

# Hair removal in hirsute women with normal testosterone levels: a randomized controlled trial of long-pulsed diode laser vs. intense pulsed light

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## Summary

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### Key words

androgen, diode laser, hirsutism, intense pulsed light, photoepilation, testosterone

### Conflicts of interest

None declared.

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**Background** Hirsutism is a common disorder in women of reproductive age, and androgen disturbances may aggravate the condition. Limited evidence exists regarding efficacy of hair removal in this specific population and no data are available for patients with verified normal testosterone levels.

**Objectives** To compare efficacy and safety of intense pulsed light (IPL) vs. long-pulsed diode laser (LPDL) in a well-defined group of hirsute women with normal testosterone levels.

**Methods** Thirty-one hirsute women received six allocated split-face treatments with IPL (525–1200 nm; Palomar Starlux IPL system) and LPDL (810 nm; Asclepion MeDioStar XT diode laser). Testosterone levels were measured three times during the study period. Patients with intrinsically normal or medically normalized testosterone levels throughout the study were included in efficacy assessments ( $n = 23$ ). Endpoints were reduction in hair counts assessed by blinded photo-evaluations at baseline and 1, 3 and 6 months after final treatment, patient-evaluated reduction in hairiness, patient satisfaction, treatment-related pain and adverse effects.

**Results** IPL and LPDL reduced hair counts significantly, with median reductions from baseline of 77%, 53% and 40% for IPL and 68%, 60% and 34% for LPDL at 1, 3 and 6 months, respectively. At 6 months follow-up, there was no significant difference between treatments in terms of hair reduction ( $P = 0.427$ ), patient assessment of hairiness ( $P = 0.250$ ) and patient satisfaction ( $P = 0.125$ ). Pain scores were consistently higher for IPL [median 6, interquartile range (IQR) 4–7] than LPDL (median 3, IQR 2–5) ( $P < 0.001$ ).

**Conclusion** Hirsute women with normal or medically normalized testosterone levels responded equally well to IPL and LPDL treatments of facial hairiness, but the efficacy declined over 6 months.

Hirsutism is defined as growth of terminal hair in women at androgen-dependent sites where normally only men develop coarse hair.<sup>1,2</sup> Approximately 5–10% of women of reproductive age suffer from hirsutism,<sup>3,4</sup> which may be associated with psychological and emotional distress causing impaired quality of life.<sup>5</sup> It is therefore pivotal to offer efficient hair removal techniques to this specific group of patients.

Lasers and intense pulsed light (IPL) devices are today regarded as the most efficient methods for reduction of unwanted hair.<sup>6–9</sup> Currently used devices perform selective photothermal destruction of the hair follicles, based on the principle of selective photothermolysis.<sup>10</sup> Available devices operate in the visible and near-infrared spectrum with pulse durations in the millisecond range: normal mode ruby laser (694 nm), normal mode alexandrite laser (755 nm),

long-pulsed diode laser (LPDL) (800–810 nm), long-pulsed neodymium:yttrium–aluminium–garnet (Nd:YAG) laser (1064 nm) and IPL sources (590–1200 nm).<sup>7</sup>

Based on randomized controlled trials (RCTs), the evidence of hair removal is most well documented for the alexandrite laser and LPDL, with hair removal efficacies of approximately 50% evaluated on random body locations at 6 months after treatments.<sup>6,11–16</sup> Limited evidence is found for IPL devices from RCTs.<sup>6,17</sup>

Hirsute women may suffer from an androgen imbalance and their response to photoepilation may, therefore, be less favourable when treatments are given to androgen-sensitive body sites.<sup>4</sup> Despite the fact that many women suffer from hirsutism there are, currently, only a few controlled studies looking specifically at the efficacy of hair removal in this patient group.<sup>15,16,18</sup> These studies report hair reduction in a range from 27% (IPL) to 46–49% (alexandrite laser) at 6 months after the final treatment. To date there have been no RCTs comparing the efficacy of IPL and LPDL in hirsute women.

Previous RCTs have not reported testosterone levels of hirsute patients in relation to the efficacy of photoepilation, which may introduce bias in reported treatment outcomes. In the present study, testosterone levels were assessed before treatment, at the end of the treatment sessions and at the end of the 6-month follow-up period. The objective of this RCT was to compare the efficacy and safety of IPL vs. LPDL treatments of facial hairiness in a population of hirsute women with intrinsically normal or medically normalized testosterone levels.

## Subjects and methods

### Patients

The ethical committee of Copenhagen and Frederiksberg, Denmark, approved this protocol KF01323966. Hirsute women were recruited consecutively from the Departments of Dermatology, Gynecology, Endocrinology, and Growth and Reproduction at Rigshospitalet, Herlev Hospital and Bispebjerg Hospital. Written and oral consent was obtained from all study participants. Recruitment took place from November 2006 to March 2008. Treatments were carried out from January 2007 to June 2008 and the study was completed in February 2009.

Inclusion criteria were: women aged  $\geq 18$  years with moderate to severe hirsutism categorized from standard photo examples;<sup>19</sup> skin types I–IV;<sup>20</sup> dark brown or black terminal facial hair; and intrinsically normal testosterone or medically normalized testosterone levels. Before inclusion all individuals were screened for causes of hirsutism by androgen status [total testosterone, free testosterone, sex hormone-binding globulin (SHBG), androstenedione, dehydroepiandrosterone sulphate (DHEAS), dihydrotestosterone (DHT)] and 17-hydroxyprogesterone (17-OHP) level. If blood test results deviated from reference intervals, patients

were referred to a gynaecologist or endocrinologist for examination and initiation of medical treatment according to national guidelines.<sup>21</sup> Congenital adrenal hyperplasia and Cushing disease were excluded by urine and blood tests. Medical treatments included metformin, spironolactone and/or oral contraceptive pills and had to be administered for at least 6 months before initiation of the IPL/LPDL treatments. Total and free testosterone levels were measured at the first and final IPL/LPDL treatments and at the end of the 6-month follow-up period. Only patients with testosterone levels respecting the upper reference range in all three blood tests were included in the statistical analyses of hair removal efficacy.

Exclusion criteria were: a historical tendency to produce hypertrophic scars or keloids; previous depilation with lasers, IPL or wax treatment of study areas; photosensitivity; pregnancy or lactation; oral retinoid drugs within the past 6 months; pigmentation after recent exposure to sun or solarium; and patients not considered capable of following the treatment protocol.

### Measurement of hormone levels

All serum hormone measurements were analysed at the same laboratory (Statens Serum Institute, Copenhagen, Denmark). Total testosterone, DHT and androstenedione were extracted by ether, then total testosterone and androstenedione were measured by chromatography with tandem mass spectrometry, and DHT was measured by radioimmunoassay preceded by chromatography. SHBG was analysed by an immunofluorometric method and DHEAS by immunoassay. Total testosterone values represented free and protein-bound testosterone, and free testosterone was calculated from the level of total testosterone and SHBG. The Danish National Accreditation organization (DANAK) has accredited the analyses according to the standard ISO 17025 issued by the International Organization for Standardization.

The following reference ranges for women were used ( $\text{nmol L}^{-1}$ ): total testosterone, fertile (f): 0.55–1.8, postmenopausal (p): 0.52–1.7; free testosterone, f: 0.006–0.034, p: 0.005–0.019; SHBG, f: 41–170, p: 46–240; androstenedione, f: 2.4–8.9, p: 0.80–4.8; DHEAS, f: 1200–9500, p: 500–4500; DHT, f: 0.24–1.2, p: 0.16–0.91; and 17-OHP, follicular phase: 0.57–5.5, in the middle of the luteal phase: 0.66–14.2, p: 0.60–5.2.

### Study design

The study was a randomized split-face trial where patients and the evaluating physician were blinded to treatments. Patients were seen for follow-up evaluations at 1, 3 and 6 months after the final treatment. Randomization and allocation were carried out by patients drawing lots between opaque, sealed envelopes containing cards with a treatment code: 'Right IPL/Left diode laser' and vice versa. The midline of the face separated the two treatment modalities.

## Interventions

Patients received six treatments of their face and/or neck at 4-week intervals with both IPL and LPDL. One side was treated with the Starlux IPL system, Lux Y handpiece (Palomar Medical Technologies, Burlington, MA, U.S.A.). A filter restricted the emitted light to wavelength bands of 525–1200 nm. Treatments were performed with a contact probe of  $16 \times 46$  mm, one pass with slightly overlapping pulses and contact cooling, 100-ms pulse duration, and energies adjusted according to skin type, ranging from 20 to  $38 \text{ J cm}^{-2}$  (median 28). According to treatment guidelines the lowest energies were used for the first treatment and increased in subsequent treatments by increments of  $2 \text{ J cm}^{-2}$ . The other side was treated with a MeDioStar XT diode laser (Asclepion Laser Technologies, Jena, Germany), wavelength 810 nm. Treatments were performed with a spot size of 12 mm, one pass with 150-ms double pulses, contact skin cooling and energies adjusted by skin type ranging from 20 to  $36 \text{ J cm}^{-2}$  (median 30). According to treatment guidelines, lowest energies were used for the first treatment and increased by increments of  $3 \text{ J cm}^{-2}$  for subsequent treatments. Single test spots were not applied. The fluence levels were determined by the individual skin reactions in the entire treatment area for both IPL and LPDL. The highest individual fluence level depended on the patient's pain sensation and intensity of biological endpoints such as perifollicular erythema and oedema. No anaesthetics were used.

## Efficacy assessment

### Hair counts

Freehand photographs were taken before and after treatments with a Canon digital camera (EOS SLR D30; Canon, Tokyo, Japan) equipped with a lens-mounted ring flash (Canon Macro Lens EF-S 60 mm 1 : 2 : 8 USM). All photographs were taken in JPEG format and standardized in terms of magnification, lighting and positioning. A physician, blinded to treatment assignment, manually counted the number of hairs using a computerized image-visualizing program (Adobe® Photoshop® version 7.1; Adobe Systems Inc., San Jose, CA, U.S.A.). The bilateral counting areas were defined on the chin using the midline of the face and physical landmarks, e.g. the corner of the mouth, wrinkles and birthmarks. Each counting area had a minimum size of  $3 \times 4$  cm and ranged up to  $5 \times 7$  cm.

### Hairiness

Patients graded their subjective severity of facial hair growth separately for left and right sides before treatment, and at each postoperative follow-up by using a mirror and comparing with pretreatment photographs (0–10 categorical scale, where 0 represented no facial hairiness and 10 a maximal degree of facial hairiness).

## Patient satisfaction

Patients evaluated their overall satisfaction with treatments at each follow-up evaluation (0–10 categorical scale, where 0 represented no satisfaction and 10 a maximal degree of satisfaction).

## Adverse effects

Patients scored the pain levels after each treatment separately for right and left sides (0–10 categorical scale, where 0 represented no pain and 10 maximally tolerated pain). A blinded onsite physician evaluated the occurrence of adverse effects in terms of pigment and textural changes.

## Statistics

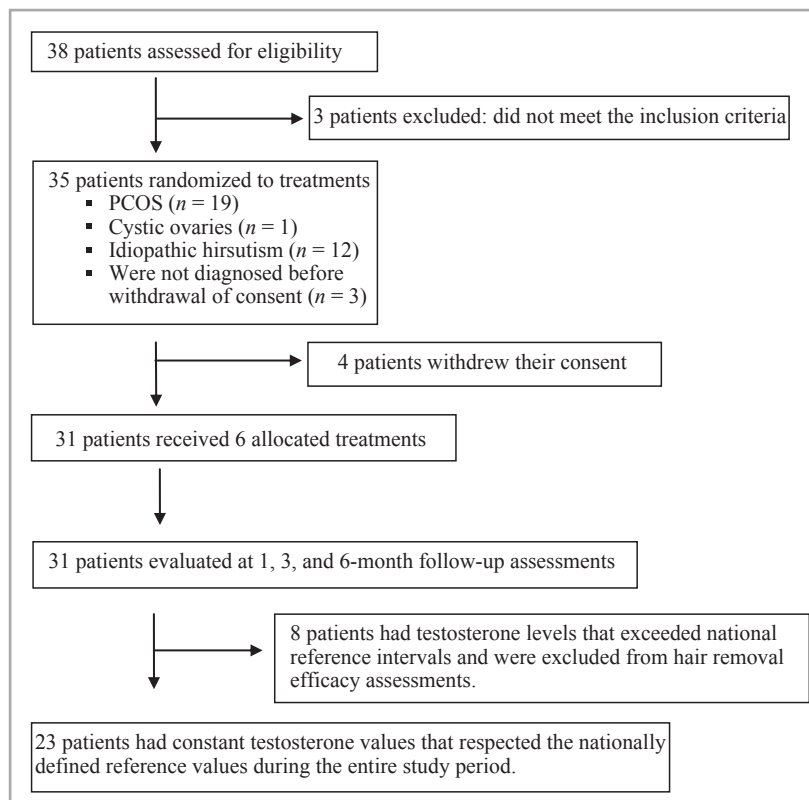
Nonparametric statistics were used, and descriptive data presented as medians with interquartile ranges (IQR). The Wilcoxon matched-pairs test was used for two paired comparisons and Friedman's test for more than two paired comparisons. Fisher's test was used to compare incidences of adverse effects. *P*-values < 0.05 were considered significant. Statistics were performed using PRISM® GraphPad, version 4.03 (GraphPad Software Inc., La Jolla, CA, U.S.A.).

Using 80% power and type I error probability of 5%, a sample size of 21 patients was calculated to detect a true 20% difference in hair counts by paired *t*-test. Because nonparametric statistics were used the required sample size was corrected for the asymptotic relative efficiency (ARE) of the Wilcoxon signed-rank test compared with the paired *t*-test;  $\text{ARE} = 3/\pi = 0.955$ . The sample size was adjusted accordingly to  $21/0.955 = 22$  patients, still detecting a relevant difference of 20% between interventions.

## Results

### Patients

A total of 35 patients were randomized to treatments and 31 patients received the six allocated treatments and completed the 1-, 3- and 6-month follow-up evaluations. A patient flow chart is illustrated in Figure 1. Testosterone levels exceeded the reference range in eight of the 31 patients at one or more of three blood tests (Fig. 2). These patients were, therefore, not included in the statistical calculations on hair removal efficacy ( $n = 23$  patients), but were included in the pain and adverse effect assessments ( $n = 31$  patients) (Fig. 1). Eleven of 23 patients received metformin ( $n = 7$ ), spironolactone ( $n = 4$ ) and/or oral contraceptive pills ( $n = 5$ ) during at least 6 months before IPL/LPDL treatments and throughout the entire study period. These patients were diagnosed with polycystic ovary syndrome (PCOS) ( $n = 9$ ) or idiopathic hirsutism ( $n = 2$ ). Twelve patients with normal testosterone levels did not receive medical treatment and were diagnosed with idiopathic hirsutism ( $n = 9$ ) and PCOS ( $n = 3$ ). The treated



**Fig 1.** A total of 35 patients were randomized to treatments with intense pulsed light and long-pulsed diode laser; 35 patients received the allocated treatments and 31 patients completed the study. A total of 23 of 31 patients had normal or medically normalized testosterone levels throughout the entire study period and were included in statistical calculations of hair removal efficacy. PCOS, polycystic ovary syndrome.

patients ( $n = 31$ ) had a median age of 38 years (range 18–59), and skin types I (one patient), II (five), III (nine) and IV (16); 11 patients were of Danish descent and 20 patients were from other ethnic background (Middle Eastern and Baltic).

## Efficacy assessment

### Hair counts

Hair count data are shown in Table 1. The baseline number of hairs was similar in IPL and LPDL areas ( $P = 0.752$ ) and hair counts were significantly reduced by both interventions at 1, 3 and 6 months after the final treatment ( $P \leq 0.001$ ).

IPL and LPDL treatments induced median hair reduction of 77%, 53% and 40% for IPL treatments and 68%, 60% and 34% for LPDL at 1 ( $P = 0.277$ ), 3 ( $P = 0.006$ ) and 6 months ( $P = 0.427$ ) after final treatment, respectively. The efficacy of hair removal declined significantly over time with both IPL and LPDL treatments (1 vs. 3 months,  $P < 0.001$ ; 3 vs. 6 months,  $P < 0.004$ ).

### Hairiness

IPL and LPDL induced similar reductions in patient-evaluated hairiness at 1, 3 and 6 months ( $P \geq 0.068$ ). Hairiness scores were most substantially reduced at the 1-month follow-up visit and increased during the post-treatment period for both IPL and LPDL, but were still significantly reduced at the 6-month assessment when compared with pretreatment levels ( $P \leq 0.001$ , Fig. 3).

### Patient satisfaction

Patients were satisfied with both IPL and LPDL treatments (Table 1). Satisfaction scores declined during the follow-up period from patients being highly satisfied at 1 month [median 8 (IQR 6–9) for IPL and median 7 (IQR 6–8) for LPDL] to moderately satisfied after 3 and 6 months [median 6 (IQR 4–7) IPL and median 5 (IQR 3–7) LPDL]. Satisfaction scores were significantly higher for IPL than LPDL at the 1-month ( $P = 0.010$ ) and 3-month ( $P = 0.047$ ) follow-up assessments but similar at 6 months ( $P = 0.125$ ).

### Adverse effects

Patients scored constant pain levels for the six treatment sessions for both IPL ( $P = 0.630$ ) and LPDL ( $P = 0.412$ ). In general, patients experienced moderate pain intensities from IPL treatments [overall median score of 6 (IQR 4–7)] and low pain intensity scores from LPDL treatments [median 3 (IQR 2–5)] ( $P < 0.001$ ). Minor transient hyperpigmentation was seen after IPL (six patients) and LPDL treatments (two patients) ( $P = 0.255$ ). Transient hypopigmentation was seen at 1 month in one patient with skin type IV in both the IPL- and LPDL-treated sides.

## Discussion

This is the first RCT of facial hair removal in a well-defined group of hirsute women with verified normal serum testosterone levels before photoepilation and throughout the entire

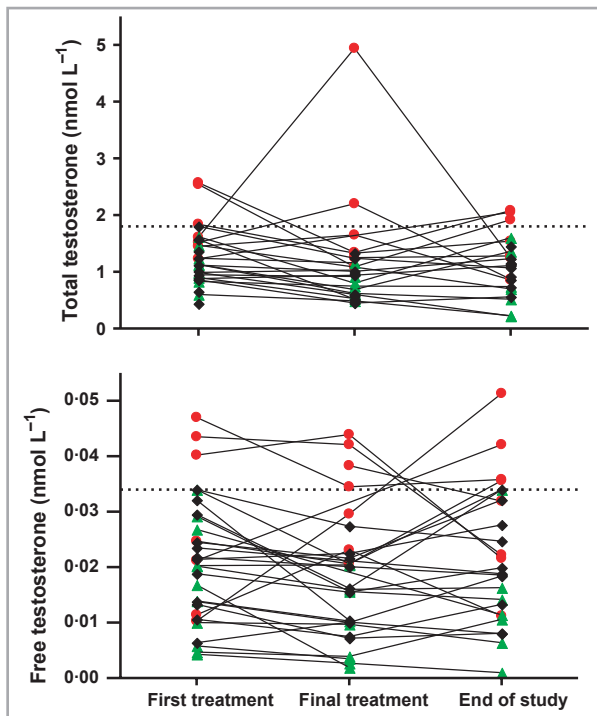


Fig 2. Total and free testosterone levels for the 31 patients completing the study. Testosterone values were measured three times during the study period at, respectively, the first and last intense pulsed light (IPL)/long-pulsed diode laser (LPDL) treatment, and at the final 6-month follow-up. Dotted lines represent the nationally defined upper levels of normal testosterone values (total testosterone: fertile women  $\leq 1.8 \text{ nmol L}^{-1}$ ; and free testosterone: fertile women  $\leq 0.034 \text{ nmol L}^{-1}$ ). Red dots, patients excluded from hair removal efficacy assessments due to elevated testosterone levels; green triangles, patients receiving medical treatment with metformin, spironolactone and/or oral contraceptives for at least 6 months before initiation of the IPL/LPDL treatments and throughout the study period; black diamonds, patients receiving no medical treatment.

study period. It is also the first RCT to compare efficacy and safety of LPDL and IPL treatments in hair reduction. Approximately 50% of the hirsute women in this study received medical treatment for hyperandrogenism, whereas the other half had intrinsic normal testosterone levels. No difference was observed between the two groups in terms of efficacy ( $P < 0.375$ ).

We found that patients responded equally well and obtained significant hair removal efficacies from IPL and LPDL treatments with 77% to 40% hair reduction for IPL and 68% to 34% for LPDL during the 1–6-month follow-up period. The achieved hair reduction declined during the observation period, but was still significantly different from baseline for both treatment modalities at 6 months post-treatment. Patient assessments of hairiness and treatment satisfaction confirmed an efficacy lasting 6 months from both IPL and LPDL treatments. Minor differences were found for the two interventions during the study period, although not consistent for one treatment modality and therefore considered of minor clinical

Table 1 Efficacy of intense pulsed light (IPL) and long-pulsed diode laser (LPDL) treatments at 1, 3 and 6 months post-treatment ( $n = 23$  patients with normal testosterone levels)

|                                                                            | IPL          |            |            |             | LPDL         |            |            |            | IPL vs. LPDL            |                         |                         |                         |
|----------------------------------------------------------------------------|--------------|------------|------------|-------------|--------------|------------|------------|------------|-------------------------|-------------------------|-------------------------|-------------------------|
|                                                                            | Baseline     | 1 month    | 3 months   | 6 months    | Baseline     | 1 month    | 3 months   | 6 months   | Baseline                | 1 month                 | 3 months                | 6 months                |
| Hair count                                                                 | 111 (84–156) | 39 (17–58) | 54 (40–81) | 69 (59–111) | 115 (98–183) | 37 (20–48) | 51 (33–75) | 81 (55–88) | $P = 0.752$<br>$n = 22$ | $P = 0.658$<br>$n = 22$ | $P = 0.196$<br>$n = 22$ | $P = 0.327$<br>$n = 20$ |
| Hair reduction from baseline (%)                                           |              | 77 (57–85) | 53 (27–72) | 40 (27–54)  |              | 68 (59–85) | 60 (41–73) | 34 (28–50) | $P = 0.277$<br>$n = 22$ | $P = 0.277$<br>$n = 22$ | $P = 0.006$<br>$n = 22$ | $P = 0.427$<br>$n = 20$ |
| Self-reported severity of hairiness (0–10 categorical scale)               | 8 (7–10)     | 3 (2–4)    | 5 (3–7)    | 6 (4–7)     | 9 (7–10)     | 4 (3–5)    | 6 (4–8)    | 6 (4–7)    | $P = 0.629$<br>$n = 23$ | $P = 0.013$<br>$n = 23$ | $P = 0.057$<br>$n = 23$ | $P = 0.250$<br>$n = 23$ |
| Reductions in self-reported severity of hairiness (0–10 categorical scale) |              | 5 (4–6)    | 3 (0–5)    | 2 (0–5)     |              | 4 (4–6)    | 3 (1–4)    | 2 (0–5)    | $P = 0.068$<br>$n = 23$ | $P = 0.305$<br>$n = 23$ | $P = 0.305$<br>$n = 23$ | $P = 0.652$<br>$n = 20$ |
| Patient satisfaction (0–10 categorical scale)                              |              | 8 (6–9)    | 6 (4–7)    | 6 (4–7)     |              | 7 (6–8)    | 5 (4–7)    | 5 (3–7)    | $P = 0.010$<br>$n = 23$ | $P = 0.047$<br>$n = 23$ | $P = 0.047$<br>$n = 23$ | $P = 0.125$<br>$n = 20$ |

Data are presented as median (interquartile range).



Fig 3. Photograph of a representative patient (a) before and (b) at 6 months after treatments with intense pulsed light (IPL, left side) and long-pulsed diode laser (LPDL, right side).

relevance. The study design was stringent with respect to persistently normal serum testosterone levels before and during the study period, and thus provides reliable estimates of the true hair removal efficacy with IPL and LPDL treatments in hirsute women with normal testosterone levels. However, it was a drawback that we had to exclude eight of the 31 (26%) included patients from efficacy assessments due to elevated testosterone levels.

The high prevalence of androgen disturbance in this group of hirsute women corresponds to the incidence described elsewhere in the literature.<sup>2-4,21</sup> This emphasizes the need for screening hirsute women for androgen disturbances and possible initiation of complementary medical treatments. In this study we measured the serum testosterone levels three times during the study period because we intended to evaluate the pure efficacy of photoepilation. However, this is hardly practicable, nor relevant, in clinical practice. We recommend that all hirsute women undergo initial blood test screening in order to highlight a possible endocrine dysfunction that may require adjunctive medical treatment.

The median hair removal efficacy in the excluded patients was 40%, 29% and 29% for IPL and 51%, 37% and 44% for LPDL at 1, 3 and 6 months post-treatment, respectively. The 1-month efficacies were significantly lower for these excluded patients ( $n = 8$ ) compared with the included patients ( $n = 23$ ) for both IPL and LPDL ( $P < 0.023$ ), whereas no differences were found at 3 and 6 months post-treatment ( $P \geq 0.195$ ).

The IPL and LPDL treatment settings were based on clinical experience and recommendations for the two devices used in this study. After both IPL and LPDL treatments a few patients responded with minor transient pigment changes. Pain intensities were consistently higher with IPL than with LPDL treatments. In general, patients experienced moderate pain intensities from IPL treatments and low pain intensities from LPDL. Pain scores remained constant from the first to last treatments, although increasing fluencies were used. This may be explained by patients getting used to treatments, and therefore, tolerating higher sensations of pain at the later treatment sessions or the decreasing hair density at later treatment sessions may account for the lower pain sensations.

At 6 months post-treatment, the hair count reduction from baseline was 34% and 40% for LPDL and IPL, respectively. The lower, but statistically insignificant, difference for LPDL ( $P = 0.427$ ) might be explained by suboptimal treatment fluencies as lower pain scores were reported with LPDL compared with IPL ( $P < 0.001$ ). However, transient pigment changes were observed in 10% (three of 31) of LPDL-treated patients and it is therefore unlikely that efficacies could be further improved by increasing laser intensities without increasing the risk of adverse effects.

Three RCTs have so far described the efficacy of photoepilation in hirsute women.<sup>15,16,18</sup> McGill *et al.*<sup>16</sup> compared the efficacy of six treatments with alexandrite laser vs. IPL in 38 women with PCOS and reported 6-month post-treatment hair reductions of 46% vs. 27% for the alexandrite laser and IPL, respectively. In the present study, we found a higher hair removal efficacy of 40% for IPL at 6 months post-treatment. This divergence in efficacy may be explained by the use of different IPL devices in the two studies, thus representing different treatment settings. Clayton *et al.*<sup>15</sup> treated 44 women with PCOS with an alexandrite laser over a 6-month period. Approximately 1 month after five treatments, the self-reported severity of facial hair was reduced from 7.3 to 3.6 (scale 1–10). We found similar efficacies of an approximately 50% reduction in self-reported hairiness from IPL and LPDL at 1 month post-treatment. Medical treatment is known to reduce hairiness in hirsute women, but a recent study by Rezvanian *et al.*<sup>18</sup> was the first to document an advantage of combining metformin and IPL in the treatment of hirsutism. The treatment with metformin was initiated and administered only during the period of IPL treatments. In the present study we initiated medical treatments at least 6 months before IPL and LPDL treatments with the intention of avoiding bias from medically induced hair reduction. Timing of initiating metformin treatment in relation to photoepilation might be an important issue, and thus needs further clarification. It is furthermore known that medical treatment of hyperandrogenicity with the antiandrogen and aldosterone antagonist spironolactone reduces the intensity of hairiness.<sup>3,4,21,22</sup>

In this study, hirsute women with normal or medically normalized testosterone levels responded equally well to IPL and LPDL treatments of facial hairiness, but the pain perception

was higher for IPL than for LPDL treatments. The efficacy of hair removal declined after both IPL and LPDL treatments by approximately 50% from 1 to 6 months post-treatment.

### What's already known about this topic?

- Limited evidence exists on the efficacy of photothermolysis for hair removal in hirsute women and no data are available for patients with normal testosterone levels.

### What does this study add?

- This study provides data about laser- and photoepilation in hirsute women with intrinsically normal or medically normalized testosterone levels.

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