Does unilateral laparoscopic diathermy adjusted to ovarian volume increase the chances of ovulation in women with polycystic ovary syndrome?

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STUDY QUESTION: Does unilateral volume-adjusted laparoscopic diathermy increase the chances of ovulation in women with polycystic ovary syndrome (PCOS)?

SUMMARY ANSWER: Although unilateral laparoscopic ovarian drilling (ULOD) using adjusted thermal doses was more efficient than bilateral laparoscopic ovarian drilling (BLOD) using fixed doses, the chances of ovulation were improved in patients irrespective of the technique used.

WHAT IS KNOWN ALREADY: The adjustment of the thermal dose to ovarian volume in BLOD increases ovulation and pregnancy rates compared with fixed-dose treatment, but BLOD causes the formation of adhesions, particularly on the left ovary, and increases the risk of damage to ovarian tissue. In contrast, ULOD with a fixed thermal dose minimizes the risk of ovarian tissue damage, and can increase the activity in both right and left ovaries, although this varies in humans and in other species.

STUDY DESIGN, SIZE, DURATION: This prospective, longitudinal, study, between September 2009 and January 2013, included 96 infertile women with PCOS who were unresponsive to clomiphene citrate treatment and had underwent either ULOD or BLOD. After surgery, the groups were followed up for 6 months to assess ovulatory response.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Patients were assigned to two groups; one group underwent laparoscopic ovarian drilling of the right ovary alone, while both ovaries were treated in the second group. The ULOD group (n = 49) received thermal doses adjusted to the volume of the right ovary (60 J/cm3). The BLOD group (n = 47) received fixed doses of 600 J per ovary, regardless of its volume. The two treatment groups were matched by the number of participants, age and baseline parameters.

MAIN RESULTS AND THE ROLE OF CHANCE: The ovulation rate during the first menstrual cycle after LOD was significantly higher in the ULOD group than in the BLOD group [73 versus 49%; absolute risk reduction (ARR), −0.25; 95% confidence interval (CI), −0.44 to −0.03; P = 0.014]. Treatment with ULOD on the right ovary significantly increased the chances of ovulation in patients with a larger right ovary compared with those who had a smaller right ovary (100 versus 36%; ARR, −0.64; 95% CI, −0.84 to −0.37; P = 0.004). Interestingly, the chances of ovulation were also significantly higher in patients in the BLOD group who had a larger right ovary compared with those who had a smaller right ovary (88 versus 33%; ARR, −0.55; 95% CI, −0.73 to −0.28; P = 0.002). The pregnancy rate was also significantly higher in patients with a larger right ovary compared with those with a smaller right ovary, regardless of the treatment group.

LIMITATIONS, REASONS FOR CAUTION: The 6-month follow-up was too short to demonstrate any long-term differences in the ovulation rates. Future research should therefore extend the follow-up beyond 6 months. Another limitation is that ULOD was used to treat only the right ovary. Future studies should investigate whether ULOD treatment of the larger ovary, whether left or right, would significantly increase the ovulation rate.

WIDER IMPLICATIONS OF THE FINDINGS: This study represents an advance in the determination of the optimal laparoscopic treatment for women with PCOS, as it was shown that improved results can be achieved using less thermal energy in volume-adjusted ULOD.

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders and the leading cause of infertility in women of reproductive age (Goldenberg and Glueck, 2008). The primary measure of the outcome of PCOS-related infertility management is the birth of a healthy child, although a prerequisite is to ensure ovulation (Zhang et al., 2010). To this end, it is essential for the patient to change her lifestyle to lose weight and become more physically active. The first line of infertility treatment is clomiphene citrate, the second line includes gonadotrophins or laparoscopic ovarian drilling (LOD) and the third is IVF (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008). The basic rule for all of these methods in PCOS is to use the lowest possible dose of a drug or of energy to induce unifollicular ovulation (Balen, 2006). The advantage of LOD over IVF is that it induces unifollicular ovulation without the risk of ovarian hyperstimulation syndrome or high-order multiple pregnancies (Balen, 2006), and its beneficial effects can last for up to 9 years (Amer et al., 2002).

The success of either unilateral (ULO D) or bilateral LOD (BLOD) depends on how much tissue is destroyed. In BLOD, statistically significant increases in rates of ovulation and pregnancy have been achieved with a thermal dose of 1 200 J (Amer et al., 2003). Although Zakherah et al. (2011) proved that thermal doses adjusted to the ovarian volume can further increase these ovulation rates in comparison with the fixed dose, their levels reached up to 2160 J. The adverse effects of BLOD with a thermal dose of 1200 J (Amer et al., 2008) and diminished ovary reserve due to tissue damage, and the use of a larger number of stitches and higher thermal doses (Naether and Fischer, 1993; Roy et al., 2009; Fernandez et al., 2011). Therefore, a less aggressive method of LOD has been recommended (Fernandez et al., 2011). Unilateral treatment induces activity in both ovaries (Balen and Jacobs, 1994) and minimizes procedure time as well as the risk of post-operative adhesions and ovarian tissue damage. However, U LOD requires further evaluation (Roy et al., 2009; Fernandez et al., 2011) because no optimal dose has yet been shown to stimulate ovulation reliably, and it has not been adopted as a sustainable surgical option (Mercorio et al., 2008; Fernandez et al., 2011).

The objective of our study was to compare and assess the efficiency of right ULOD using thermal doses adjusted to ovarian volume (60 J/cm³) with that of BLOD at a constant dose and assess ovulatory response based on clinical parameters (right or left ovary and its volume) and the thermal doses received.

Materials and Methods

Subjects

This prospective, longitudinal, cohort study was carried out in the Clinical Hospital of Split, Croatia, from September 2009 to January 2013. The study included 96 infertile women with PCOS who were resistant to clomiphene citrate treatment (150 mg/day for 5 days) and aged between 25 and 35 years at the time of enrolment. The diagnostic criteria for PCOS (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) were: oligomenorrhea/anovulation, hyperandrogenaemia (serum testosterone >2.5 nmol/l on cycle days 2–5) and/or polycystic ovaries, as determined by ultrasound, with diagnostic parameters of >12 follicles and a diameter of 2–9 mm or an ovarian volume > 10 cm³ (Balen et al., 2003). Other inclusion criteria, which needed to be met, were: body mass index <30 kg/m², infertility period of 1–3 years, luteinising hormone >10 or luteinising hormone/follicle-stimulating hormone ratio ≥ 2, free androgen index > 4, normal semen findings in the partner and normal oral glucose tolerance test. Only patients with a phenotype characterized by oligomenorrhea/anovulation, hyperandrogenaemia and polycystic appearance of the ovaries on ultrasound examination were enrolled in the study. Women with adrenal hyperplasia, thyroid disease, Cushing’s syndrome, hyperprolactinaemia and a tumour-related excess of androgen were excluded from the study.

All procedures were approved by the Ethics Committee of the Clinical Hospital of Split, and all patients provided informed consent for participation in the trial and separate informed consent for the surgical procedure and anaesthesia before enrolment.

The sample size was estimated from a pilot study based on ovulation rates during the first month after LOD. With an assumed ovulation rate of 44% in BLOD and 69% in ULOD, a power of 80% and a type II error (alpha) criterion of 0.05, the minimal sample size required to detect whether the ULOD method was more efficient than BLOD was 48 per group.

The study design is presented in Fig. 1. The patients were alternately assigned into two groups according to their registration into the protocol for the operation and their menstrual cycle (the first day); one group underwent LOD of the right ovary and the other group was treated by BLOD. Hormone measurements and ultrasound monitoring procedures were identical in both groups.

All patients were assessed for ovarian volume using ultrasound on Days 2–5 of the cycle after enrolment and again before surgery. The volume of each ovary was calculated as follows: length x width x height x 0.523 (Swanson et al., 1981). In this study, we used an Aloka ultrasound color Doppler SSD-3500SX with an UST-9124 vaginal probe (Aloka Co., Tokyo, Japan).

Surgery was performed on patients under general anaesthesia as follows: three incisions were made in the abdominal wall; the laparoscope was inserted through the first 10-mm incision, and the remaining two 5-mm incisions were used for the instruments. For the procedure, we used an Evis Exera II video system center model CV-180 with a UES-40040 electro surgical unit (Olympus, Tokyo, Japan) and a monopolar HF electrode needle (Olympus).

Although successful treatment of PCOS with clomiphene and metformin is associated with the left ovary (Zhang et al., 2010), we decided to treat only the right ovary in the ULOD group, because drilling the left ovary appears to entail greater formation of adhesions (at a rate of 64%; Mercorio et al., 2008). Furthermore, some authors have suggested that oocytes from the right ovary have a greater fertility potential, for reasons that are as yet unknown (Fukuda et al., 2000). The thermal dose received by the ULOD group was a mean dose calculated from three ULOD studies (Balen and Jacobs, 1994; Yousef and Atallah, 2007; Roy et al., 2009), i.e. 627 J/10 cm³ or 60 J/cm³.
The number of punctures ($N_p$) per ovary was calculated according to the following formula:

$$N_p = \frac{60 \text{ J/cm}^3}{30 \text{ W} \times 4 \text{ s}}.$$

The comparator group underwent BLOD. Each ovary received 600 J, to give a total of 1200 J for both ovaries. All patients received five punctures per ovary at 30 W for 4 s each (i.e. 600 J = 5 punctures $\times$ 4 s $\times$ 30 W; Fig. 2).

Therefore, patients in the ULOD group received various numbers of drillings and varying thermal doses in the right ovary, while those in the comparator group received the same number of drillings and thermal doses in both ovaries. The ovaries were cooled after drilling by irrigating the abdominal cavity with 200–300 ml physiological saline (Naether and Fischer, 1993).

**Post-operative follow-up**

Ovarian ultrasound follow-up was scheduled for Days 2–5 of the menstrual cycle at 1, 3 and 6 months after LOD. On cycle day 21, progesterone was measured and ovulation was proved when the levels were above 25 nmol/l. In patients with serum progesterone levels below 25 nmol/l, the measurement was repeated on cycle day 28 and ultrasound was carried out to verify ovulation.

**Data analysis**

For each ovary in the BLOD group where the thermal energy doses were unadjusted, and for the untreated, left ovary of the ULOD group, the suboptimal energy difference (SED) was calculated. The SED is the difference between the energy that should have been received by the ovary based on its preoperative volume ($60 \text{ J/cm}^3$ of ovarian tissue) and the thermal dose.
actually applied. Similarly, the SED per patient was calculated by subtracting the total energy applied in a patient from the optimal energy based on total ovarian volume at baseline to determine the effect of both the energy applied and the SED on the outcome of ovulation.

For data analysis, we used descriptive and inferential statistics. Absolute risk reduction (ARR) with the 95% confidence interval (CI) was used to estimate the strength of the relationship between ovulation and the treatment used, while Fisher’s exact test was used to test its significance. Kaplan–Meier curves were constructed to predict the success of pregnancy within 6 months after LOD for each group and were compared using the log-rank test. Means of measurements were also compared between the treatment groups using the independent sample t-test. Alternatively, we used the Mann–Whitney U-test for skewed distributions. For the correlation between measured variables and ovulation, we used the point biserial correlation coefficient (rpb). Multiple logistic regression was used to create an optimal model for predicting ovulation by determining the strongest predictors.

The results were interpreted at a significance level of $P \leq 0.05$. For statistical analysis, we used the Statistica 10.0 package (StatSoft, Tulsa, OK, USA).

### Results

All patients completed the trial. The demographic data and baseline features of the groups did not differ (Table I), and the observed difference in the levels of total testosterone was considered to be clinically insignificant (Tang et al., 2012).

The ovulation rate during the first menstrual cycle after LOD was significantly higher in the ULOD than that in the BLOD group (ARR, $-0.25, 95\%\ CI, -0.44$ to $-0.03; P = 0.014$), whereas the increase in the total ovulation rate over the 6-month period after LOD in the ULOD group over that in the BLOD group was borderline (ARR, $-0.18, 95\%\ CI, -0.35$ to $0.02; P = 0.050$; Table I).

With respect to ovulation (within 6 months after LOD), we observed an interesting relationship with ovarian volume. Whereas responders and non-responders showed no significant difference in the volume of their right ovary (mean difference, $0.46\ cm^3; 95\%\ CI, -0.47$ to $1.38$; t-test $P = 0.332$), the non-responders had a significantly larger left

### Table I Preoperative data for the 96 patients with PCOS included in the trial.

<table>
<thead>
<tr>
<th>Preoperative data</th>
<th>Mean ± SD or median (IQR)</th>
<th>ULOD group (n = 49)</th>
<th>BLOD group (n = 47)</th>
<th>MD (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td>29.3 ± 3.31</td>
<td>29.3 ± 3.05</td>
<td>0.08 (−1.23, 1.38)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>25.1 ± 1.94</td>
<td>25.0 ± 2.10</td>
<td>0.02 (−0.81, 0.85)</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td></td>
<td>5.5 ± 1.19</td>
<td>5.1 ± 1.15</td>
<td>0.38 (−0.09, 0.86)</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td></td>
<td>13.0 ± 2.64</td>
<td>12.3 ± 3.50</td>
<td>0.68 (−0.58, 1.95)</td>
</tr>
<tr>
<td>FAI</td>
<td></td>
<td>7.8 (1.4)</td>
<td>8.0 (3.3)</td>
<td>−0.4 (−1.4, 0.2)</td>
</tr>
<tr>
<td>T (nmol/l)</td>
<td></td>
<td>2.7 (0.6)</td>
<td>3.0 (1.1)</td>
<td>−0.2 (−0.5, −0.1)</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td></td>
<td>35.0 ± 9.32</td>
<td>39.0 ± 10.45</td>
<td>−4.02 (−8.07, 0.03)</td>
</tr>
<tr>
<td>Mean total ovarian volume (cm³)</td>
<td></td>
<td>11.3 ± 1.79</td>
<td>11.4 ± 2.74</td>
<td>−0.13 (−1.08, 0.82)</td>
</tr>
<tr>
<td>Volume of the left ovary (cm³)</td>
<td></td>
<td>11.1 ± 2.53</td>
<td>11.7 ± 3.67</td>
<td>−0.03 (−1.13, 1.26)</td>
</tr>
<tr>
<td>Volume of the right ovary (cm³)</td>
<td></td>
<td>11.6 ± 1.54</td>
<td>11.5 ± 2.47</td>
<td>0.04 (−0.80, 0.88)</td>
</tr>
</tbody>
</table>

BLOD, bilateral laparoscopic ovarian drilling; BMI, body mass index; FAI, free androgen index; FSH, follicle-stimulating hormone; IQR, interquartile range; LH, luteinising hormone; n, number; PCOS, polycystic ovary syndrome; SD, standard deviation; SHBG, sex hormone-binding globulin; T, total testosterone; ULOD, unilateral laparoscopic ovarian drilling.

*Mean or median difference (MD) with 95% CI.

†Significant at $\alpha = 0.05$ level, but clinically insignificant.
Larger ovary | ULOD group (n = 49) | BLOD group (n = 47)
--- | --- | ---
| Ovulation (n = 49) | No ovulation (n = 9) | Total | Ovulation (n = 30) | No ovulation (n = 17) | Total
Right, n (%) | 35 (100%) | 0 (0%) | 35 (100%) | 23 (88%) | 3 (12%) | 26 (100%)
Left, n (%) | 5 (36%) | 9 (64%) | 14 (100%) | 7 (33%) | 14 (67%) | 21 (100%)

BLOD, bilateral laparoscopic ovarian drilling; LOD, laparoscopic ovarian drilling; n, number; ULOD, unilateral laparoscopic ovarian drilling.

**Table IV** Best fitting multiple logistic regression model for predicting ovulation after BLOD.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larger right ovary</td>
<td>8.10</td>
<td>1.37–48.02</td>
<td>0.021</td>
</tr>
<tr>
<td>Left ovary SED</td>
<td>0.99/1 J</td>
<td>0.984–0.997</td>
<td>0.006</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio; SED, suboptimal energy difference.
In line with these findings, the pregnancy rate was higher in patients with a larger right ovary in both treatment groups (log-rank, $P < 0.001$ for both comparisons; Fig. 4).

**Discussion**

Our findings confirmed that the ULOD method using thermal doses adjusted to the ovarian volume (60 J/cm$^3$) was more effective than the BLOD method with constant thermal doses for both ovaries (totaling 1200 J) in the first post-operative month. Patients in the ULOD group had a 25% greater chance of ovulating than patients in the BLOD group. These results confirmed earlier findings that ULOD requires lower thermal doses to achieve ovulation (Balen and Jacobs, 1994; Youssef and Atallah, 2007; Roy et al., 2009) and that adjustment of the dose optimizes the efficiency of LOD (Zakherah et al., 2011).

However, the difference in ovulation rates after ULOD and BLOD diminished with time, and the 6-month follow-up was too short to establish any long-term superiority of ULOD in improving ovulation rates. Furthermore, the optimal effect of ULOD treatment applied to the right ovary on ovulation may be partly due to the fact that most ULOD patients had a larger right ovary which received an optimal level of energy. Therefore, future research should extend the follow-up beyond 6 months and should investigate whether ULOD treatment of the larger ovary, whether left or right, would significantly increase the ovulation rate.

Our study also established a strong correlation between a larger right ovary and the success of ovulation, regardless of the treatment used. The patients, in either the ULOD or BLOD group, with a larger right ovary had a significantly greater chance of ovulation than the patients with a smaller right ovary (ULOD: 100 versus 36%, respectively; BLOD: 88 versus 33%, respectively). Our results are in line with the findings of Jokubkiene et al. (2012), who showed that in fertile and infertile women without PCOS aged 20–29 years, the right ovary is greater in volume and holds more follicles. They also established that this difference disappears with time (0.19%). A reason for the difference may be related to the fact that the right ovary vein drains into the inferior vena cava, whereas the left ovary vein drains into the kidney vein (Deb et al., 2011). A 9-year study by Fukuda et al. (2000), which encompassed data from over 2000 cycles in fertile and infertile women, showed that right-sided ovulation was more frequent than left-sided ovulation (55 versus 45%, respectively); that pregnancies from right-sided ovulation were more frequent (64.6%); and that testosterone and estradiol levels on post-ovulation Day 7 were higher in the right than in the left ovary. The authors suggested that anatomical asymmetry and differences in vasculature may be the responsible reasons. However, this does not preclude the possibility that oocytes from the right ovary have a greater fertility potential for reasons that are still unclear (Fukuda et al., 2000). The authors further suggested that asymmetrical ovarian activity is not limited to humans. Animal studies have also shown the dominance of either the left or right ovary (Fukuda et al., 2000). In birds, whales and chinchillas, the left ovary is active while the right ovary rests (Fukuda et al., 2000). In contrast, right-sided ovulation (and pregnancy) is more frequent in cows (Nation et al., 1999) and mice (Wiebold and Becker, 1987).

Finally, our results showed no correlation between the thermal doses applied and the ovulation rates in or between the groups. However, in the ULOD group, there is no strong correlation between the thermal dose (60 J/cm$^3$) received by the larger, right ovary and the ovulation rate but a strong negative correlation between the same thermal dose received by the smaller, right ovary and the ovulation rate, suggesting that the chances of ovulation are lower when ULOD is applied to the smaller right ovary, even when the thermal dose is adjusted to ovarian volume.
As mentioned above, the main limitation of our study is that ULOD was applied only to the right ovary. Future trials should investigate whether ULOD treatment of a larger, left ovary would significantly increase the ovulation rate, and, in contrast, whether ULOD treatment of a smaller left ovary would significantly lower the chances of ovulation, although this could be ethically unacceptable.

In the BLOD group, the strongest predictors of ovulation were whether the right or left ovary was the larger and the SED of the left ovary. Patients with a larger right ovary had an 8-fold greater chance of ovulating than patients with a larger left ovary, whereas an increased SED in the left ovary decreased the chance by 0.99 with each suboptimal joule. Theoretical probability curves showed a very limited SED range for BLOD to achieve clinically significant ovulation in patients with a larger, left ovary. This finding needs to be verified in future studies with a different sample. In this respect, our results confirmed previous reports that the use of BLOD with thermal doses adjusted to ovarian volume would result in higher ovulation rates (in our case particularly for the left ovary, as it would receive an optimal thermal dose; Zakherah et al., 2011). However, this would increase the total dose received by both ovaries.

In our 6-month follow-up, we did not establish any significant difference in the probability of pregnancy between the two groups. In either group, pregnancy was most likely to occur between the fourth and fifth months. However, when we took into consideration the side of the larger ovary, we observed a significantly higher pregnancy rate in patients with a larger right ovary, regardless of the treatment group.

In conclusion, our study has shown that ULOD using adjusted thermal doses (60 J/cm$^3$) is more efficient in clomiphene-resistant infertile women than BLOD using fixed doses. Treatment of the larger, right ovary improved the chances of ovulation and pregnancy, regardless of whether ULOD or BLOD was used.

However, further research is needed to clarify whether volume-adjusted ULOD yields a better ovulation outcome and whether treatment of the left, right or of the larger ovary is more effective.

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**Authors’ roles**
M.S., T.C. and D.P.B. planned and designed the study. M.S. recruited the patients and controls, and performed surgical procedures. I.P. collected the data and monitored the patients. M.T. was involved in the biochemical analysis and acquisition of data. A.J. analysed the data. All authors contributed to the interpretation of data, and drafting and editing of the manuscript. They all approved the final version of the manuscript and take full responsibility for its content.

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Conflict of interest

The authors declare no conflicting interests.

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