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EDITORIAL

Primum Non Nocere

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Abstract Surgical ovarian wedge resection was the first established treatment for women with anovulatory polycystic ovary syndrome (PCOS) but was largely abandoned both due to the risk of postsurgical adhesions and the introduction of medical ovulation induction. Laparoscopic ovarian drilling (LOD) is an alternative method to induce ovulation in PCOS patients with clomiphene citrate resistance instead of gonadotropins. Surgical therapy with LOD may avoid or reduce the need for gonadotropins or may facilitate their use. However, the procedure, though effective, can be traumatic on the ovaries, which may cause postoperative adhesions and/or diminished ovarian reserve. In over-enthusiastic hands, this day-care procedure might lead to iatrogenic premature ovarian failure in young women. Some trials have compared LOD with gonadotropins, but, because of variations in study design and small sample size, the results are inconsistent and definitive conclusions about the relative efficacy of LOD and gonadotropins cannot be extracted from the individual studies. Today, evidence-based reviews conclude that there is no

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evidence of a significant difference in rates of clinical pregnancy, live birth or miscarriage in women with clomiphene-resistant PCOS undergoing LOD compared to other medical treatments. The reduction in multiple pregnancy rates in women undergoing LOD is the only pro-LOD argument. However, there are ongoing serious concerns about the long-term effects of LOD on ovarian function.

Keywords Surgical ovarian wedge resection · Laparoscopic ovarian drilling (LOD) · PCOS

Introduction

Primum non nocere is a Latin phrase that means "first, do no harm." The phrase is sometimes recorded as primum nil nocere. Another way to state it is that, "given an existing problem, it may be better not to do something, or even to do nothing, than to risk causing more harm than good." [1] It reminds the healthcare provider that they must consider the possible harm that any intervention might do. Gonadotropin therapy and laparoscopic ovarian drilling (LOD) are treatment options for ovulation induction (OI) in clomiphene citrate (CC)-resistant polycystic ovary syndrome (PCOS) patients. Surgical ovarian wedge resection was the first established treatment for women with anovulatory PCOS but was largely abandoned both due to the risk of severe postsurgical adhesions and the introduction of medical OI. However, women with PCOS who are treated with medical OI, with drugs such as gonadotropins, may be at high risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. It was next proposed that LOD may avoid or reduce the need for medical OI, or may facilitate its usefulness. This procedure was demonstrated to have fewer postoperative adhesions than with traditional surgical approaches. Many uncontrolled observational studies have claimed that ovarian drilling is followed, at least temporarily, by a high rate of spontaneous ovulation and conception, or that subsequent medical OI becomes easier [2–4]. LOD was reported to have an overall spontaneous ovulation and pregnancy rates of 30–90 and 13–88 %, respectively, for CC-resistant PCOS women [5]. The mechanism of LOD is still unknown. The reduction in serum androgen level is believed to be the possible mechanism of LOD to improve spontaneous ovulation and promote fertility in women with PCOS. In addition, LOD may cause a significant reduction in serum luteinizing hormone and insulin levels. However, it should be kept in mind that postoperative adhesions are the most common adverse effect of LOD, and excessive drilling may be responsible for premature ovarian failure [5]. 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_2 laser or monopolar electrocoagulation [6].

Although multiple pregnancy rates are reduced with ovarian drilling procedures, postoperative adhesion formation is a potential complication in up to 85 % of the women subjected to laparoscopic destructive ovarian procedures [7]. Mercorio et al. [8] set up a prospective study to determine the incidence, site and grade of ovarian adhesion formation after LOD and analyze the association between the number of punctures made and the incidence and grade of adhesions, and evaluate the lateral distribution of the adhesions. Women were randomized into two study groups of 48 women each, one treated with six punctures on the left ovary and 12 on the right, and the other treated with six punctures on the right ovary and 12 on the left. A short-term second-look mini-laparoscopy was performed to evaluate postsurgical adhesion formation. Adhesion formation was detected in 54 of the 90 women (60 %) and in 83 of the 180 ovaries treated (46 %). Dense adhesions were more likely to develop on the left ovaries to a statistically significant extent, and independently of the number of ovarian punctures performed. Logistic regression analysis showed that the incidence of ovarian adhesions was independent of both number of punctures and side. The incidence of ovarian adhesion formation after LOD was high, and their extent and severity were not influenced by the number of ovarian punctures; however, the left ovary appeared more prone to develop severe adhesions than the contralateral one [8].

Discussion

A Cochrane review was published in 2012 to determine the effectiveness and safety of LOD compared with OI for subfertile women with clomiphene-resistant PCOS [9]. Nine trials, including 1210 women, reported on the primary outcome of live birth rate per couple. Live births were reported in 34 % of women in the LOD groups and 38 % in other medical treatment groups. There were five different comparisons with LOD, and there was no evidence of a difference in live births when compared with clomiphene citrate + tamoxifen (OR 0.81; 95 % CI 0.42–1.53; $P = 0.51$, 1 trial, $n = 150$), gonadotropins (OR 0.97; 95 % CI 0.59–1.59; $P = 0.89$, $I^2 = 0$ %, 2 trials, $n = 318$), aromatase inhibitors (OR 0.84; 95 % CI 0.54–1.31; $P = 0.44$, $I^2 = 0$ %, 2 trials, $n = 407$) or CC (OR 1.21; 95 % CI 0.64–2.32; 1 trial, $n = 176$, $P = 0.05$). There was evidence of significantly fewer live births following LOD compared with clomiphene citrate + metformin (OR 0.44; 95 % CI 0.24–0.82; $P = 0.01$, $I^2 = 78$ %, 2 trials,

$n = 159$); the high heterogeneity in this subgroup could not be explained by population differences or differences in quality of the trials. Thirteen trials reported on multiple pregnancies ($n = 1305$ women). There were no cases of multiple pregnancies in either group for CC or aromatase inhibitors compared with LOD. The rate of multiple pregnancies was significantly lower in the LOD group compared with trials using gonadotropins. The authors concluded that there was no evidence of significant difference in rates of clinical pregnancy, live birth or miscarriage in women with clomiphene-resistant PCOS undergoing LOD compared to other medical treatments. The reduction in multiple pregnancy rates in women undergoing LOD is the only pro-LOD argument. However, there are ongoing concerns about the long-term effects of LOD on ovarian function [9].

A retrospective health-economic evaluation was performed from a societal perspective in which human menopausal gonadotropin (hMG) therapy ($n = 43$) was compared with LOD ($n = 35$), followed by OI with CC and/or hMG if spontaneous ovulation did not occur within 2 months [10]. Data were collected until the patients were pregnant, with a time limit of 6 months after the onset of treatment. Outcomes were expressed as ongoing pregnancy rate and number of live-born children. The ongoing pregnancy rate was 21/35 (60 %) after LOD and 30/43 (69.8 %) after hMG treatment. The societal cost per patient, up to an ongoing pregnancy, was significantly higher after LOD versus hMG treatment (adjusted mean difference EUR 1073, 95 % CI 180–1967). This economic evaluation based on real-life data shows that the societal cost up to an ongoing pregnancy is less after hMG treatment when compared with LOD surgery in CC-resistant PCOS patients [10].

A complete electronic literature search in databases including EMBASE, MEDLINE, Cochrane Library and Google Scholar for some specific keywords was accomplished by an Iranian group [11]. Six trials, covering 499 women, reported on the primary outcome of pregnancy rate. There was no evidence of a difference in pregnancy rate when LOD compared with gonadotropins (OR 0.534; 95 % CI 0.242–1.176, $P = 0.119$, 6 trials, 499 women, $I^2 = 73.201$ %). There was evidence of significantly fewer live births following LOD compared with gonadotropin (OR 0.446; 95 % CI 0.269–0.74, $P = 0.02$, 3 trials, 318 women, $I^2 = 3.353$ %). The rate of multiple pregnancies was significantly lower in the LOD arm compared to the gonadotropins arm (OR 0.127; 95 % CI 0.028–0.579, $P = 0.008$, 3 trials, 307 women, $I^2 = 0$ %). Their paper revealed that there was no evidence of a significant difference in rates of clinical pregnancy and miscarriage in women with CC-resistant PCOS undergoing LOD compared to the gonadotropin arm. However, more focus on the long-term effects of LOD on ovarian function was suggested [11].

All ovarian drilling procedures result in reproductive endocrine changes [12, 13]. It is not known which of these changes are the result of ovarian drilling and which are related to the surgery per se. A prospective controlled study was performed at an outpatient academic fertility clinic where a total of 21 oligo- or amenorrheic PCOS patients were included with all three of the Rotterdam criteria and luteinizing hormone (LH) > 6.5 U/l [14]. All PCOS patients had an indication for diagnostic laparoscopy due to subfertility. There were 12 PCOS patients who chose to undergo ovarian laser evaporation (CO_2 laser, 25 W, 20 times/ovary) and 9 PCOS who chose a diagnostic laparoscopy only (controls). Reproductive endocrinology was measured before, and until 5 days after, surgery, and four gonadotropin-releasing hormone (GnRH) "double pulse" tests were included. The main outcome measures were changes in reproductive endocrinology and pituitary sensitivity/priming to GnRH after laser evaporation compared with diagnostic laparoscopy only. In the first hours after surgery, both groups showed an increase in LH, follicle-stimulating hormone, estrogen and a decrease in testosterone, androstenedione, AMH and insulin growth factor-1 ($P < 0.05$). Inhibin B increased in the laparoscopy-only group ($P < 0.05$). In the first days after surgery, testosterone, androstenedione and AMH remained at lower than baseline levels exclusively in the laser group ($P < 0.05$). Pituitary sensitivity/priming to GnRH was not altered after either laser evaporation or laparoscopy only. The limitations of this study are the short follow-up period and the relatively small groups. The strength of this study is the integrally measured endocrine profiles in combination with an optimal control group of PCOS patients undergoing diagnostic laparoscopy only. Interestingly, the authors concluded that most of the immediate endocrine changes after laser evaporation could be related to the surgical context and not to the ovarian drilling procedure itself [14].

The adjustment of the thermal dose to ovarian volume in bilateral laparoscopic ovarian drilling (BLOD) increases ovulation and pregnancy rates compared with fixed-dose treatment, but BLOD causes the formation of adhesions, particularly on the left ovary, and increases the risk of damage to ovarian tissue [15]. In contrast, unilateral laparoscopic ovarian drilling (ULOD) with a fixed thermal dose minimizes the risk of ovarian tissue damage and can increase the activity in both right and left ovaries, although this varies in humans and in other species. A prospective, longitudinal study included 96 infertile women with PCOS who were unresponsive to CC treatment and had underwent either ULOD or BLOD [15]. After surgery, the groups were followed up for 6 months to assess ovulatory response. Patients were assigned to two groups; one group

underwent LOD of the right ovary alone, while both ovaries were treated in the second group. The ULOD group ($n = 49$) received thermal doses adjusted to the volume of the right ovary (60 J/cm^3). The BLOD group ($n = 47$) received fixed doses of 600 J per ovary, regardless of its volume. The two treatment groups were matched by the number of participants, age and baseline parameters. The ovulation rate during the first menstrual cycle after LOD was significantly higher in the ULOD group than in the BLOD group. Treatment with ULOD on the right ovary significantly increased the chances of ovulation in patients with a larger right ovary compared with those who had a smaller right ovary. The pregnancy rate was also significantly higher in patients with a larger right ovary compared with those with a smaller right ovary, regardless of the treatment group. The 6-month follow-up was too short to demonstrate any long-term differences in the ovulation rates. Future research should therefore extend the follow-up beyond 6 months. This study has shown that improved results can be achieved using less thermal energy in volume-adjusted ULOD [15].

Weerakiet et al. [16] evaluated the ovarian reserve with hormones and sonography in women with PCOS undergoing LOD. Twenty-one PCOS women undergoing LOD were enrolled in the study (the LOD group). Their day-3 anti-Müllerian hormone (AMH), inhibin B, follicle-stimulating hormone (FSH) levels, antral follicles count (AFC) and summed ovarian volume representing ovarian reserve were compared with those of PCOS women who did not undergo LOD (the PCOS group) and those of normal ovulatory women (the control group). AMH levels seemed to be lower in the LOD (4.60 ± 3.16 ng/ml) than in the PCOS (5.99 ± 3.36 ng/ml) groups, but did not reach statistical significance. Day-3 FSH levels were significantly higher, and AFC was significantly lower in the LOD than in the PCOS group. This study showed that ovarian reserve assessed by hormonal levels and sonography seems to be lower in the LOD than in the PCOS group [16].

Setting eligibility criteria based on the existing evidence concerning predictors of success of LOD is critical not only to improve its outcome, but also to avoid unnecessary surgery with possible risk of impairment of ovarian reserve and other complications. Abu Hashim [17] in his elegant evidence-based publication summarized that based on the current evidence, LOD could be predicted to result in poor reproductive outcome in women with CC-resistant PCOS when they are obese (BMI > 25 kg/m^2), long duration of infertility >3 years, low basal LH levels <10 IU/l, marked biochemical hyperandrogenism (testosterone levels ≥4.5 nmol/l, free androgen index >15) and high basal AMH ≥ 7.7 ng/ml.

Pirwany and Tulandi [18] evaluated the role of LOD and treatment with metformin in the management of the PCOS. A literature search was conducted using the keywords laparoscopy, LOD, laparoscopic ovarian diathermy, PCOS, metformin and ovulation. The MEDLINE and EMBASE databases and the Cochrane Database of Systematic Reviews were searched. No randomized comparisons have been made between LOD and metformin therapy. However, the ovulation and pregnancy rates appear to be similar for both techniques. Both treatments decrease the incidence of ovarian hyperstimulation and the cancellation rate of IVF cycles. However, unlike LOD, metformin may decrease the incidence of type 2 diabetes and coronary heart disease. Given the similar magnitude of the results without the potential risks and complication of surgery, the authors proposed that LOD should be used sparingly in favor of less invasive treatment with metformin [18]. Rosiglitazone, an insulin-sensitizing agent, is used currently in women with CC-resistant polycystic ovarian syndrome (PCOS). A prospective randomized study compared the efficacy of rosiglitazone and CC with LOD and CC in terms of biochemical effects, ovulation rate and pregnancy rate in patients of PCOS resistant to CC [19]. This trial included 43 patients of PCOS resistant to CC. Twenty-two women were assigned to the rosiglitazone (4 mg twice daily) and CC group, and other 21 patients underwent unilateral LOD and then received CC and multivitamins. The treatment continued for six cycles in both the groups. The biochemical response, ovulation rate and pregnancy rate over a follow-up period of 6 months were compared. Treatment with rosiglitazone and CC or LOD and CC resulted in increased ovulation (80.8 vs. 81.5 %) and pregnancy (50 vs. 42.8 %), respectively. There was no statistical difference between the two groups in terms of biochemical response, ovulation rate and pregnancy rate. To avoid the risk of adverse effects of LOD, preference may be given to the use of rosiglitazone and CC therapy in patients of PCOS resistant to CC [19].

Recent Advances

Shehata et al. [20] investigated the feasibility of using high-intensity focused ultrasound (HIFU), under dual-mode ultrasound arrays (DMUAs) guidance, to induce localized thermal damage inside ovaries without damage to the ovarian surface. Different ablation protocols were tested, and thermal damage within the treated ovaries was histologically characterized. The absence of damage to the ovarian surface may eliminate many of the complications linked to current LOD techniques. HIFU may be used as a less traumatic tool to perform LOD [20].

Conclusions

As gynecologists treating young PCOS patients presenting with fertility problems, we must first ensure that any intervention we suggest must not harm the patient by pushing them into an iatrogenic complication such as pelvic adhesions or premature ovarian failure requiring IVF or donor egg IVF, respectively. Recent evidence suggests that relatively novel oral methods of OI, e.g., CC plus metformin, CC plus tamoxifen, rosiglitazone plus CC and aromatase inhibitors, represent a successful alternative to LOD in CC-resistant PCOS [21]. Meanwhile, current evidence does not support LOD as a first-line approach in PCOS-related anovulation or before IVF. LOD is currently recommended as a successful and economical highly selective second-line treatment for OI in women with CC-resistant PCOS [21].

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