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REPRODUCTIVE MEDICINE

Three decades after Gjönnaess's laparoscopic ovarian drilling for treatment of PCOS; what do we know? An evidence-based approach

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Abstract
Background The introduction of laparoscopic ovarian drilling (LOD) by Gjönnaess in 1984 as a substitute for ovarian wedge resection created opportunities for extensive research given its worldwide application for ovulation induction in women with polycystic ovary syndrome (PCOS).
Purpose To critically evaluate and summarize the current body of literature regarding the role of LOD for the management of PCOS entailing its different preoperative, operative and postoperative aspects. In addition, long-term efficacy, cost-effectiveness, patient preference and health-related quality of life issues will be evaluated together with other available alternatives of ovulation induction treatments.
Methods A PubMed search was conducted looking for the different trials, reviews and various guidelines relating to the role of LOD in the management of PCOS.
Results LOD whether unilateral or bilateral is a beneficial second-line treatment in infertile women with clomiphene citrate (CC)-resistant PCOS. It is as effective as gonadotrophin treatment but without the risk of multiple pregnancy or ovarian hyperstimulation and does not require intensive monitoring. Increased responsiveness of the ovary to CC especially in patients who remain anovulatory following LOD is another advantage. Recent evidence suggests that relatively novel oral methods of ovulation induction, e.g. CC plus metformin, CC plus tamoxifen, rosiglitazone plus CC and aromatase inhibitors represent a successful alternative to LOD in CC-resistant PCOS. Meanwhile current evidence does not support LOD as a first-line approach in PCOS-related anovulation or before IVF.
Conclusion LOD is currently recommended as a successful and economical second-line treatment for ovulation induction in women with CC-resistant PCOS.

Keywords Laparoscopic surgery · Polycystic ovary syndrome · Laparoscopic ovarian drilling · Laparoscopic ovarian diathermy · Laparoscopic ovarian electrocautery

Introduction

Polycystic ovary syndrome (PCOS) is a predominant cause of anovulatory infertility [1] and represents the most common endocrine abnormality in women in their reproductive age, with a prevalence of 4–8 % [2–5]. However, some recent studies suggest higher prevalence rates of 17.8 and 19.9 % based on the Rotterdam diagnostic criteria [6, 7]. Clomiphene citrate (CC) is still used as the first-line therapy for ovulation induction in patients with PCOS [8–10], with a reported ovulation rate of 75–80 % per woman and a cumulative pregnancy rate of 70–75 % after 6–9 cycles of treatment [11, 12]. CC-resistant patients are defined as those who did not ovulate in response to CC doses of up to 150 mg for at least three consecutive cycles, while CC failure comprises patients who failed to conceive

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with CC despite successful regular ovulation for 6–9 cycles [13].

In 1930s, bilateral ovarian wedge resection (BOWR) was found to restore regular menses and allow conception in women with PCOS [14]; however, it became unpopular because of postoperative pelvic adhesion formation and the introduction of ovulation-inducing drugs such as CC and human menopausal gonadotropins in the 1960s [15]. In 1984, laparoscopic ovarian drilling (LOD) using a unipolar electrode was first reported by Halvard Gjönnaess, as a less invasive alternative to BOWR [16]. Ovulation was restored in 92 % of patients, with a pregnancy rate of up to 80 % [16]. The procedure has also been referred to as laparoscopic ovarian diathermy, laparoscopic ovarian electrocautery or laparoscopic electrocoagulation [15, 17].

Laparoscopic ovarian drilling is currently recommended as a second-line treatment in patients with CC-resistant PCOS being as effective as gonadotrophin treatment and is not associated with an increased risk of multiple pregnancy or OHSS [8, 13, 15, 18]. The mechanism of action is still not clear; however, the most plausible one is that this procedure encompasses destruction of ovarian follicles and parts of the ovarian stroma, causing a reduction of serum androgens and inhibin levels and results in an increase of FSH and recovery of the ovulation function [15, 19–22]. Surgery may also provoke an increased blood flow to the ovary, allowing increased delivery of gonadotropins and post-surgical intra-ovarian inflammatory changes increasing local growth factors [19, 22, 23]. Improved insulin sensitivity after LOD has also been suggested [24].

The introduction of LOD as a less invasive substitute for BOWR was followed by extensive research, spanning three decades, regarding its potential for inducing ovulation in women with PCOS. The aim of this review, therefore, is to critically evaluate and summarize the current body of literature regarding the role of LOD for the management of PCOS entailing its different preoperative, operative and postoperative aspects. In addition, long-term efficacy, cost-effectiveness, patient preference and health-related quality of life issues will be evaluated together with other available alternatives of ovulation induction treatments.

Materials and methods

A PubMed search (data locking point July 19, 2012) was done using the keywords 'Laparoscopic surgery', 'polycystic ovary syndrome', 'laparoscopic ovarian drilling', 'laparoscopic ovarian diathermy', 'laparoscopic ovarian electrocautery'. Limits activated were publication date from 01/01/1984, Humans, English. This resulted in 284 articles. Relevant evidence was identified and assessed for quality and suitability for inclusion in the following order: systematic reviews, meta-analyses, guidelines, randomized controlled trials (RCTs) and prospective cohort studies followed by other observational studies and non-systematic reviews. Clinical trials were included in which reproductive (ovulation, clinical pregnancy and miscarriage rates) as well as endocrine outcomes were reported. Case reports, small case series and duplicate studies were excluded. At the end, 100 of those 284 studies were included in this review. Additional studies were identified by manual systematic review of reference lists of the original studies. Importantly, newly published articles of clinical importance (after July 19, 2012) were also added.

Operative technique and dose response

Laparoscopic ovarian drilling is most commonly performed using monopolar electrocautery (diathermy) or laser, with comparable outcomes [25]. To date, electrocautery using an insulated unipolar needle electrode with a non-insulated distal end measuring 1–2 cm is the most common method worldwide. Nevertheless, patient specific dose–response assessment has not yet been conducted. This represents a major controversy when deciding to offer LOD to patients with PCOS. In the LOD procedure originally described by Gjönnaess [16], three to eight diathermy punctures were performed in each ovary, with each puncture having a diameter of ~3 mm and a depth of 2–4 mm using a power setting of 200–300 W for 2–4 s. Gjönnaess reported that ovulation occurred more frequently if ten or more punctures were performed in the two ovaries together [16]. At a later stage, increasing the number of punctures raised concerns about the occurrence of postoperative pelvic adhesions and the effects on ovarian reserve [26–29]. Armar et al. [30] first described LOD with only four punctures per ovary, each for 4 s at a power setting of 40 W, thus delivering 640 J per ovary as the lowest effective dose. These authors reported ovulation and pregnancy rates of 86 % [31]. Subsequently, this practice became widely adopted by many operators around the world.

In a prospective dose-finding study by Amer et al. [28] including thirty women with CC-resistant PCOS, a standardized amount of energy of 150 J/puncture was applied. Ovulation occurred in 67, 44, 33 and 33 % of women treated with four, three, two and one puncture/ovary, respectively. The corresponding pregnancy rates were 67, 56, 17 and 0 %. The reductions of the free androgen index and the serum concentrations of testosterone and androstenedione after LOD were observed only in women treated with three or four punctures/ovary [28]. These authors concluded that the clinical response to LOD appears to be dose-dependent, with an increase in the frequency of ovulation and conception with an increasing dose of thermal energy of up to 600 J/ovary. However, this study was underpowered to draw a definite conclusion [28]. Recently, Zakherah et al. [32] randomized 120 patients with CC-resistant PCOS to an adjusted thermal dose based on ovarian volume with the use of a new model for dose calculation (60 J/cm^3 of ovarian tissue) versus 600 J per ovary through four ovarian punctures regardless of ovarian size. This study showed that an adjusted diathermy dose based on ovarian volume has a better reproductive outcome compared with a fixed thermal dosage. The ovulation and pregnancy rates were 81.8 versus 62.2 % and 51.7 versus 36.8 %, $p < 0.05$ %, respectively. Also, more patients resumed regular cycles in the adjusted diathermy dose group (87.9 vs. 75.4 %, $p < 0.05$ %). No difference was found between groups regarding post-drilling adhesions [32].

The safety and efficacy of the bipolar LOD for treatment of PCOS-related anovulation has been the focus of extensive research in recent years. Fernandez et al. [33] proposed bipolar LOD (using a 5-French bipolar energy probe) as a potentially safer method compared to unipolar energy in terms of the risk of postoperative adhesions and the risk of overtreatment that could lead to ovarian failure. This novel technique was performed in six cases with restoration of ovulation in five cases [33]. However, in a recent experimental in vitro study on 18 fresh bovine ovaries, ovarian drilling using bipolar electrocoagulation was compared with CO2 laser and monopolar electrocoagulation (6 ovaries per technique) [34]. The bipolar electrocoagulation method resulted in significantly more tissue damage than the CO2 laser and monopolar coagulation (2,876 vs. 599 and 700 mm^3, respectively) [34]. However, the bovine ovary model for investigating the damage inflicted by the use of different energy modalities of LOD techniques has several shortcomings owing to volume, morphologic, functional and endocrinological differences compared with the human polycystic ovaries [35]. Moreover, ovarian reserve marker reduction after LOD could be interpreted as either a harmful effect or an intentional goal of the procedure [36].

Amer et al. [37] investigated the outcomes in eighty-three women with CC-resistant PCOS who had been allocated to undergo LOD using a bipolar insulated needle electrode with 5–10 punctures created on each ovary, followed by CC when anovulation persisted as part of a RCT. In total, 76 of the 83 women (92 %) had at least one ovulation and 41 women (49 %) reached an ongoing pregnancy that resulted in live birth [37]. In a pilot study, 20 infertile women with CC-resistant PCOS were randomly assigned to unipolar or bipolar LOD (10 patients in each group) to evaluate clinical and endocrine outcomes [38]. This study showed that ovulation and pregnancy rates after bipolar LOD were similar to unipolar LOD. However, bipolar LOD may be preferred because of its relatively lower risk of tissue destruction and probably less postoperative adhesions, although they admitted the need for a larger study to confirm these findings [38].

Another important question when considering LOD is whether to perform unilateral or bilateral drilling. In a small study, Balen and Jacobs [39] randomized 10 CC-resistant PCOS patients to unilateral (4 patients) or bilateral LOD (6 patients). They observed that unilateral LOD with four punctures using 40 W for 4 s resulted in bilateral ovulation as did bilateral drilling. This observation indicates that the mechanism of action of LOD is mediated via a correction of disturbed ovarian-pituitary feedback [39]. These findings were subsequently corroborated in RCTs [40–42] and further supported by a recent Cochrane review reporting no significant difference between unilateral and bilateral drilling with regard to ovulation rate (76 vs. 72 %; OR 1.20; 95 % CI 0.59–2.46), pregnancy rate (51.7 vs. 50.5 %; OR 1.00; 95 % CI 0.55–1.83) or live birth rate (36.4 vs. 41 %; OR 0.83; 95 % CI 0.24–2.78) [43]. A recent randomized double-blind placebo-controlled pilot study demonstrated that *N*-acetyl-cysteine as an adjunctive therapy following unilateral LOD for CC-resistant PCOS women may further improve the reproductive outcome. However, larger RCTs are necessary before adopting this approach [44].

Notably, different modified techniques of the classic needle electrode were proposed, e.g. laparoscopic ovarian multi-needle intervention [45], LOD using a monopolar hook electrode [46] and office microlaparoscopic ovarian drilling [47]. In addition, different transvaginal methods were developed for ovarian drilling in women with PCOS, e.g. transvaginal hydrolaparoscopy (fertiloscopy) [48] and transvaginal ultrasound-guided ovarian interstitial laser treatment [49]. However, concerns were raised regarding inaccurate placement with inadvertent ovarian and adjacent pelvic organ damage [50]. Importantly, further prospective randomized studies concerning the use and efficacy as well as the long-term outcome for these alternative techniques are still needed.

Pre-operative patient selection and predictors of success

Clomiphene citrate-resistant PCOS women should have no additional infertility factors when selected for LOD. When PCOS is the only cause of infertility, 84 % of patients become pregnant after LOD [51]. In contrast, the pregnancy rates are reported to be limited to 36 % in women who also have an additional tubal factor, endometriosis, or an oligozoospermic male partner [51]. Importantly, why about 20–30 % of anovulatory PCOS women fail to respond to LOD is still unknown [22]. Table 1 shows important studies that examined different predictive factors.

Table 1 Studies evaluating predictors of success of LOD in women with PCOS

Methodology/objective	Main findings	References
A retrospective analysis using multiple logistic regression to identify independent predictors of success of LOD in terms of ovulation and pregnancy ($n = 200$ patients with anovulatory infertility due to PCOS)	Marked obesity (BMI ≥ 35 kg/m^2), marked hyperandrogenism (serum T concentration ≥4.5 nmol/l, free androgen index ≥15 and/or long duration of infertility (>3 years) seem to predict poor response to LOD. In LOD responders, high LH levels (>10 IU/l) appear to predict higher probability of pregnancy	[37]
A retrospective analysis using multiple logistic regression to identify independent predictors of success of LOD in terms of pregnancy ($n = 118$ anovulatory patients with PCOS)	LOD is more likely to be successful if the duration of infertility is <3 years, and the pre-operative LH level is >10 IU/l	[52]
A prospective analysis using multiple logistic regression to determine factors influencing pregnancy rate following LOD ($n = 70$ women with CC-resistant PCOS)	Elevated LH levels (>10 IU/L), short duration of infertility (<3 years), and absence of preexisting tubal disease were associated with better outcomes	[53]
A meta-analysis evaluating the impact of obesity on reproductive outcomes in terms of ovulation and pregnancy rates after ovarian ablative therapy in PCOS (15 data sets included 905 subjects in the obese group and 879 subjects in the lean group)	Lean women (BMI < 25 kg/m^2; $n = 879$) respond better to LOD than obese ones (BMI > 25 kg/m^2) (RR 1.43, 95 % CI 1.22–1.66; RR 1.73, 95 % CI 1.39–2.17 for ovulation and pregnancy rates, respectively). In addition, lean PCOS women have better reproductive outcomes following surgery if they were young (≤30 years) with a shorter duration of infertility (≤3.5 years), and reported in recent RCTs published after 2005	[54]
A prospective analysis using multivariable logistic regression to determine factors influencing ovulation rate following LOD ($n = 83$ women with CC-resistant PCOS)	Menarche <13 years, LH/FSH ratio <2 and a glucose level <4.5 mmol/l seem to predict poor response to LOD	[55]
A cohort study to evaluate endocrine and reproductive outcomes following LOD in CC-resistant patients with PCOS in relation to their ovarian size. ($n = 371$; 211 with ovarian volume >8 cm^3 or cross-sectional area >10 cm^2 vs. 160 with normal size ovary)	Ovarian size is not a prognostic factor for LOD response in CC-resistant patients with PCOS. Comparable ovulation (90.99 vs. 88.75 %) and pregnancy (73.45 vs. 71.25 %) rates in both groups	[56]
A prospective study to evaluate the effect of LOD for ovulation induction in women with CC-resistant PCOS comparing between high ($n = 19$) and normal testosterone ($n = 13$) groups (using a cut-off value of 50 ng/dl).	No significant differences regarding rates of spontaneous ovulation (84.2 vs. 69.2 %) or pregnancy (42.1 vs. 76.9 %) after LOD between both groups.	[20]
A retrospective uni and multivariate analysis to predict spontaneous ovulation within 3 months after LOD ($n = 100$ women with CC-resistant PCOS)	High LH (≥12.1 IU/l) and androstenedione levels (≥3.26 ng/ml) prior to LOD are independent predictors of spontaneous ovulation within 3 months of surgery	[57]
A retrospective study to evaluate LOD outcome in PCOS patients with metabolic syndrome ($n = 89$; 19 with vs. 70 without metabolic syndrome)	Patients with metabolic syndrome should not be precluded from LOD as no differences were found in ovulation rates (68 vs. 61 %) or cumulative pregnancy rates (68 vs. 61 %) between both groups	[58]
A prospective analysis using multivariate logistic regression to evaluate pre-operative AMH level for prediction of ovulation after LOD ($n = 29$ anovulatory infertile patients with PCOS)	Pretreatment circulating AMH level of 7.7 ng/ml had a sensitivity of 78 % and a specificity of 76 % in the prediction of no ovulation after LOD	[59]

AMH anti-Mullerian hormone, *BMI* body mass index, *CC* clomiphene citrate, *LOD* laparoscopic ovarian drilling, *LH* luteinising hormone, *PCOS* polycystic ovary syndrome, *T* testosterone

Elevated serum LH concentrations (>10 IU/l) and a duration of infertility of less than 3 years have been linked to a higher likelihood of success in different studies [37, 52, 53].

In a recent meta-analysis, we studied the impact of obesity on reproductive outcomes after ovarian ablative therapy in PCOS [54]. We concluded that lean women (BMI < 25 kg/m^2; $n = 879$) respond better to LOD than their obese counterparts (BMI > 25 kg/m^2; $n = 905$) (RR 1.43, 95 % CI 1.22–1.66; RR 1.73, 95 % CI 1.39–2.17 for ovulation and pregnancy rates, respectively). Moreover, lean PCOS women were shown to have better reproductive outcomes following surgery if they were young (≤30 years) and had a shorter duration of infertility (≤3.5 years), as reported in recent RCTs published after 2005 [54].

In a prospective cohort part of a RCT ($n = 83$ CC-resistant PCOS women), van Wely et al. [55] reported that women who had an age at menarche <13 years, an LH/FSH ratio <2 and a glucose level <4.5 mmol/l were more likely to remain anovulatory following LOD. Importantly, in another prospective cohort study ($n = 371$ CC-resistant PCOS women), Alborzi et al. [56] concluded that ovarian size was not a prognostic factor for response to LOD. Some studies reported that hyperandrogenism (serum testosterone concentration >4.5 nmol/l, free androgen index >15) seems to be associated to poor response to LOD [37], but not all studies confirm this finding [20, 57].

Recently, in a retrospective review of 89 infertile anovulatory PCOS patients, a Chinese group tried to answer the question whether LOD would work effectively in PCOS patients with metabolic syndrome [58]. No differences were found in spontaneous ovulation rates (68 vs. 61 %), cumulative pregnancy rates (68 vs. 61 %) and risk for diabetes during pregnancy (64 vs. 42 %) between patients with ($n = 19$) or without metabolic syndrome ($n = 70$). Accordingly, the authors advised that patients with PCOS and metabolic syndrome should not be excluded from LOD, an intervention allowing full tubo-peritoneal assessment at the same time [58].

Measuring anti-Mullerian hormone (AMH) and ovarian stromal 3D power Doppler blood flow for women with anovulatory PCOS undergoing LOD may provide a useful tool in evaluating its outcome [59, 60]. In a RCT comparing LOD ($n = 29$) versus CC ($n = 18$) as a first-line method of ovulation induction in women with PCOS, Amer et al. [59] reported that using a pretreatment cut-off level of 7.7 ng/ml, AMH had a sensitivity of 78 % and a specificity of 76 % in the prediction of anovulation after LOD. In addition, after LOD the median AMH concentration significantly decreased to 4.7 (0.3–15.1) ng/ml and remained low at 3- and 6-month follow-up. It was speculated that the decrease in AMH after LOD could lead to ovulation by increasing the sensitivity of the follicles to circulating FSH [59]. A recent RCT ($n = 37$) demonstrated that IVF outcome is improved after LOD in CC-resistant PCOS patients with AMH levels greater than 4 ng/dl [61]. Although the numbers of retrieved and MII oocytes were lower in LOD group, a significantly higher fertilization and pregnancy rate was achieved in cases undergoing IVF after LOD ($n = 11$) compared to the non-LOD groups ($n = 8$) (73 vs. 59.8 % and 45 vs. 25 %, respectively) [61]. Failure of LOD in women with relatively high power Doppler indices and with high levels of AMH may be explained by the severity of the PCOS condition in these women, with an insufficient degree of follicle destruction by LOD to reduce intra-ovarian AMH to a level consistent with resumption of ovulation [60].

Endocrine changes and reproductive outcomes after LOD

A significant reduction within the first 5 days postoperatively in serum LH (in pulse amplitude rather than frequency) and testosterone levels with no significant change in serum FSH levels is a remarkable observation in different studies [22]. In addition, androstenedione, LH/FSH, free androgen index and dehydroepiandrosterone sulfate are reduced while sex hormone binding globulin is increased in most studies assessing these variables [15, 16]. Although hyperinsulinemia plays a major role in the pathophysiology of PCOS, the effect of LOD on the amelioration of insulin resistance in these women is still controversial [15, 22]. Of note, these immediate postoperative hormonal changes persisted during extended follow-up of these patients [22, 62, 63].

In Gjönnaess's initial reports, 92 % of women treated with LOD achieved ovulation within 3 months with a pregnancy rate of 69 % after LOD alone and up to 80 % after adding CC [16]. In a recent report, Seow et al. [22] found that spontaneous ovulation varied from 30 to 90 % after LOD and pregnancy rates were between 50 and 80 % within 1 year of the procedure. This variability may be due to differences in the type of energy source, number and depth of the punctures, power levels and duration in addition to differences in selection criteria, duration of follow-up as well as the treatment of one or both ovaries [15, 22].

In a RCT, Bayram et al. [64] compared LOD with rFSH in 168 CC-resistant PCOS women. They reported an ovulation rate of 70 and 69 % per cycle and pregnancy and live birth rates 37, 75 and 34, 60 % of patients, respectively, following LOD and FSH therapy. Moreover, a recent Cochrane review found no evidence of a difference in the proportion of women who ovulated following treatment (52 vs. 62 %; OR 0.66, 95 % CI 0.21–2.07), pregnancy rate per woman (44.2 vs. 44.8 %; OR 1.01; 95 % CI 0.72–1.42) or the live birth per couple (39.5 vs. 41.7 %; OR 0.97; 95 % CI 0.59–1.59) in the LOD and gonadotropins groups, respectively. Importantly, multiple pregnancy rates were lower with LOD than with GnHs (1.2 vs. 17 %; OR 0.13, 95 % CI 0.03–0.52) [43].

PCOS women have a higher miscarriage rate compared with non-PCOS women (24.7 vs. 8.7 %, respectively) [65]. Moreover, the prevalence of PCOS among women with recurrent miscarriage appears to be increased and was as high as 82 % in these women in an earlier study [66]. However, a recent study demonstrated a considerably lower prevalence than previously accepted (8.3–10 % using the Rotterdam criteria) [67]. A significant difference in the miscarriage rate between obese and non-obese PCOS women (OR, 3.05; 95 % CI, 1.45–6.44) [68] and in oligo-anovulatory PCOS women versus ovulatory counterparts (61.5 vs. 10.4 %) was reported [65]. The possible mechanisms by which PCOS could cause recurrent miscarriage are elevated LH concentration, hyperandrogenemia, obesity and hyperinsulinemia [22, 69, 70].

In a long-term follow-up study, Amer et al. [71] reported that the miscarriage rate after LOD was reduced to 17 % compared to 54 % prior to LOD. According to a recent report, the overall miscarriage rate varied from 0 to 36.5 %

after LOD [22]. LOD may contribute to lower miscarriage rates in PCOS patients by normalizing high LH levels, reduction in androgen levels and insulin resistance, thus improving oocyte quality or endometrial receptivity [70]. However, there was no evidence of a difference in miscarriage rates between the LOD and gonadotropins groups (9.4 vs. 12.4 %; OR 0.73, 95 % CI 0.40–1.33) or between unilateral versus bilateral LOD (9.2 vs. 9 %; OR 1.02, 95 % CI 0.31–3.33) [43]. A recent retrospective study demonstrated a tendency toward elevated rates of early miscarriage (20 vs. 10 %), twin pregnancy (12.5 vs. 7.5 %), and preterm delivery (14.9 vs. 8.8 %) for pregnancies after CC and LOD in women pre-treated with metformin. However, these data failed to reach statistical significance ($p > 0.05$) [72].

Evaluation of LOD performance in PCOS patients without CC-resistance

Although LOD is advocated as a second-line approach in patients with CC-resistant PCOS [8, 13, 15, 18], current evidence does not support the use of LOD as a first-line approach for PCOS-related anovulation nor for PCOS patients with CC failure or before ART as follows.

LOD as a first-line therapy in PCOS

Few literature data addressed the use of LOD as a first-line treatment for ovulation induction in patients with PCOS. Cleemann et al. [73] prospectively evaluated this point among 57 infertile PCOS women with a reported pregnancy rate of 61 % after a median follow-up of 135 days. Suggested benefits were shortening of time-to-pregnancy and decreasing the need for pharmacological ovulation induction as well as identification of tubal factor subfertility [73]. On the other hand, a recent RCT by Amer et al. [74] concluded that LOD is not superior to CC as a first-line treatment of ovulation induction in women with PCOS. No significant difference was found regarding the ovulation rate either per woman (64 vs. 76 %, $p = 0.32$), or per cycle (70 vs. 66 %), pregnancy rate per woman (27 vs. 44 %, $p = 0.13$), cumulative pregnancy rate (52 vs. 63 %, $p = 0.26$) and live birth rate (46 vs. 56 %, $p = 0.27$) after 12 months among 72 PCOS women who were randomized to undergo LOD versus six cycles of CC as a first-line approach for anovulatory infertility [74].

LOD for CC failure in PCOS

As mentioned above, CC failure refers to patients who failed to conceive with CC despite successful regular ovulation with CC for 6–9 cycles [13]. Arguably, in those patients, LOD may offer several theoretical advantages. It induces repeated mono-ovulatory cycles potentially associated with pregnancy and circumvents unfavorable peripheral anti-estrogenic effects of CC on both endometrium and cervical mucus and the possible abnormal hypersecretion of LH leading to premature luteinisation in response to CC responsible for CC failure [75–80]. Consequently, this might be translated into achieving a higher pregnancy rate. However, in a recent RCT, we evaluated this issue and reported that despite achieving more pregnancies with LOD than continued CC (39 vs. 33.7 % for clinical pregnancy rate per patient and 47 vs. 39.2 % for the cumulative pregnancy rate after six cycles), the difference was not statistically significant [81].

LOD prior to ART

Several studies have reported that LOD prior to ART may be beneficial in decreasing the risk of severe OHSS and improving the ongoing clinical pregnancy rate in women who have previously had an IVF treatment cycle cancelled due to risk of OHSS or who suffered from OHSS in a previous treatment cycle [82–84]. This finding may be attributed to a reduced ovarian blood flow velocity and serum vascular endothelial growth factor (VEGF) concentrations following LOD [85–87]. However, none of the above studies were properly randomized and hence susceptible to selection bias.

Only one RCT in 50 patients with PCOS compared ART outcome with and without prior LOD [88]. Although patient enrollment had been randomized, there was a statistically significantly larger number of women in the LOD/ART group who had a cancelled treatment cycle previously or who had developed moderate or severe OHSS. The authors of this study concluded that prior LOD can significantly reduce the cancellation rate of an ART treatment cycle because of developing OHSS. Although in completed cycles the incidence of moderate or severe OHSS was lower in women with prior LOD, this difference was not statistically significant (4 vs. 16 %; OR 0.22; 95 % CI 0.02–2.11). Furthermore, there were no significant differences in pregnancy rate (36 vs. 32 %, OR 1.20; 95 % CI 0.37–3.86), miscarriage rate (10 % in each, OR 1.00; 95 % CI 0.18–5.51) or live birth rate (24 vs. 20 %, OR 1.26; 95 % CI 0.33–4.84) between both groups [43, 88].

LOD and PCOS androgenic symptoms

Sixty-five to 85 % of all women with androgen excess are diagnosed as having PCOS [89]. Although there is evidence that LOD decreases androgen levels significantly, the evidence that this translates into a clear improvement in hirsutism and acne is less clear [90]. In a prospective study ($n = 45$ CC-resistant PCOS patients), Api et al. [91]

reported that LOD significantly reduced the percentage of patients with a Ferriman–Gallwey score of >8 from 57.7 % preoperatively to 51.1 % at 2 months following LOD. Others reported improvement of acne and hirsutism in 23–50 % of patients at 3–9 years following LOD [71, 92]. However, no difference was reported in acne or hirsutism at 6-months follow-up after LOD in a RCT comparing LOD versus gonadotropins [93]. Overall, further high-quality clinical research, including data from randomization, would be required to clarify this important issue.

Long-term efficacy of LOD

There are published data suggesting that the effect of LOD may persist beyond the first year of treatment in terms of regular ovulation, menstrual pattern and occurrence of pregnancy. Gjönnaess [62] reported a persistent ovulation rate of 74 % among 31 patients monitored for more than 10 years (initial group of 165 women). In a retrospective study, Amer et al. [71] compared 116 women with PCOS who had LOD vs. 34 women who had not undergone this technique. 76 % of patients were monitored for 3 years and 38 % were monitored for 7–9 years after LOD. The odds of having regular menstrual cycles after LOD were 2.6 at 3 years' and 2.2 at 9 years' follow-up. Felemban et al. [19] reported a total pregnancy rate of 82 % at 24 months with a 100 % follow-up rate at 36 months. Other studies reported a total pregnancy rate of 68 and 73 % at 24 months [52, 94].

A recent long-term follow-up study of 168 women with CC-resistant PCOS previously included in a RCT comparing LOD vs. rFSH showed that 54 % of the women allocated to undergo LOD had a regular menstrual cycle 8–12 years after randomization vs. 36 % in those allocated to rFSH (RR: 1.5; 95 % CI 0.87–2.6) [95]. Treatment with LOD resulted in a significantly lower need for ovarian stimulation in order to reach a live birth (53 vs. 76 %; RR: 0.69; 95 % CI 0.55–0.88 after LOD and rFSH, respectively). The cumulative proportion of women with a first child after 8–12 years was 86 % in the LOD group versus 81 % in the rFSH group (RR: 1.1; 95 % CI 0.92–1.2). Meanwhile, the cumulative proportion of women having a second child was 61 % after LOD versus 46 % after rFSH (RR: 1.4; 95 % CI 1.00–1.9). The authors concluded that LOD for women with CC-resistant PCOS is as effective as ovulation induction with rFSH treatment in terms of live births, but reduces the need for ovulation induction or ART in a significantly higher proportion of women and increases the chance for a second child [95].

What is after LOD failure?

Increased responsiveness of the ovary to oral ovulation induction agents and GnHs, especially in those patients who remain anovulatory following LOD is another potential advantage for the procedure. However, literature data to support this important aspect of LOD are scarce [20, 64, 96]. In a recent prospective study, we investigated whether LOD in CC-resistant PCOS patients led to the restoration of CC-sensitivity [97]. LOD was performed in 234 CC-resistant PCOS patients. In 150 patients ovulation occurred. The remaining 84 anovulatory patients were treated again with CC. Ovulation occurred in 30/84 patients (35.7 %), and pregnancy occurred in 13/84 patients (15.5 %). Hyperandrogenism and insulin resistance appeared to be negative predictors of ovulation [97]. Farhi et al. [98] reported an increased ovarian sensitivity to GnHs after LOD. In a retrospective study, the authors compared outcomes of GnHs-stimulated cycles before and after LOD among 22 CC-resistant PCOS women with high basal serum LH concentrations who failed to ovulate spontaneously or conceive after LOD. They demonstrated significantly higher rates of ovulation and pregnancy after LOD as well as a significant reduction of the number of ampules, daily effective dose, and duration of the induction phase with hMG and a significant reduction of the daily effective dose of FSH [98].

What about ovarian re-drilling?

The effectiveness of a second LOD, i.e. re-drilling, in women with PCOS was assessed in a retrospective study including 20 women who had undergone LOD 1–6 years previously [99]. Of them, 12 had initially responded to the first LOD with the occurrence of ovulatory cycles, but the anovulatory status recurred, whereas eight subjects had not responded at all. The authors reported an overall ovulation rate and pregnancy rate of 60 and 53 %, respectively, after the second LOD. Re-drilling resulted in significantly higher ovulation and pregnancy rates in previous LOD responders compared with previous non-responders (83 and 67 % vs. 25 and 29 %, respectively). The authors concluded that repeat LOD is highly effective in women who previously responded to the first procedure [99]. Undoubtedly, a clear need for a large RCT addressing this issue is overwhelming; however, concerns about the potentially detrimental effect on ovarian reserve using this approach may preclude the feasibility of such a study.

LOD versus oral ovulation induction treatments

Oral ovulation induction treatment modalities, such as metformin [100], CC plus metformin [101, 102], CC plus tamoxifen [103], rosiglitazone plus CC [104] and aromatase inhibitors [105, 106] have recently been investigated as alternative second-line approaches for ovulation induction in CC-resistant women with PCOS (Table 2).

Table 2 Recent comparative trials between LOD and alternative therapies in women with CC-resistant PCOS

Methodology/objective	Main findings	References
Cochrane database systematic review to determine the effectiveness and safety of LOD compared with ovulation induction for subfertile women with CC-resistant PCOS (Nine trials, $n = 1{,}210$ women, reported on the primary outcome of live birth rate per couple)	There was no evidence of a significant difference in rates of live birth (34 vs. 38 %), clinical pregnancy (39.7 vs. 40.5 %), or miscarriage (7.3 vs. 6.6 %) in women with CC-resistant PCOS undergoing LOD compared to other medical treatments. Significant reduction in multiple pregnancy rates occurred in women undergoing LOD (0.7 vs. 3.5 %). There was no evidence of a difference in live births when LOD was compared with CC+ tamoxifen (OR 0.81; 95 % CI 0.42–1.53), gonadotropins (OR 0.97; 95 % CI 0.59–1.59), aromatase inhibitors (OR 0.84; 95 % CI 0.54–1.31) or CC (OR 1.21; 95 %CI 0.64–2.32). There was evidence of significantly fewer live births following LOD compared with CC+ metformin (OR 0.44; 95 % CI 0.24–0.82)	[43]
A RCT to compare the hormonal-metabolic profiles and reproductive outcomes in CC-resistant patients with PCOS and insulin resistance between women receiving metformin and those undergoing LOD ($n = 110$)	Although metformin results in a better attenuation of insulin resistance, LOD is associated with more regular cycles (76.4 vs. 58.2 %) and higher rates of ovulation (50.8 vs. 33.5 %) and pregnancy (38.2 vs. 20.0 %)	[100]
A RCT to compare the effectiveness of LOD vs. CC plus metformin (6-cycle course) in infertile patients with CC-resistant PCOS ($n = 50$)	LOD and CC plus metformin seem to be effective approaches to treat infertile patients with CC-resistant PCOS with no significant difference in rates of pregnancy (16.3 vs. 13.1 %) and live birth (14.1 vs. 11.2 %)	[101]
A RCT to compare the effect of metformin plus CC with LOD for ovulation induction in CC-resistant women with PCOS ($n = 282$)	Metformin plus CC and LOD are equally effective for inducing ovulation (67 vs. 68.2 % per cycle) and achieving pregnancy (15.4 vs 17 % per cycle) in CC-resistant PCOS patients	[102]
A RCT to compare the effect of CC plus tamoxifen with LOD for ovulation induction in CC-resistant women with PCOS ($n = 150$)	CC plus tamoxifen and LOD are equally effective for inducing ovulation (81.3 vs. 85.3 %) and achieving pregnancy (53.3 vs. 50.7 %) and live births (49.3 vs. 44.0 %) in CC-resistant PCOS patients	[103]
A RCT to compare the effect of rosiglitazone (4 mg twice daily) plus CC with LOD for ovulation induction in CC-resistant women with PCOS ($n = 43$)	Rosiglitazone plus CC and LOD are equally effective for inducing ovulation (80.8 vs. 81.5 %) and achieving pregnancy (50 vs. 42.8 %) in CC-resistant PCOS patients	[104]
A RCT to compare the effect of letrozole (6-cycle course, 2.5 mg daily for 5 days) with LOD for ovulation induction in CC-resistant women with PCOS ($n = 260$)	Letrozole and LOD are equally effective for inducing ovulation (65.4 vs. 69.3 % per cycle) and achieving pregnancy (28.12 vs. 28.03 % per woman) in CC-resistant PCOS patients	[105]
A RCT to compare the clinical outcomes of letrozole (6-cycle course, 5 mg daily for 5 days) and LOD in patients with CC-resistant PCOS ($n = 140$)	A significantly higher ovulation rate was found in the letrozole group (59.0 vs. 47.5 % per cycle). Meanwhile no significant difference regarding the rates of pregnancy (35.7 vs. 28.6 %) and live birth (32.9 vs. 22.9 %) for letrozole and LOD group, respectively	[106]

CC clomiphene citrate, *LOD* laparoscopic ovarian drilling, *PCOS* polycystic ovary syndrome, *RCT* randomized controlled trial

Importantly, a recent Cochrane review addressing these trials [43, 100–106] showed no evidence of any difference in live births when LOD was compared with CC plus tamoxifen (OR 0.81; 95 % CI 0.42–1.53) or compared with aromatase inhibitors (OR 0.84; 95 % CI 0.54–1.31). Although there was evidence of significantly fewer live births following LOD compared with CC plus metformin (OR 0.44; 95 % CI 0.24–0.82), there was no evidence of a significant difference in ovulation and pregnancy rates when LOD was compared to CC plus metformin (OR 0.89; 95 % CI 0.27–2.93; OR 0.79; 95 % CI 0.53–1.18), CC plus tamoxifen (OR 1.34; 95 % CI 0.68–2.63; OR 0.97; 95 % CI 0.59–1.59), aromatase inhibitors (OR for ovulation rate was not included: OR 0.89, 95 % CI 0.58–1.37) or rosiglitazone plus CC (OR 0.67; 95 % CI 0.13–3.44; OR 0.75; 95 % CI 0.23–2.50) [43]. Notably, as regards the pregnancy rate, LOD versus metformin was the only comparison with evidence of a significant benefit in favor of LOD (OR 2.47; 95 % CI 1.05–5.81) [43, 100]. Furthermore, compared with LOD, there was no difference in either multiple pregnancy or miscarriage rate and the incidence of OHSS for any of these treatments [43].

Oocyte in vitro maturation as a potential alternative approach in CC-resistant patients with PCOS

Although in vitro maturation of oocytes has been applied in a wide range of indications, including normo-ovulatory patients [107] and in the setting of fertility cryopreservation [108], this minimal-approach ART is mostly used in women with polycystic ovaries and PCOS [109]. The simplicity of its clinical approach and the total absence of OHSS have attracted increasing interest from ART practitioners and patients in recent years, although pregnancy rates are still low compared to conventional ART. Outcomes vary importantly between different centers, and reduced oocyte competence in currently available IVM culture systems precludes a wider acceptance of this technology in human ART. Nevertheless, in patients with PCOS and very increased circulating levels of AMH, conventional ART can be cumbersome and clinical outcomes may be reduced compared to patients with moderately elevated AMH serum levels [110]. Hence, there may be important promise in the further development of this ART, especially in women with PCOS whose dysovulation appears refractory to conventional methods of ovulation induction. Moreover, there is preliminary evidence that ovarian puncture for IVM could be associated with an improved number of mature oocytes retrieved and total number of embryos produced in conventional ART following IVM [111], although the effect of immature egg retrieval on ovarian function remains to be further investigated.

Post-operative complications

Besides the possible risks of any minimally invasive laparoscopic surgical intervention, the main shortcomings of LOD are the risk of postoperative adhesions and the concern that the procedure could negatively impact on the ovarian reserve secondary to excessive damage to the ovarian follicular pool [19, 112].

Surprisingly, only one case report of ovarian atrophy following high-energy drilling (10 times more than usual, i.e. eight coagulation points at 400 W, for 5 s) has been published in the literature [113]. Importantly, the findings of this unique case have not been replicated by other studies. On the other hand, an important finding of a prospective comparative study was that the extent of destruction of ovarian tissue was rather limited, ranging from 0.4 % after four to 1 % after eight coagulation punctures (each at 40 W for 5 s, i.e. 800 or 1,600 J per ovary) [114]. In addition, a recent prospective study reported that the ovarian trauma after LOD in patients with CC-resistant PCOS does not result in significant production of anti-ovarian antibodies, which could result in the development of autoimmune premature ovarian failure and worsening of reproductive potential [115].

Practically speaking, the concern that LOD might affect ovarian reserve is currently not supported; a recent report concluded that LOD, when applied correctly, does not appear to compromise the ovarian reserve in women with PCOS [36]. In addition, most of the changes in the ovarian reserve markers (i.e. circulating day 3 FSH and inhibin B levels, ovarian volume and antral follicle count) observed after LOD could be interpreted as normalization of ovarian function rather than a reduction of ovarian reserve [36]. Of note, there are no available data regarding the relationship between LOD and age at menopause.

The incidence of postoperative adhesion formation varies considerably [22, 31, 112]. Mercorio et al. [112] randomized ninety-six anovulatory subfertile women with PCOS treated with LOD into two groups of 48 women each; in one group, patients were treated with 6 punctures on the left ovary and 12 on the right and in the other group patients were treated with 6 punctures on the right ovary and 12 on the left. A short-term second-look laparoscopy was performed to evaluate post-surgical adhesion formation. The authors reported a high incidence of ovarian adhesion formation after LOD (60 % per women and 46 % per treated ovaries) but their extent and severity was not influenced by the number of ovarian punctures [112]. In addition, a higher rate of postoperative adnexal adhesion formation was reported with the use of laser compared to unipolar cautery [19, 116, 117]. Theoretically speaking, these adhesions could cause mechanical infertility although there is no available evidence to support this hypothetical concern [118].

Liberal peritoneal lavage has been advised to reduce adhesions [119]. Other strategies suggested were the application of anti-adhesion substances (adhesion barrier) at the time of LOD or the performance of adhesiolysis at an early second-look laparoscopy [117, 119]. However, the effects of the former approach on de novo adhesion formation after LOD has not been proven in RCTs [117] and the performance of the latter technique does not improve pregnancy rates following laparoscopic Nd-YAG laser photocoagulation of PCOS (47 vs. 55 % in the second-look and the expectant-management groups, respectively, OR 0.66; 95 % CI 0.18–2.35) [43, 120].

Cost-effectiveness

Theoretically speaking, compared with gonadotropins treatment, LOD may be more cost-effective, because one treatment, in principle, results in several mono-ovulatory cycles, i.e. allows multiple attempts of conception, whereas one course of GnHs therapy yields a single ovulatory cycle with the inherent need for intensive monitoring. Economic analysis of two RCTs from The Netherlands and New Zealand showed a cost difference in favor of LOD [43, 121, 122]. In the Dutch study, the total cost of treatment was 4,664 ± 1,967 € and 5,418 ± 3,785 € in the LOD and GnHs-only groups, respectively (the difference was 754 €;

95 % CI 155.1–1,666.1 €) [121]. In addition, it was estimated that the cost per term pregnancy would be 14,489 € for GnHs and 11,301 € for LOD followed by medical induction therapy if needed (22 % less) [121]. The higher rates of multiple pregnancies in the GnHs group were considered to be responsible for the increased costs [43, 121]. In the New Zealand trial, the cost of a live birth was one-third lower in the LOD group compared with those women who had received gonadotropins (19,640 NZ$ and 29,836 NZ$, respectively) [43, 122]. A recent study demonstrated that the long-term costs per first live birth within a mean follow-up time of 8–12 years were significantly lower for the LOD compared to gonadotropins (mean difference 3,247 €; 95 % CI 650–5,814 €) [123].

Patient preference and health-related quality of life issues

In a RCT including thirty-two CC-resistant PCOS patients, Bayram et al. [124] reported that the majority of patients (88 %) would prefer LOD over ovulation induction with rFSH if both treatment strategies resulted in similar pregnancy rates. The main reason was the reduced need of daily hormonal injections and the observation that LOD leads to less multiple follicular development and fewer multiple pregnancies [124]. in another RCT, van Wely et al. [125] compared LOD and rFSH among 168 CC-resistant PCOS. Using the SF-36, Rotterdam Symptom Checklist and depression scales, no statistically significant treatment effect was found with regard to health-related quality of life, although women who did not conceive found the use of rFSH slightly more difficult to bear [43, 125].

Conclusion

LOD using a unipolar electrode as first proposed by Gjönnaess in 1984 is currently recommended as a successful second-line treatment for ovulation induction in women with CC-resistant PCOS. It is as effective as gonadotropins treatment and is not associated with an increased risk of multiple pregnancy or OHSS. In addition, a LOD cost less, when successful allows multiple attempts of conception without the need for intensive monitoring and is preferred by the majority of patients. Current evidence does not support its use as a first-line approach in PCOS-related anovulation or before IVF.

The main shortcomings of LOD are the risk of postoperative adhesions and the theoretical risk of affecting the ovarian reserve in case of excessive damage. Evidence suggests that unilateral LOD is equally efficacious as bilateral drilling in inducing ovulation and achieving pregnancy and live birth in CC-resistant PCOS patients.

A significant immediate postoperative reduction in serum LH and testosterone levels is a remarkable finding in different studies as well as the restoration of regular ovulation and menses in the vast majority of patients which persists for many years. Another advantage is the increased responsiveness of the ovary to CC especially in patients who remain anovulatory following LOD. There is some evidence that insulin sensitivity, acne, and hirsutism may be improved after LOD. Elevated serum LH concentrations (>10 IU/l), infertility of less than 3 years duration and a BMI of less than 25 kg/m^2 were frequently linked to a higher likelihood of success among different studies. Measuring AMH and ovarian stromal 3D power Doppler blood flow may provide a useful tool in evaluating the outcome of LOD. Recently, there is evidence that relatively novel oral methods of ovulation induction, e.g. CC plus metformin, CC plus tamoxifen, rosiglitazone plus CC and aromatase inhibitors represent a successful alternative second-line therapy for ovulation induction in CC-resistant PCOS.

Conflict of interest We declare that we have no conflict of interest.

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