Transvaginal, ultrasound-guided, ovarian, interstitial laser treatment in anovulatory women with clomifene-citrate-resistant polycystic ovary syndrome

WJ Zhu, XM Li, XM Chen, Z Lin, L Zhang

Objective To assess the effectiveness of transvaginal, ultrasound-guided, ovarian, interstitial laser coagulation treatment in anovulatory women with polycystic ovary syndrome (PCOS).

Design A pilot study.

Setting Assisted reproductive technology unit.

Sample Twenty-three anovulatory women with clomifene-citrate-resistant PCOS.


Main outcome measures Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, prolactin and estradiol levels, spontaneous ovulation rate and pregnancy rate were measured over 6 months of follow-up.

Results Regular ovulation occurred in 19 out of 22 (86.4%) women in the 6 months following ovarian treatment (one woman was lost to follow up). On the postoperative second, fourth and sixth month, the mean serum LH levels were 4.54 SD 1.21 iu/l, 4.90 SD 1.21 iu/l and 4.42 SD 1.03 iu/l, significantly \( P < 0.001 \) lower than the preoperative level of 13.89 ± 3.62 iu/l; the mean serum testosterone levels were 2.69 SD 1.83 nmol/l, 2.42 SD 1.11 nmol/l and 2.28 SD 1.96 nmol/l and significantly \( P < 0.001 \) lower than the preoperative baseline value of 5.37 SD 3.09 nmol/l; the mean LH/FSH ratios of 0.93 SD 0.26, 0.88 SD 0.17 and 0.81 SD 0.14 were also significantly lower than the preoperative value of 2.78 SD 1.21 \( P < 0.001 \). Pregnancy occurred in eight women and there was a cumulative pregnancy rate at 6 months of 36% \( (8/22) \) among the subjects. There were no significant operative complications.

Conclusion Ultrasound-guided, transvaginal, ovarian, interstitial laser treatment appears effective in improving hormonal profiles and inducing ovulation and successful pregnancy in women with clomifene-resistant PCOS.

Keywords Laser, ovarian interstitial, polycystic ovary syndrome, transvaginal, ultrasound-guided.

Introduction

Laparoscopic ovarian diathermy or drilling (LOD) has been used in the management of anovulatory women with clomifene-citrate(CC)-resistant polycystic ovary syndrome (PCOS) for the past two decades. With ovulation rates of 70–80% and pregnancy rates of 30–60% within 6–12 postoperative months, the effectiveness of LOD has been well documented in the literature.\(^1\)–\(^8\) However, about 20–30% of women fail to respond to LOD, and about 50% of those who initially respond to the treatment became anovulatory again after a few months.\(^1\) Some workers have reported that women who have had LOD develop mild to moderate postoperative abdominal adhesions,\(^9\) although it is unclear whether these adhesions can induce a subfertile state. Furthermore, the risk of general anaesthesia needed for LOD must also be considered. To avoid these disadvantages, we evaluated the value of transvaginal, ultrasound-guided, ovarian, interstitial laser treatment in 23 anovulatory women with PCOS.
Subjects and methods

Between May 2003 and July 2005, 129 women with PCOS were treated for infertility, 28 of them were found to be CC resistant. Twenty-three out of these 28 women were enrolled into this study. All participants had received incremental doses of CC (50, 100 and 150 mg), to which they had failed to respond. Of the 23 women, 16 suffered from ovarian hyperstimulation syndrome (OHSS) and the remaining seven were at a high risk of ovarian hyperstimulation during previous ovulation induction treatments with a step-up protocol of gonadotrophin (Gn). Exclusion criteria included any contraindications to surgery, previous treatment with metformin or LOD and the presence of tubal or male factors for infertility. The mean body mass index of the subjects was 32.36 SD 4.15 kg/m² and their history of infertility ranged from 3–10 years. All participants fulfilled the diagnosis for PCOS, having polycystic ovaries on transvaginal ultrasound scan (TVS) (Aloka-1000, UST-985, 5 MHz transvaginal probe; Aloka Co. Ltd, Tokyo, Japan), biochemical evidence including elevated luteinizing hormone (LH) and serum testosterone levels ≥2.5 nmol/l, secondary amenorrhoea (<2 cycles per year) and anovulation. Ovarian enlargement and at least one ovary with 10–30 subcapsular follicles of 3–8 mm in diameter were present in each case. Serum follicle-stimulating hormone (FSH) (5.15 SD 1.33 iu/l), LH (13.89 SD 3.62 iu/l) and testosterone (5.37 SD 3.09 nmol/l) levels were assessed at the third day of progesterone (natural progesterone injection; Guangzhou Minxin pharmaceutical company, Guangzhou, China)-induced bleeding. All subjects were informed that this procedure was a new technique, the effectiveness of which has not yet been confirmed, although LOD, tested for the same goal, has proven to be efficient. Informed consent was obtained from all participants. Five eligible subjects opted not to participate when counselled about the possible risk. This study was approved by the Ethics Committee of Shenzhen Maternity and Child Healthcare Hospital and the Institutional Review Board of Shenzhen Bureau of Science and Technology of China.

Transvaginal, ultrasound-guided, ovarian, interstitial laser treatment was performed on the third day of progesterone-induced menstruation.

1. The preparation of surgical instruments and materials: A fibre optic cable of 400 μm in diameter was stripped of its outer insulation layer for a length of 10 mm at the end, making the tip bare. A special knife was then used to cut the tip perpendicularly in order to achieve a flat surface. The optical fibre was marked from this tip at a distance equal to the length of a 17-gauge, 35-cm-long needle. Laser power was adjusted with a power meter (LP-3B Type Laser Power meter; Beijing Wuko Photoelectricity Co. Ltd, Beijing, China). A power of 3–5 W and current of 9–10 A was deemed suitable for effecting treatment. 

2. The ovarian interstitial laser treatment: An intramuscular injection of 50–100 mg of pethidine (pethidine hydrochloride injection; Shenyang First Pharmaceutical, NEPG, Shenyang, China) was administered to each woman about 30 minutes before starting the operation. After emptying their bladder, women were placed in lithotomy. They were then prepped using an aseptic vulva and vaginal douche. TVS was performed. If one ovary could not be clearly visualised on TVS, or its position meant that the procedure would be technically difficult, the procedure was abandoned.

Surgical procedure

1. Location and puncture: The probe was moved from one side to the other side in order to find the widest ovarian plane; the operator then punctured the fornix with the long needle mentioned above into the predetermined intraovarian point. Usually, three to five intraovarian points can be predetermined in accordance with the size of the largest plane. These points were always at least at a 10-mm distance from the surface of the ovary and 5-mm distance from each other. If intraovarian coagulation occurred at a spot 10 mm in diameter, the coagulation was confined to at least a 5-mm distance from the surface so that there was minimal damage to the ovarian surface. If three to five points could not be accomplished in the largest ovarian plane, the next largest ovarian plane was chosen as the next option.

2. The fibre optic cable was then passed through the needle in the following manner: The blood or follicular fluid present inside the long needle was aspirated, then the assistant cut
the soft tube connected to the end of the needle and inserted the fibre optic cable into the needle up to the marked point (Figure 2). The tip of the fibre optic cable had to reach the tip of the long needle, so the operator could draw the long needle back about a distance of 10 mm until the bare fibre was out of the tip of long needle (Figure 3).

3. Laser coagulation: The electrical laser was activated and was projected persistently for 1–2 minutes with a power of 3–5 W and a current of 9–10 A, until a 10-mm light spot appeared on the ovarian plane (Figure 4).

4. The fibre optic cable was then carefully withdrawn from the long needle with care taken not to pull the needle out of the ovary while withdrawing it toward the surface. In order to give three to five treatments to the ovarian stroma, the next point was then located and punctured, the procedure from 2 to 4 was repeated until three to five spots of unilateral ovary were treated, and then the long needle was withdrawn carefully out of the ovary and pelvic cavity. This procedure was repeated on the contralateral ovary. The aim was that each ovary had only one puncture site on the surface. The women stayed in bed for 2–3 hours after the surgery, after which time they were re-examined with TVS in order to rule out intra-abdominal haemorrhage prior to discharge.

Postoperative monitoring
1. Serum hormone level: Following ovarian interstitial laser treatment, serum concentrations of LH, FSH, testosterone, prolactin (PRL), estradiol (E2) and progesterone were measured (PerkinElmer Co. Ltd, Boston, Massachusetts, USA) at the second, fourth and sixth month after the operation, respectively. At these times, the LH/FSH ratio was also calculated. If there was significant change in hormone concentration following the surgery, the subject was categorised as a responder, while if no change occurred, the subject was categorised as a nonresponder. In general, a blood sample was taken on day 3 of the menstrual cycle if the woman had a regular menstrual cycle. If not, the blood sample was taken on day 3 of progesterone-induced withdrawal bleeding.

2. The dimensions of the ovary and the number of subcapsular follicles were measured by TVS during postoperative second, fourth and sixth months between days 3–5 of menstruation or withdrawal bleeding period.

3. Postoperative follicle development was monitored by serial ultrasound scans every month. Usually, this was performed at 4- to 5-day intervals. The follicular sizes presented here are the average of two dimensions. Scanning was repeated after 2–3 days when the leading follicle was >12 mm. When the dominant follicles reached a diameter of 16 mm, the LH surge was detected using urinalysis, and depending on this result, the timing of sexual intercourse was suggested. If the follicle reached 18 mm in diameter without the occurrence of an LH surge, 10 000 units of human chorionic gonadotrophin (hCG) was injected intramuscularly. The woman was asked to begin sexual intercourse on the second or third day after hCG administration. Ovulation was confirmed using ultrasound scan performed several days after the LH surge or using midluteal serum progesterone levels. If the ovulation intervals during the 6 postoperative months were within a range of 21–35 days, the woman was documented as having regular ovulation. A urine pregnancy test was performed if spontaneous menstruation did not occur during 16–19 days following ovulation. The pregnancy rate was calculated based on the women who conceived.

4. Adverse effects of the operation: Adverse effects were recorded, including intra-abdominal haemorrhage, infection, injuries of internal organs and failure of ovarian function.
The means ± SD of the baseline and postoperative second, fourth and sixth month values were calculated for the ovary size, numbers of subcapsular follicles, serum LH, FSH, testosterone, PRL, progesterone, E₂ levels and LH/FSH ratios. Student’s t test was used for statistical analysis. The spontaneous ovulation rate and pregnancy rate were calculated based on the cases of postoperative spontaneous ovulation and pregnancy, with $P < 0.05$ considered statistically significant.

Results

Twenty-three women underwent ovarian interstitial laser treatment, 21 of whom had bilateral treatment. Two women had unilateral treatment because the opposite ovaries were not clearly visible. One subject failed to attend for follow up.

The hormone data of the participants were obtained from 111 monitored cycles. Nineteen women responded to the ovarian interstitial laser treatment. On the postoperative second, fourth and sixth month, their mean serum LH levels were 4.54 SD 1.21 iu/l, 4.90 SD 2.18 iu/l and 4.42 SD 1.03 iu/l and significantly ($P < 0.001$, $P < 0.001$, $P < 0.001$) lower than preoperative level of 13.89 SD 3.62 iu/l; the mean serum testosterone levels were 2.69 SD 1.83 nmol/l, 2.42 SD 1.11 nmol/l and 2.28 SD 1.96 nmol/l and significantly ($P < 0.001$, $P < 0.001$, $P < 0.001$) lower than preoperative level of 5.37 SD 3.09 nmol/l; the mean LH/FSH ratios were 0.93 SD 0.26, 0.88 SD 0.17 and 0.81 SD 0.14, the reverse of the preoperative value of 2.78 SD 1.21 with a statistically significant ($P < 0.001$) change (Table 1). There were, by definition, no changes in serum LH, testosterone levels and LH/FSH ratio in the three women who did not respond to treatment. No statistically significant changes occurred in the postoperative serum levels of FSH, PRL and E₂ in any woman.

Table 1. The comparison of hormone level between preoperation and postoperation (mean ± SD) in 19 responders

<table>
<thead>
<tr>
<th>Hormones (units)</th>
<th>Preoperation</th>
<th>Postoperation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (iu/l)</td>
<td>13.89 ± 3.62</td>
<td>4.62 ± 1.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSH (iu/l)</td>
<td>5.15 ± 1.33</td>
<td>5.56 ± 1.59</td>
<td>NS</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>5.37 ± 3.09</td>
<td>2.46 ± 1.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRL (microgram per litre)</td>
<td>12.10 ± 6.82</td>
<td>11.29 ± 5.73</td>
<td>NS</td>
</tr>
<tr>
<td>E₂ (pmol/l)</td>
<td>58.05 ± 15.37</td>
<td>57.77 ± 12.78</td>
<td>NS</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>2.78 ± 1.21</td>
<td>0.87 ± 0.19</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NS, statistically not significant.
P value is the result of comparison between the mean of postoperative second, fourth and sixth month and the basic value of preoperation.
On the postoperative second, fourth and sixth month, the mean subcapsular follicle number of unilateral ovary for responders was $16.79 \pm 4.35$, greatly less than preoperative number of $25.16 \pm 5.60$ ($P < 0.001$) (Table 2). Following laser treatment, regular spontaneous ovulation and menstruation with cycles of 27–35 days occurred monthly in 19 responders, all of whom demonstrated a significant reduction of serum LH and testosterone levels. The spontaneous ovulation rate was $86\%$ (19 out of 22 subjects) or $87\%$ (97 out of 111 monitored cycles), including two women who received only unilateral treatment but had bilateral ovulation. In one instance, a woman’s cycle required hCG to trigger ovulation. Spontaneous singleton pregnancies occurred in eight women, one of whom was treated by intrauterine insemination because of evidence of a cervical factor. The cumulative pregnancy rate after 6 months was $36\%$ (8/22). Of the eight spontaneous pregnancies, seven achieved full term and seven healthy babies were born and one is continuing at 6 months. There were no miscarriages. Spontaneous ovulation and pregnancy did not occur in three women (14%), who needed progesterone to induce bleeding.

All of the women finished their surgical procedure of transvaginal, ultrasound-guided, ovarian, interstitial laser treatment and there were no adverse events. The surgical procedure lasted approximately $38.1 \text{ SD } 7.9$ minutes.

**Discussion**

In this study, we observed and evaluated the efficiency of transvaginal, ultrasound-guided, ovarian, interstitial laser treatment in 23 anovulatory clomifene-resistant women with PCOS. This is the first study of the use of this new treatment procedure in women with PCOS. Before this, traditional ovarian wedge resection and LOD were two typical surgical approaches used in the management of anovulatory women with PCOS. Several potential mechanisms of action of surgical intervention for PCOS have previously been discussed. It has been postulated that ovarian trauma may impair local androgen synthesis with associated reduction of intraovarian androgen-producing tissue. According to the report of long-term follow up of women with PCOS after LOD, the ovarian volume decreased significantly from 11 to 8.4 ml. With similar potential mechanisms of action, the ovarian interstitial laser treatment of three to five points can ablate about 1.5–3 ml of ovarian volume. In a previous study of ovarian interstitial neodymium:ytrrium-aluminium-garnet (YAG) laser treatment in goats, the extent of direct thermal damage to both ovaries was assessed by a laparotomy. The results indicated that interstitial laser treatment of the ovary was feasible and that lesions without postoperative adhesions could be produced at low powers of 2 and 4 W for 5 minutes. In addition, the YAG laser-induced thermal lesion has been used to treat brain tumours and other diseases. In some preliminary experiments, we performed YAG laser application on human placenta tissue, pig kidney and pig lung tissue in the laboratory. With a fibre optic cable of 400 μm in diameter, thermal damage of 10 mm in diameter was produced by a power of 3–5 W for 1–2 minutes without any smoke or excessive heat damage. In addition, transvaginal follicular aspiration is commonly performed in in vitro fertilisation programs worldwide, so the technique of ovarian localisation and puncture is well established. We also found that when interstitial laser therapy was performed using a similar technique, the extent of thermal damage locally can be monitored by ultrasound scanning. Therefore, the safety of transvaginal, ultrasound-guided, ovarian, interstitial laser coagulation can be considerably increased by using ultrasound guidance.
Clearly, only two dimensions can be measured in two-dimensional sonography. In the ovarian plane, the two measurable dimensions of the coagulation spot can be used to judge the plane of coagulation. However, two dimensions are not enough to judge the extent of the coagulation zone. Under these conditions, we must rely on training and practical experience to control the transvaginal probe. For these reasons, we recommend the selection of the largest or the second largest ovarian plane as the location for ablation, with the tip of the fibre optic at its centre. It is possible that three-dimensional ultrasound scan could be useful in this context.

Our results from interstitial therapy are similar to those reported from LOD.\(^1\)–\(^8\) However, we consider that our technique is preferable to LOD. First, the stay in hospital is reduced. Second, there are no anaesthetic risks, which is particularly important in very obese women or in women with intra-abdominal adhesions. Third, costs are lower (in developing countries, many women with PCOS are not able to afford the LOD treatment). Finally, in many of the responders, the effect of LOD is only transient and women become anovulatory again after several months.\(^12\) Some of the women who undergo LOD treatment will have mild to moderate postoperative abdominal adhesion formation.\(^9\) We do not know whether the women who undergo ovarian interstitial laser treatment will have recurring clinical or hormonal problems, but because of a minimal surface damage of the ovaries, it is possible that ovarian interstitial laser treatment can be an improved surgical approach to restore ovulation with a minimal risk of adhesion formation in women with PCOS who are CC resistant or unresponsive to hormone therapy. Several previous studies have shown electrocautery to be superior to laser for LOD in terms of safety, simplicity, effectiveness and costs.\(^5\)–\(^7\)\(^,\)\(^16\)\(^,\)\(^17\) however, interstitial therapy is greatly superior to electrocautery or LOD in safety, simplicity and costs and in our experience is at least equal in effectiveness.

Some other minimally invasive approaches to this problem, such as minilaparoscopy under local anaesthesia and fertiloscopy, have been proposed by Zullo \(^18\) et al. and Watrelot \(^19\) et al. These two techniques are interesting because they permit direct visualisation of the pelvic organs and assessment of tubal function. Compared with the above-mentioned minimally invasive approaches, the ovarian interstitial laser treatment leads to the coagulation of stroma present in the deeper ovarian structure which is visible by TVS, although tubes and ovaries cannot be visualised directly. Therefore, it may reduce the risk of adhesion formation that can and sometimes does result from LOD.\(^9\)\(^,\)\(^20\)\(^,\)\(^21\)

Compared with transvaginal, ultrasound-guided follicular aspiration\(^13\)\(^,\)\(^14\) this new procedure causes thermal effects not only on the intraovarian subcapsular follicles but also on intraovarian stromal tissue. Therefore, a reduced serum testosterone level follows the surgery, which further leads to a reduction of LH levels and LH/FSH ratios.

About 20% of women with PCOS are clomifene resistant and require Gn therapy to achieve ovulation. Although the two major risks, OHSS and multiple pregnancies, can be reduced by the low-dose, step-up and step-down protocols,\(^22\) it is difficult to induce ovulation in women with more severe PCOS. In addition, the major inconvenience of step-up protocols is a longer duration of FSH administration and a high cost. Ovarian interstitial laser treatment may be an effective way to manage these women.

It is not clear why three women with PCOS in this study did not respond to ovarian interstitial laser coagulation. A possible explanation is that the amount of ovarian interstitial laser coagulation was not enough to produce the required effect. The unchanged numbers of subcapsular follicles before and after the operation seem to support this hypothesis. If so, repeating the ovarian interstitial laser coagulation might be tried, similar to repeating ovariectomy in LOD.\(^4\) Alternatively, one might recommend clomifene and Gn therapy since some studies\(^23\)\(^,\)\(^24\) have demonstrated that LOD renders the ovaries more sensitive to clomifene.

Our study shows that, in women with clomifene-resistant PCOS, interstitial ovarian laser treatment results in significant endocrinological improvements in the majority of subjects, often resulting in ovulation and pregnancy. This is the first study showing the efficiency of this procedure, so there are still many questions raised by this new technique. What is the true risk of bowel or vessel injuries? Is the technique really reproducible? Can the procedure induce the premature ovarian failure? Although the lack of complications in 22 women suggests that the procedure is relatively safe, this is certainly too small a number to be confident of safety. It requires larger studies with longer follow up to evaluate its full effectiveness and risks.

To prevent bowel injury, the probe with the needle and laser fibre mounted must be kept still while the electrical laser is activated because the intraovarian laser fibre moving or breaking can lead to extravasation laser injury. In our opinion, the scope of the coagulation zone of the ovaries can be controlled to within a precision of 10-mm diameter if intraovarian location is accurate, making injury external to the ovaries, especially to the bowel, very unlikely. A major concern with destructive approaches to the ovary in treating PCOS is the potential impact on ovarian functional reserve. In this study, no appreciable change in the serum FSH was demonstrated in any postoperative woman. Being performed in outpatient clinics, with a lower cost, less complexity and higher safety and effectiveness, we consider our approach to be an advance but further studies are of course needed.

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