

# Chapter 5

## **Extensive tissue damage of bovine ovaries after bipolar ovarian drilling compared to monopolar electrocoagulation or carbon dioxide laser**

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## ABSTRACT

**Objective:** To evaluate the size of ovarian damage caused by ovarian drilling in polycystic ovary syndrome, the amount of inflicted damage was assessed for the most frequently used ovarian drilling techniques.

**Design:** Experimental prospective design.

**Setting:** University clinic.

**Patients:** Six fresh bovine ovaries per technique.

**Interventions:** Carbon dioxide (CO<sub>2</sub>) laser, monopolar electrocoagulation, and bipolar electrocoagulation were used for in vitro ovarian drilling.

**Main Outcome Measures:** Amount of inflicted ovarian damage per procedure.

**Results:** Bipolar electrocoagulation resulted in significantly more destruction per burn than the CO<sub>2</sub> laser and monopolar electrocoagulation (287.6 versus 24.0 and 70.0 mm<sup>3</sup>, respectively). The damage found per lesion was multiplied by the regularly applied number of punctures per procedure in daily practice (based on the literature). Again, the bipolar electrocoagulation resulted in significantly more tissue damage than the CO<sub>2</sub> laser and monopolar coagulation (2,876 versus 599 and 700 mm<sup>3</sup>, respectively).

**Conclusions:** Ovarian drilling, especially bipolar electrocoagulation, causes extensive destruction of the ovary. Given the same clinical effectiveness of the various procedures, it is essential to use the lowest possible dose that works; thus, the first choice should be CO<sub>2</sub> laser or monopolar electrocoagulation.

## INTRODUCTION

Ovarian drilling for restoring ovulation in polycystic ovary syndrome (PCOS) has been used for more than 70 years (1) and started as the only treatment option for anovulatory patients with PCOS. With the introduction of clomifene, ovarian drilling was used less frequently, and its current place in treatment is as a second-line option in clomifene citrate resistant patients. Ovarian drilling has good results in terms of ovulation (approximately 70%–80%) and pregnancy rates (approximately 40%–60%) (2) as well as several other advantages,

such as lower chance of multiples, overstimulation, no need of extensive monitoring, and cost-effectiveness compared with gonadotropin treatment (3, 4). Several surgical approaches have been used over the years. Ovarian reduction surgery started with classical wedge resection in the 1930s (1) and has been replaced by laparoscopic procedures such as monopolar and bipolar coagulation, laser vaporization, and ovarian biopsies. In addition to these frequently used techniques, multiple other ovarian drilling procedures have been tried, such as ovarian multiple follicle aspiration (5), celioscopic ovarian resection (6), laparoscopic multineedle intervention (7), ovarian stroma hydrocoagulation (8), ovarian marsupialization (9), and unilateral oophorectomy (10). All of these techniques result in restoration of regular cycles in the majority of anovulatory patients with PCOS and share a common goal of creating ovarian damage.

Despite many years of experience with ovarian drilling, the extent of ovarian damage caused by most of these procedures is not quantified. This is remarkable, as the inflicted ovarian damage is permanent and could bear essential consequences for the long term fertility prognosis. There are concerns for imminent and premature ovarian failure as several studies have found signs of diminished ovarian reserve after ovarian drilling (11–16). Ovarian atrophy has been reported as well (17).

The most destructive ovarian drilling technique seems to be the classic ovarian wedge resection, which removes 50%–75% of both ovaries (1). The more recent techniques probably inflict less ovarian damage, but the amount of damage can be highly variable because of differences in the power setting, duration of each puncture, and number of the punctures. There are a few studies reporting the effects of monopolar electrocoagulation. Ovarian volume was assessed by three-dimensional ultrasound, and a decrease after the procedure of 1.2–6 mL per ovary (using 2–20 drills per ovary) was found (13–15, 18, 19). The limitation of these studies is that the destruction is assessed by ultrasound, not recognizing the full extent of the cellular damage in the ovary. Ovarian biopsy is estimated to remove approximately 0.75 cm<sup>3</sup> of tissue per ovary (6), but the inflicted ovarian damage is probably more extensive. There are no known publications that report the ovarian damage caused by laser vaporization or bipolar electrocoagulation.

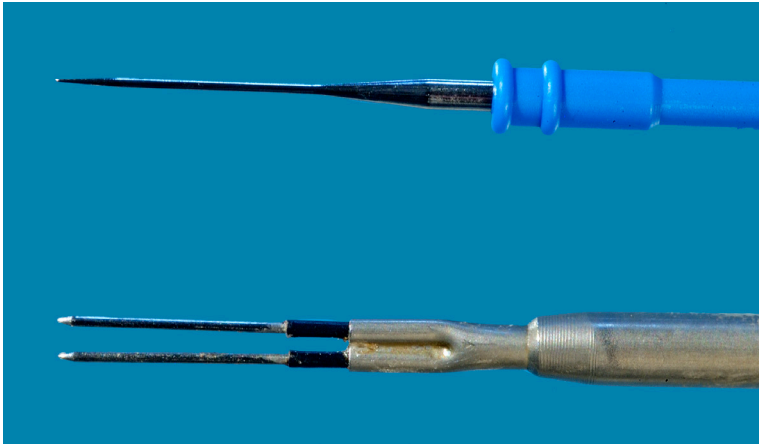
Because of the limited data on the quantitative effects of the various ovarian drilling procedures, this study was designed to evaluate the extent of ovarian damage caused by the most frequently used ovarian drilling techniques, namely the carbon dioxide (CO<sub>2</sub>) laser, monopolar electrocoagulation and bipolar electrocoagulation.

## MATERIALS AND METHODS

We tested the CO<sub>2</sub> laser, monopolar electrocoagulation, and bipolar electrocoagulation for *in vitro* ovarian drilling on 18 fresh bovine ovaries (6 ovaries per technique). The bovine ovaries came from a local slaughterhouse, where the cows were slaughtered and the ovaries were processed on the same day. The power setting, duration of each puncture, and depth of needle insertion were based on the literature (Table 1). The power setting used for the CO<sub>2</sub> laser varies between 20–50 W, during 5–10 seconds on 10–40 sites per ovary (20–22). Within this study, the CO<sub>2</sub> laser (Lumenis CO<sub>2</sub> laser; Lumenis, Santa Clara, CA) was set at 25W power and used for 6 seconds per burn. Monopolar electrocoagulation is usually performed with 30–300 W power, during 2–5 seconds, and 3–15 punctures per ovary are made (23–25). Within this study, the monopolar coagulator (Valleylab Force 40, in combination with Valleylab Needle Electrode E1552; Valleylab, Boulder, CO) was set at 30W, and the needle was inserted into the tissue (10 mm deep) and activated for 4 seconds at each point. Bipolar electrocoagulation is usually performed using 25 W, and 5–12 punctures per ovary are made, with auto-stop function (4, 26, 27); therefore, the electrocoagulator (Erbotom ICC 350, in combination with Bipolar Electrode Erbe 20195-073; Tübingen, Germany) was set at 25W, the needles were inserted their whole length (15mm), and the “auto-stop” function (variable stimulation time, approximately 3–5 seconds) was used. High-frequency modulated current was used for the monopolar and bipolar electrocoagulation. Figure 1 shows the monopolar and bipolar needles used. All treatments were performed by the same experienced operator, and three punctures per ovary were made.

**Table 1.** Current and activation time used per ovarian drilling technique.

Technique	Power (Watt)	Length of stimulation (seconds)	Length of needle inserted (mm)
CO <sub>2</sub> laser	25	6	Not applicable
Monopolar electrocoagulation	30	4	10
Bipolar electrocoagulation	25	Variable approx. 3-5 (Auto-stop function)	15



**Figure 1.** Monopolar (top) and bipolar electrode used for ovarian drilling.

The histopathologic examination was performed by clinicians in our pathology department. The ovaries were processed after at least 24 hours of formalin fixation. To assess the microscopic cellular damage, the ovaries were placed in graded alcohols, embedded in paraffin, and sliced. The slices were evaluated under a light microscope. The extent of microscopic cellular damage (i.e., cellular disruption and loss of tissue anatomy) was found to be comparable with macroscopic damage (i.e., charring or pathologic whitening); therefore, the macroscopic damage was used as a marker for tissue destruction. To assess the macroscopic affected area, the formalin-fixed ovaries were sliced and photographed. The depth and width of the affected region were measured using ImageJ 1.37c (Wayne Rasband, National Institutes of Health, Washington, D.C.). Depending on the shape of the scar, the total amount of tissue destruction was calculated by using the formula of a cylinder ( $\pi \cdot r^2 \cdot \text{height}$ ) or cone ( $\frac{1}{3} \pi \cdot r^2 \cdot \text{height}$ ). Each ovary was analyzed separately and up to three representative completely evaluable lesions per ovary were used to calculate the average tissue damage per burn per ovary. The ovaries were analyzed as independent, unpaired entities. Statistical analysis was performed by one-way ANOVA (Bonferroni Post-Hoc test) and a P-value of less than 0.05 was considered significant.

## RESULTS

The CO<sub>2</sub> laser induced a superficial cone-shaped scar. The affected area on the cortex had a mean surface area of 14.7 (+/-3.7) mm<sup>2</sup>, and the burn reached a depth of 4.8 (+/-1.2) mm. The mean destroyed volume per vaporization was 24.0 (+/-8.5) mm<sup>3</sup>. Monopolar electrocoagulation resulted in deeply penetrating, cylinder-shaped burns. The affected outer area had a mean

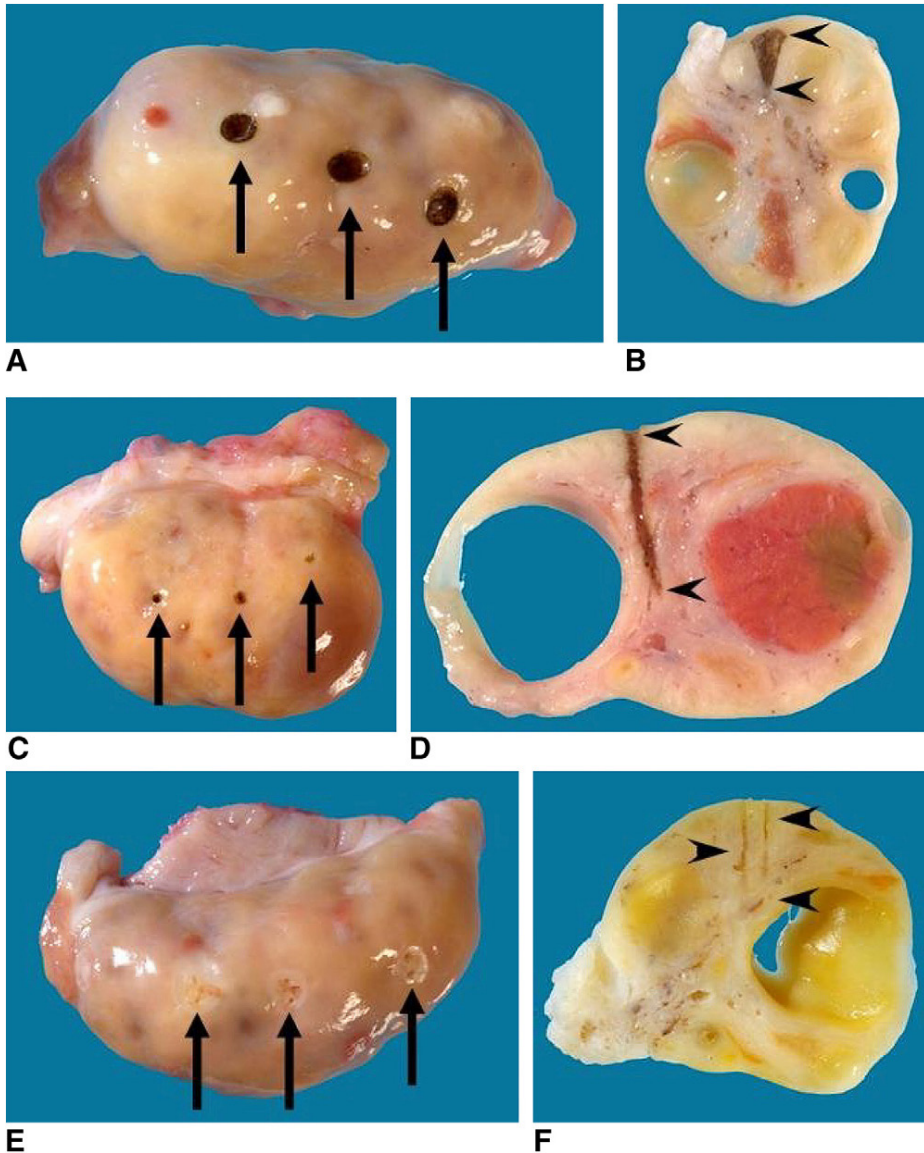
surface area of 5.9 (+/-2.2) mm<sup>2</sup>, the average depth of the puncture was 12.2 (+/-2.0) mm, and the mean destroyed volume per drill reached 70.0 (+/-21.4) mm<sup>3</sup>. Lastly, bipolar electrocoagulation induced cylinder-shaped burns, which deeply penetrated into the ovary (mean depth 16.0 (+/-1.8)mm). The affected area on the cortex had a mean surface area of 17.9 (+/-3.7) mm<sup>2</sup>. The average tissue damage per coagulation was 287.6 (+/-65.1) mm<sup>3</sup> (Table 2, Figure 3). A single drill with the bipolar electrocoagulator resulted in significantly more ovarian destruction than the other techniques (P<0.001). The CO<sub>2</sub> laser and monopolar electrocoagulation did not differ significantly from each other in terms of ovarian damage per burn (P=0.261). Figure 2 shows examples of ovaries with three drillings per ovary and sliced fragments after formalin fixation.

To have an estimation of the total ovarian damage per technique, the mean damage per lesion was multiplied with the usual applied number of punctures in daily practice per procedure (based on the literature, see Materials and Methods and Table 3). Furthermore, Table 4 shows the range of destruction when using the minimum and maximum used number of punctures in the literature. Again, the bipolar electrocoagulation resulted in significantly more tissue damage in both the minimally and maximally expected damage, compared to the CO<sub>2</sub> laser and monopolar electrocoagulation (P<0.001). The CO<sub>2</sub> laser and monopolar electrocoagulation did not differ significantly from each other in terms of total ovarian damage (P=1.0).

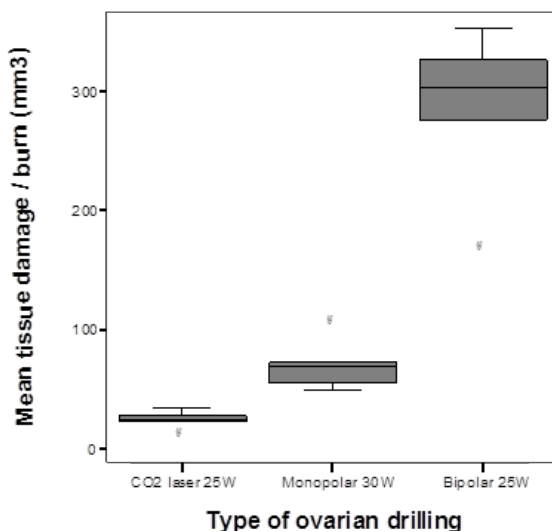
## DISCUSSION

The amount of ovarian damage caused by CO<sub>2</sub> laser, monopolar electrocoagulation, and bipolar electrocoagulation is substantial and differs highly among the techniques used. In particular, bipolar electrocoagulation in the currently used clinical regimen seems to cause extensive destruction of the ovary, ranging from 1.4–3.4 cm<sup>3</sup>. This is approximately one fourth the size of an average ovary with PCOS, which varies between 9.9–14.6 cm<sup>3</sup> (28–30). Both CO<sub>2</sub> laser and monopolar electrocoagulation destroy approximately 0.2–1.0 cm<sup>3</sup> of the ovary, which is approximately 5% of an average ovary with PCOS. One could postulate that the tissue loss in vivo may be even larger than the observed loss in this study, as formalin fixation prevents posttreatment tissue inflammation, which results in more extensive cellular damage. Furthermore, the ovarian tissue shrinks because of the formalin fixation, causing the measured volume to be an underestimation of the real affected volume. On the other side, vascularized tissue might result in less damage than produced in vitro, as differences in water content and/or a heat sink effect might reduce the ovarian damage.

It is difficult to compare the results from the present study to the literature, as there are few publications reporting the amount of ovarian damage after ovarian drilling procedures. A few



**Figure 2.** (A, B) A CO<sub>2</sub> laser was used on bovine ovaries (25 W, 6 seconds per burn). (A) Three laser burns (arrows) on the ovarian surface, identified by charring. (B) Sliced formalin-fixed fragment of bovine ovary. The extent of tissue damage is identified by charring (arrowheads). (C, D) Monopolar electrocoagulation was used on bovine ovaries (30W, 4 seconds per burn, 10-mm needle). (C) Three monopolar coagulations (arrows) on the ovarian surface, identified by charring. (D) Sliced formalin-fixed fragment of bovine ovary. The extent of tissue damage is identified by charring (arrowheads). (E, F) Bipolar electrocoagulation was used on bovine ovaries (25W, auto-stop function, 15-mm needle). (E) Three bipolar coagulations (arrows) on the ovarian surface, identified by pathological whitening. (F) Sliced formalin-fixed fragment of bovine ovary. The extent of tissue damage is identified by pathological whitening (arrowheads).



**Figure 3.** Box-and-whisker plot of the mean tissue damage per single burn ( $\text{mm}^3$ ) of the various ovarian drilling techniques. The upper line of the box represents the upper quartile, the thick line in the middle represents the median, and the lower line represents the lower quartile. The open circles are the outliers.

**Table 2.** Tissue damage per lesion by three ovarian drilling techniques.

Technique	Average tissue damage per burn ( $\text{mm}^3$ ) (+/- SD) n=6
CO2 laser	24.0 (+/-8.5)
Monopolar electrocoagulation	70.0 (+/-21.4)
Bipolar electrocoagulation	287.6 (+/-65.1) <sup>a</sup>

<sup>a</sup>  $P < 0.05$  (ANOVA, with Bonferroni Post-Hoc test).

**Table 3.** Assumed damage after extrapolation to regular clinical application.

Technique	Number of punctures normally applied	Estimated total damage ( $\text{mm}^3$ ) (+/- SD)
CO2 laser	25	599 (+/-213)
Monopolar electrocoagulation	10	700 (+/-214)
Bipolar electrocoagulation	10	2876 (+/-651) <sup>a</sup>

<sup>a</sup>  $P < 0.05$  (ANOVA, with Bonferroni Post-Hoc test).



**Table 4.** Estimated minimal and maximal damage per ovary, based on minimally and maximally applied number of punctures in literature.

Technique	Minimum number of punctures applied	Estimated minimal damage (mm <sup>3</sup> ) (+/- SD)	Maximum number of punctures applied	Estimated maximal damage (mm <sup>3</sup> ) (+/- SD)
CO2 laser	10	240 (+/-85)	40	959 (+/-340)
Monopolar electrocoagulation	3	210 (+/-64)	15	1049 (+/-320)
Bipolar electrocoagulation	5	1438 (+/-325) <sup>a</sup>	12	3452 (+/-781) <sup>a</sup>

<sup>a</sup> P<0.05 (ANOVA, with Bonferroni Post-Hoc test)

studies assessed the effect of monopolar electrocoagulation by three-dimensional ultrasound, and all studies found a decrease after the procedure of 1.2–6mL per ovary (using 2–20 drills) (13–15, 18, 19). Another study showed destruction of approximately 1% of the ovary (in 42–45-year-old patients without PCOS), using 8 punctures of 40W over 5 seconds; this was assessed by removing the ovaries after drilling (31). Because of different power settings, activation times, and the use of patients without PCOS, it is difficult to compare this study to our results. There are no publications addressing the ovarian damage caused by CO2 laser or bipolar electrocoagulation; thus, the results from the present study are the first to show the enormous differences among the various techniques.

### Bovine versus human ovaries

Fresh humane ovarian tissue is difficult to obtain in large quantities; therefore, bovine ovaries were used in this experiment. The resemblance between human and bovine ovaries is high, as the size, cellular morphology, and physiology approximately match. Furthermore, the cow is also monoovulate, and the ovarian cycle and endocrinology are similar to that of the human (32). Direct interpolation of the bovine result to the human clinical situation cannot be done, but the high degree of resemblance does allow interpolation to provide a good indication of the amount of expected tissue damage and the differences among the techniques.

### Ovarian reserve

Destruction of a substantial part of the ovary by ovarian drilling is certain to lead to reduction of the ovarian reserve, as the pool of human oocytes are enclosed in the inner part of the cortex. This finding is supported by the fact that several studies found signs of diminished ovarian reserve after ovarian drilling. Lower ovarian volume, antral follicle count, inhibin and anti-Müllerian hormone levels, and higher follicle stimulating hormone concentrations were seen after surgery (11–16). Furthermore, less ovarian hyperstimulation syndrome is found in

in vitro fertilization cycles performed after ovarian drilling (33), which is suggestive of a smaller follicular pool. On the other hand, reduction of the substantial amount of pre- and antral follicles in patients with PCOS does not necessarily have to lead to a diminished reserve. Only one case report has been published reporting ovarian atrophy after ovarian drilling, which was probably related to disruption of the blood supply (17). There are no publications reporting premature ovarian failure after ovarian drilling. One study evaluated the reserve in patients with PCOS after ovarian drilling, and it was found to be lower than in nonsurgical patients with PCOS, but greater than in age-matched non-PCOS controls (12). Thus, ovarian drilling seems to cause a direct reduction in the ovarian reserve without leading to ovarian failure in the short term.

The long-term effects of these ovarian drilling procedures, in terms of ovarian reserve, are still unclear and give rise to ongoing concerns. Ovarian drilling is usually performed on women younger than 30 years, and these women seem to be especially vulnerable to the destructive effects of ovarian surgery (34). Young women have a higher concentration of primordial, primary, and preantral follicles, and ovarian drilling could cause a relatively more significant depletion of the follicular pool, with possible implications for the long-term fertility prognosis. Currently, there are a few studies evaluating the long-term effects of ovarian reductive surgery. Two studies showed no cases of premature ovarian failure after ovarian drilling in patients ranging from 32–48 years (18,35), but a reduction in ovarian volume and less polycystic ovarian morphology was observed (18). One study found that women with PCOS after wedge resection reached menopause later than controls without PCOS (36). Another study showed an earlier onset of menopause after wedge resection, compared with nonsurgical controls, especially in the patients who had surgery before age 30 years, with a mean age of menopause as young as 40.3 years (34). Unfortunately, some studies of long-term effects could not draw conclusions regarding the age of menopause, because in these studies large proportions of women were still menstruating (36,37). Furthermore, the use of non-PCOS controls is debatable (38). Controls consisting of women with PCOS but without surgery would be ideal, and only then can a definite answer be given as to whether ovarian drilling reduces the age of menopause.

We cannot conclude that ovarian drilling does not alter the age at which menopause occurs. It seems that, from published literature, the surgery causes a long-term reduction or normalization in the ovarian reserve without leading to premature ovarian failure.

### **Clinical protocol**

There is currently no uniformly accepted protocol for the number of punctures to apply per procedure or how much energy should be used. The number of punctures is empirical and usually depends on the size of the ovary. Optimally, the lowest possible dose, without compromising the efficacy of the procedure, should be used. There are a few studies evaluating

the minimum dose needed for good clinical results, and it varies between 3–4 monopolar diathermy holes per ovary (power setting 30–40 W for 4–5 seconds) (23, 39, 40). Unfortunately, there are many different techniques used for ovarian drilling, with various instruments as well as differences in power settings, penetration depth, and number of punctures applied. Thus, it is difficult to extrapolate the results of these optimal dose studies to all clinical applications. The results from our study indicate that the most commonly applied CO<sub>2</sub> laser, monopolar electrocoagulation, and bipolar electrocoagulation protocols seem to result in substantial ovarian damage. Bipolar electrocoagulation with the Erbe 20195-073 needle should not be applied in the currently used clinical regimen. Because bipolar needles have double tissue contact, compared with the monopolar needle, one could postulate that the number of punctures should be much lower than the number used for monopolar electrocoagulation. To limit the ovarian tissue loss, fewer punctures and/or less damage per puncture (shorter duration of burning, lower power setting, or decreasing the needle penetration depth) can be applied. Given the same clinical effectiveness of the various ovarian drilling procedures, it is essential to use the technique with the lowest possible ovarian damage; thus, the first choice should be CO<sub>2</sub> laser or monopolar electrocoagulation. The optimal way to perform ovarian drilling is not clear yet. One could assume that the greater the ovarian surface damage, the higher the risk for periovarian adhesions. However, a recent study showed that the adhesion formation after ovarian drilling was not influenced by the number of punctures (41).

Thus, it is not clear which is the best method to apply the energy. More studies are needed to evaluate the minimum yet optimal working dose and the best method to perform the procedure.

In conclusion ovarian drilling, especially bipolar electrocoagulation, leads to substantial tissue loss and the currently used clinical regimen should not be applied. The question remains whether the substantial ovarian loss caused by ovarian drilling leads to problems in the long-term fertility prognosis. Given the same clinical effectiveness of the various ovarian drilling procedures, it is essential to use the technique with the lowest possible ovarian damage; thus, the first choice should be CO<sub>2</sub> laser or monopolar electrocoagulation.

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