.404 \); and time × treatment group effect, \( P = 0.344 \)). Similar results were found for trunk fat assessments (28) (time effect, \( P = 0.765 \); treatment group effect,

### Table 2. Evaluation of Hirsutism at the Baseline and During Follow-Up

<table>
<thead>
<tr>
<th>Target Variables</th>
<th>Treatment</th>
<th>T0</th>
<th>T6</th>
<th>T12</th>
<th>6 Months After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDI Chin(^a)</td>
<td>OCP + BC</td>
<td>Mean = 16.9</td>
<td>Mean = 5.5</td>
<td>Mean = 3.6</td>
<td>Mean = 8.4</td>
</tr>
<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 10</td>
<td>Mean = 7.1</td>
<td>Mean = 4.5</td>
<td>Mean = 18.6</td>
</tr>
<tr>
<td></td>
<td>SD = 43.9</td>
<td>SD = 19.8</td>
<td>SD = 15.2</td>
<td>SD = 34.6</td>
<td>SD = 18.6</td>
</tr>
<tr>
<td></td>
<td>SD = 20</td>
<td>SD = 20</td>
<td>SD = 18.5</td>
<td>SD = 20.8</td>
<td>SD = 20.8</td>
</tr>
<tr>
<td>Thorax/upper abdomen(^a)</td>
<td>OCP + BC</td>
<td>Mean = 7</td>
<td>Mean = 1.5</td>
<td>Mean = 1.1</td>
<td>Mean = 3.7</td>
</tr>
<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 5.1</td>
<td>Mean = 3.5</td>
<td>Mean = 2.7</td>
<td>Mean = 2</td>
</tr>
<tr>
<td></td>
<td>SD = 7.1</td>
<td>SD = 0.9</td>
<td>SD = 0.4</td>
<td>SD = 5.25</td>
<td>SD = 0.187</td>
</tr>
<tr>
<td></td>
<td>SD = 20</td>
<td>SD = 20</td>
<td>SD = 18.5</td>
<td>SD = 20.87</td>
<td>SD = 20.87</td>
</tr>
<tr>
<td>Lower abdomen(^b)</td>
<td>OCP + BC</td>
<td>Mean = 20.5</td>
<td>Mean = 6.4</td>
<td>Mean = 4.7</td>
<td>Mean = 13</td>
</tr>
<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 20.3</td>
<td>Mean = 6.4</td>
<td>Mean = 6.5</td>
<td>Mean = 13</td>
</tr>
<tr>
<td></td>
<td>SD = 8.9</td>
<td>SD = 6.4</td>
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<td></td>
<td>SD = 20</td>
<td>SD = 20</td>
<td>SD = 18.5</td>
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<tr>
<td>mF&amp;G Total</td>
<td>OCP + BC</td>
<td>Mean = 21.8</td>
<td>Mean = 12.9</td>
<td>Mean = 9.7</td>
<td>Mean = 15.4</td>
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<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 21.4</td>
<td>Mean = 13.8</td>
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<td>SD = 2.3</td>
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<td>SD = 4.0</td>
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<td>Chin</td>
<td>OCP + BC</td>
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<td>Mean = 1.1</td>
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<td>EP + P</td>
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<td>SD = 1.38</td>
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<td>SD = 1.2</td>
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</tr>
<tr>
<td>Thorax/upper abdomen</td>
<td>OCP + BC</td>
<td>Mean = 1.6</td>
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<td>Mean = 0.3</td>
<td>Mean = 1.6</td>
</tr>
<tr>
<td></td>
<td>EP + P</td>
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<td>Mean = 0.8</td>
<td>Mean = 0.5</td>
<td>Mean = 0.9</td>
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<td>SD = 0.7</td>
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<td>SD = 0.4</td>
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<td>SD = 0.8</td>
<td>SD = 0.6</td>
<td>SD = 0.99</td>
<td>SD = 0.99</td>
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<tr>
<td>Lower abdomen</td>
<td>OCP + BC</td>
<td>Mean = 3.1</td>
<td>Mean = 1.8</td>
<td>Mean = 1.3</td>
<td>Mean = 2.3</td>
</tr>
<tr>
<td></td>
<td>EP + P</td>
<td>Mean = 3.1</td>
<td>Mean = 2.1</td>
<td>Mean = 1.6</td>
<td>Mean = 2.2</td>
</tr>
<tr>
<td></td>
<td>SD = 1.1</td>
<td>SD = 0.6</td>
<td>SD = 0.8</td>
<td>SD = 0.93</td>
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</tr>
<tr>
<td></td>
<td>SD = 1.1</td>
<td>SD = 0.6</td>
<td>SD = 0.8</td>
<td>SD = 0.93</td>
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</tbody>
</table>

\(^a\)RM-ANOVA analyses were performed considering, for each target variables, only values on T0, T6, and T12.

\(^b\)Statistical analyses were applied on logarithmic transformation of the values, and results were reported after back transformation.

Data were collected using the mF&G index and the VDI and are expressed as geometrical mean (±SD).
$P = 0.746$; and treatment $\times$ time effect, $P = 0.387$) as shown in Table 1.

**Tolerability of combined OCP + BC therapy**

The pharmacological treatment of hirsutism aimed at slowing the growth of new hair. The expected estimated percentage of reduction in the number of terminal hair follicles, registered by our software in the critical androgen-dependent skin areas using an observational field of 4 cm$^2$, was around 35%. The duration of the therapy was 12 months, a period of time that was necessary to evaluate the success of the treatment and its tolerability. In this context, we carefully examined, as a secondary outcome of this study, the onset of several side effects such as headache, weight gain, breast tenderness, nausea, loss of libido, edema, hepatotoxicity, fatigue, and mood changes. Therapy was well tolerated, and only one patient in the BC group discontinued it because of weight gain. In the P group, four patients discontinued therapy for tolerability reasons; one because of headache that was noncorrectable with painkiller drugs; one because of nonsatisfaction with the effects of the therapy on hirsutism; one because of nausea; and one because of “heaviness of the lower limbs” with no objective signs on physical examination.

The RM-ANOVA analyses showed a significant difference in the overall total cholesterol mean during the follow-up times (time effect, $P < 0.001$) and between the two treatment groups over time (treatment $\times$ time effect, $P = 0.002$). After the adjustment for baseline values, the overall mean difference between the OCP + BC combined therapy group and the OCP + P therapy group was also significant ($P = 0.004$; Table 3). With respect to the calculated LDL, we observed a significant difference in the overall mean between the OCP + BC group and the OCP + P group (treatment effect, $P$-adjusted = 0.004) and in the overall mean between times (time effect, $P$-adjusted = 0.036) and between the two treatment groups over time (treatment $\times$ time effect, $P$-adjusted = 0.024).

As regards the total bilirubin values, we observed a significant difference between the two therapy groups.
Adverse events

A careful physical, abdominal, and general examination was performed, and a careful history was taken into account every 6 months to monitor liver and kidney functions (Supplemental Table 3), with a blood count of patients to highlight the presence of disorders related to OCP and BC therapy (nausea, vomiting, abdominal pain, edema). Overall during the study, serious adverse events were not experienced, and the adverse events reported were not different (in terms of proportions) across assigned treatments (consistently, P > 0.40; Supplemental Table 3). The main adverse events reported were a rise in the plasma levels of cholesterol and/or triglycerides and intermenstrual spotting. Liver function remained normal during BC treatment. Other events reported were nausea, mild anemia, hot flashes, libido reduction, and dry skin. None of these symptoms/signs required the treatment to be stopped, and there was no statistical difference between the two study groups (Supplemental Table 3).

Discussion

This study shows that both OCP and antiandrogen BC in association with OCP were effective in reversing severe hirsutism in hyperandrogenic women affected by PCOS. Performing the hair follicular count and establishing the VDI score, we were able to demonstrate that when BC is given in association with OCP, the efficacy is significantly improved compared with OCP alone.

Hirsutism is an important clinical sign of androgen excess (7), and its treatment is based on two major approaches that can also be used in combination. The first is cosmetic treatment (mainly the removal by laser of unwanted hair) and the second is hormonal treatment (OCP alone or in combination with antiandrogens), which, considering the time of cyclical hair growth renewal, may take several months for positive effects to appear (31). The peripheral disruption of androgen pathways at the level of the pilosebaceous unit may represent a useful

<table>
<thead>
<tr>
<th>Target Variables</th>
<th>Treatment</th>
<th>T0</th>
<th>T6</th>
<th>T12</th>
<th>Time</th>
<th>Treatment</th>
<th>Time × Treatment</th>
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</thead>
<tbody>
<tr>
<td>Liver, renal, and metabolic parameters</td>
<td>EP + B50</td>
<td>Mean = 19.8 SD = 11.01</td>
<td>Mean = 16 SD = 7.69</td>
<td>Mean = 17.5 SD = 6.94</td>
<td>R2, 100) = 1.913, R1, 50) = 1.638, R2, 100) = 0.402, P = 0.153, P = 0.207, P = 0.207,</td>
<td>P-adjusted = 0.001</td>
<td>P-adjusted = 0.673, P-adjusted = 0.810,</td>
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<td>ASTa</td>
<td>EP + Placebo</td>
<td>Mean = 15.6 SD = 7.8</td>
<td>Mean = 13.6 SD = 5.75</td>
<td>Mean = 16.4 SD = 7.46</td>
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<tr>
<td>GGT</td>
<td>EP + B50</td>
<td>Mean = 14.7 SD = 5.2</td>
<td>Mean = 16 SD = 5.9</td>
<td>Mean = 15.1 SD = 6.4</td>
<td>R2, 100) = 0.335, R1, 50) = 2.002, R2, 100) = 1.128, P = 0.716, P = 0.163, P = 0.328,</td>
<td>P-adjusted = 0.138</td>
<td>P-adjusted = 0.053, P-adjusted = 0.268,</td>
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<tr>
<td>TOT CHOL</td>
<td>EP + B50</td>
<td>Mean = 163.6 SD = 28.9</td>
<td>Mean = 208.6 SD = 35.3</td>
<td>Mean = 206.3 SD = 30.7</td>
<td>R2, 100) = 13.751, R1, 50) = 2.002, R2, 100) = 6.495, P &lt; 0.001</td>
<td>P = 0.163, P = 0.002,</td>
<td></td>
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<tr>
<td>HDL</td>
<td>EP + B50</td>
<td>Mean = 57.8 SD = 17.4</td>
<td>Mean = 71.1 SD = 15.5</td>
<td>Mean = 71.1 SD = 12</td>
<td>R2, 100) = 12.796, R1, 50) = 0.292, R2, 100) = 0.195</td>
<td>P &lt; 0.001, P = 0.591, P = 0.823,</td>
<td></td>
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<tr>
<td>Triglycerides</td>
<td>EP + B50</td>
<td>Mean = 86.5 SD = 39.9</td>
<td>Mean = 114.9 SD = 55.6</td>
<td>Mean = 133.6 SD = 48.4</td>
<td>R2, 100) = 6.980, R1, 50) = 2.848, R2, 100) = 1.304</td>
<td>P &lt; 0.001, P = 0.098, P = 0.276,</td>
<td></td>
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<tr>
<td>LDL chol</td>
<td>EP + B50</td>
<td>Mean = 89.1 SD = 23.3</td>
<td>Mean = 115.1 SD = 22.8</td>
<td>Mean = 111.6 SD = 24.9</td>
<td>R2, 100) = 2.071, R1, 50) = 0.048, R2, 100) = 6.121</td>
<td>P = 0.131, P = 0.827, P = 0.003,</td>
<td></td>
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<tr>
<td>Glucose</td>
<td>EP + B50</td>
<td>Mean = 78.5 SD = 37.5</td>
<td>Mean = 79.9 SD = 35.9</td>
<td>Mean = 80.3 SD = 6.7</td>
<td>R2, 100) = 0.859, R1, 50) = 0.800, R2, 100) = 2.387</td>
<td>P = 0.427, P = 0.375, P = 0.097,</td>
<td></td>
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</tbody>
</table>

(Continued)
method of treatment of this symptom, assuming that the activation of the AR is crucial for hair shaft growth through the differentiation of keratinocytes produced by the hair follicle (32). Current literature about hair follicle biology based on in vitro and in vivo studies demonstrates that androgens modulate important general molecular and cellular processes, inducing regeneration, pigment, and stem cell proliferation, through the action of local diffusible growth factors acting as paracrine-intracrine modulators (32–34).

OCPs may lower plasma androgens and reduce the biological effect of androgens through the suppression of ovarian androgen production and by increasing hepatic production of SHBG, whereas their association with antiandrogens produces competitive antagonism of the AR. It has been recently shown that contraceptive preparations with estradiol + cyproterone acetate and the AR. It has been recently shown that contraceptive preparations with antiandrogens produce competitive antagonism of androgenic functions, but it may cause unpleasant side effects such as menstrual irregularities, fatigue, headaches, and gastritis (40). Six-month treatment with 100 mg/d spironolactone compared with P was associated with a statistically significant subjective improvement in hair growth and a decrease in total mF&G scores. It has been demonstrated that spironolactone 100 mg/d is superior to finasteride 5 mg/d and low-dose cyproterone acetate 12.5 mg/d (first 10 days of cycle) in improving androgen excess symptoms at skin level (41).

A combined therapy with OCP + different dosage (125 to 375 mg) of flutamide, an oral nonsteroidal antiandrogen, has been proposed for the treatment of hirsutism in association with estrogen in the OCP, as in the case of PR analogs, or in combination with OCP (2, 6, 35).

Even if hirsutism is present in 60% to 80% of women with PCOS, sometimes some severely hirsute women may present regular ovulatory menstrual cycles and normal circulating androgen levels (38). These findings have focused attention on the increased sensitivity of the pilosebaceous unit and the therapeutic role of antiandrogens (39). The currently used steroidal and nonsteroidal antiandrogens are spironolactone, finasteride, flutamide, and cyproterone acetate (39). Spironolactone is an AR blocker that competes with androgens to bind the AR without activating the AR’s transcriptional functions, but it may cause unpleasant side effects such as menstrual irregularities, fatigue, headaches, and gastritis (40). Six-month treatment with 100 mg/d spironolactone compared with P was associated with a statistically significant subjective improvement in hair growth and a decrease in total mF&G scores. It has been demonstrated that spironolactone 100 mg/d is superior to finasteride 5 mg/d and low-dose cyproterone acetate 12.5 mg/d (first 10 days of cycle) in improving androgen excess symptoms at skin level (41).

A combined therapy with OCP + different dosage (125 to 375 mg) of flutamide, an oral nonsteroidal antiandrogen...
drug that blocks ARs and inhibits hair growth, has been shown to be more effective in treating androgen excess symptoms within 6 to 12 months compared with OCP alone (35). Even if dry skin is very frequent during treatment with flutamide (42), a matter for debate is the drug-induced hepatotoxicity that is excluded by some authors (43, 44) but claimed by others at high, low, or ultralow dosages (45).

Several reports demonstrate that in all hirsute women, with or without hyperandrogenism, the 5α-reductase activity in the skin is elevated (46). Finasteride is a member of the 4-azasteroid family of compounds that is effective in inhibiting the enzyme 5α-reductase (35) at the level of dermal papilla in the hair follicle (47), thereby blocking the conversion of testosterone to the more potent DHT (48). This compound at a daily dosage of 5 mg may reduce DHT levels up to 60% and may be an important therapy support to reduce excess androgen symptoms (49) without important side effects, but its use in association with OCP presents variable results and is considered relatively ineffective in severe hirsutism (50). However, the relative efficacy of antiandrogens for the treatment of hirsutism is still a matter of debate because of the lack of large randomized trials, alone or in combination (51). Furthermore, because of its teratogenic potential, the Endocrine Society and the American Association of Clinical Endocrinologists recommend avoiding antiandrogen monotherapy for the treatment of hirsutism unless adequate contraception is used (6, 7).

In the present randomized, double-blind, controlled study we have demonstrated the efficacy and tolerability of a combination of OCP plus a daily 50 mg dose of BC in the treatment of severe hirsutism. BC, a potent non-steroidal antiandrogen compound that prevents the action of testosterone and DHT at the level of target tissues by binding the intracellular AR and preventing gene expression (10, 11), is the most widely used antiandrogen drug for the treatment of prostate cancer in males (52). BC is a racemate, and its antiandrogen activity is mainly in the R(−) enantiomer, with little activity in the S(+)-enantiomer. The selective affinity for the AR among other steroid hormone receptors explains why BC can be considered a pure antiandrogen (53). Few studies that have used this compound in women affected by androgen excess syndrome are available (40). Furthermore, its efficacy at a low dose (25 mg/d) has been investigated in only one open trial with a group of 42 women affected with hirsutism (12). Antiandrogen therapy has been proposed in women with breast cancer given that BC has been shown to inhibit the 5α-DHT-mediated proliferation of breast cancer cell lines in vitro (54).

Here we have demonstrated that by monitoring women for 18 months for blood pressure, fasting insulin and glucose, and waist circumference, with blood tests for hepatic and kidney functions and all the metabolic parameters, the daily dose of 50 mg/die of BC used in combination with OCP was well tolerated by the women studied. BC 50 mg once daily was the selected dose because there is evidence in the literature that it has a good pharmacological effect and is well tolerated in humans (55). None of the treated women dropped out for clinically relevant adverse effects: They did so for personal reasons (n = 5 in OCP + BC 50 mg and n = 10 in OCP + P, as indicated in Fig. 1). Moreover, the overall condition of the patients seemed to improve not only because of the remission of the androgen excess symptoms, which was statistically significant, but also because of relief from psychological distress. Side effects have been described in the administration of the antiandrogens most commonly used for the treatment of androgen excess in PCOS women (6). As mentioned earlier, spironolactone may induce hyperkalemia, headaches, dizziness, breast discomfort, dry skin, gastritis, and, frequently, intermenstrual spotting (56). None of these side effects was observed in the group of women with PCOS under BC who were treated for a long time in this controlled study. The only important parameter to be monitored is cholesterol, which we found increased more in women under treatment with OCP + BC 50 mg.

In the group of patients that we studied, the PCOS phenotype was established as type A (2) by the presence of hirsutism, PCOM, and oligoamenorrhea, with a lower definition of hyperandrogenemia, due to the impossibility of using liquid chromatography coupled with tandem mass spectrometry to assess the steroid profiling (57). All the patients studied showed a first-degree PCOS family history. This point strengthens the need for further investigations into women affected with “familial” PCOS with the aim of speculating on what the prevalence of genes involved in the expression of the classic A phenotype of the syndrome. In this context, new antiandrogens could be useful in the treatment of this syndrome, such as enzalutamide (in the past called MDV3100), a second-generation antiandrogen that binds the AR at its ligand-binding domain, inhibiting its activation, and is 5 to 8 times more potent than its first-generation predecessor BC (58).

Another key point of this study relates to the methods used for the evaluation of the severity of hirsutism. These were both subjective and objective. In this study, applying the modified score system described by Ferriman and Gallwey (14) and the simplified Ferriman and Gallwey hair growth scoring system (59), we were able to describe in women under both OCP + P and OCP + BC a significant reduction in the total hirsutism score. When the reduction in the mF&G score was examined in
the individual androgen-dependent areas, there was no possibility of registering a significant mF&G difference between the two treatment regimens given the wide variation of the SD due to the subjective method of calculating the score. In contrary fashion, the effectiveness of the antiandrogen therapy was well documented using the VDI hair growth scoring to quantify the regression of hair in the individual androgen-sensitive areas of the body. Videodermoscopy, a technique used by dermatologists to evaluate areas of reduced hair density usually at the level of the scalp at $\times 20$ to $\times 160$, was able to evaluate the excess of hair and demonstrate the effect of therapy in a significant way. The system allowed us to collect and store the pictures of the androgen-dependent areas in basal condition plus 6 and 12 months of therapy and 6 months after the end of treatment. Therefore, we propose this technique as a way of objectively following the reduction of the hair density in specific body areas by quantifying the reduction of hirsutism during the observational period of the study.

A secondary outcome of the study was the evaluation of the impact of BC on body composition, especially on fat mass and trunk fat, in particular at the level of visceral fat assessment (Table 1). It is known that, in men, BC treatment of prostate cancer at a dose of 150 mg/d induces an increase in fat mass (60). In women, androgen excess is associated with visceral fat adiposity (61), so we would expect a different effect of antiandrogens on body composition related to the different effects of androgens in men and women of the reproductive age (61). During the 12 months of treatment, we found no significant statistical changes in fat mass and percentage of trunk fat between the two study groups, and patients did not experience a statistically significant weight gain while undergoing therapy. Many factors can influence body composition and changes in its characteristics, especially food intake habits and physical exercise.

As mentioned previously, a limitation of this multicenter trial was represented by the inability to analyze the steroids using tandem mass spectrometry as suggested by the current scientific reports (57, 62). Another limitation of this study was that, despite the fact that all the patients were encouraged to take physical exercise and have a regular diet (a normal or hypocaloric one based on their initial body composition status), only a few of them followed our instructions. As a consequence, the results in body composition evaluation were influenced by this behavior as well.

To conclude, we have provided evidence that either OCP alone and in combination with an antiandrogen are useful therapeutic options to reduce hirsutism. The antiandrogen BC combined with OCP seems to be more efficacious compared with OCP alone and is suggested as an excellent treatment of severe hirsutism. Further studies devoted to exploring the dynamic changes of pilosebaceous unit in its renewal cycles will be needed to achieve a better understanding of whether androgen-depleting therapies targeting skin, in association with cosmetic treatment, can produce a full recovery from severe hirsutism.

Acknowledgments

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Disclosure Summary: The authors have nothing to disclose.

References


47. Dallof AL, Sadick NS, Unger W, Lipert S, Geissler LA, Gregoire SL, Nguyen HH, Moore EC, Tanaka WK. The effect of finasteride, a 5 alpha-reductase inhibitor, on scalp skin testosterone and


