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Review Article

Surgical Ovulation Induction in Women with Polycystic Ovary Syndrome: A Systematic Review

Mohammad Ebrahim Parsanezhad[1], Afsoon Zarei[1], Mojgan Sayadi[1], Atyeh Jaafarzadeh[3], Abdolreza Rajaeefard[2], Vivian Frank[4], Ernst Hienrich Schmidt[4]

Abstract

Background: Currently clomiphene citrate is the first-line treatment to induce ovulation in women with polycystic ovarian syndrome (PCOS). Surgical therapy with laparoscopic ovarian drilling (LOD) may avoid or reduce the need for gonadotropins.

Objective: To determine the effectiveness and safety of LOD compared with ovulation induction in subfertile women with clomiphene-resistant PCOS.

Search Strategy: A systematic search was performed on PubMed (1966 to August 2007), the Ovid database (1966 to August 2007), and EMBASE (1974-2007). The search terms included: infertility, menstrual disorder, hirsutism, PCOS, surgical intervention, electrocautery, electrocoagulation, diathermy, drilling, and laparoscopic ovarian drilling, ovulation, pregnancy rate, post operation adhesions and ovarian blood flow.

Selection Criteria: Randomized controlled trials of women with clomiphene-resistant PCOS who were treated with LOD to induce ovulation were included.

Data Collection and Analysis: 3141 patients from 35 trials preformed in different geographic settings were included. All trials were assessed for quality criteria. We included those trials which followed hormonal changes, ovulation, and pregnancy rates after LOD**.** The primary outcomes measured were hormonal changes, ovulation, and pregnancy rates as well as ovarian artery blood flow, and the secondary outcome was rate of pelvic organ adhesion.

Main Results: The overall ovulation rate after LOD was 79.2% (74.9%-83.5% 95% CI). Of all women who ovulated only 66.6% (60.8%-72.4% 95% CI) conceived. The mean periadnexal adhesion rate was 22.7% (21.4%-24% 95% CI).

Conclusion: Compared with medical therapy, LOD has many advantages including: to be done once, no need for intensive monitoring, no chance of multiple pregnancy or ovarian hyperstimulation syndrome. LOD effectively decreases ovarian androgens and improves folliculogenesis and increases chance of ovulation and pregnancy rate. Finally, in vitro fertilisation should be considered as the last resort.

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[1]Departments of obstetrics and Gynecology,
[2]Epidemiology,
Shiraz University of Medical Sciences, Shiraz, Iran.
[3]Reseearch Section, Health Vice Chancellor,
Jahrom University of Medical Sciences, Jahrom, Iran.
[4]Division Infertility and GYN Endoscopy, Department of OB&GYN, Götingen University, Diako Teaching center, Bremen, Germany.

Correspondence:
Abdolreza Rajaeefard PhD,
Department of Epidemiology,
Shiraz University of Medical Sciences,
Shiraz, Iran.
Tel: +98 711 7251009
Fax: +98 711 7260225
Email: rajaeefard@sums.ac.ir
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Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder in women of reproductive age and the most common cause of anovulatory infertility, accounting for more than 70% of all cases.[1] Affecting 5%−10% of women of reproductive age,[2] PCOS is a heterogeneous disorder of unknown etiology characterized by hyperinsulinemia with insulin resistance and hyperandrogenemia.[3] Most of these manifestations, including menstrual irregularity, hirsutism, and chronic anovulation are related to the hyperandrogenic state in these women.[4] Common endocrine abnormalities in PCOS include chronic high luteinizing hormone (LH) levels,[5,6] hyperandrogenism,[7,8] hyperinsulinemia, insulin resistance,[9] and dyslipidemia.[7,10] These endocrine disturbances may cause oligo- or anovulation, and can also increase the risk of metabolic syndrome.[11,12]

The most common presenting feature of PCOS is anovulatory infertility, which accounts for 45% of all presenting symptoms. This symptom characterizes a distinct group of eugonadotropic women with World Health Organization (WHO) group 2 anovulation.[13,14] The first line of treatment to induce ovulation is clomiphene citrate (CC).[15] More than 80% of patients treated for PCOS will ovulate,[16-18] although about 20% of CC-treated women fail to ovulate.[19]

There are many modalities of treatment for CC-resistant women with PCOS, including the use of glucocorticoids,[20] insulin sensitizers,[21] bromocriptine,[22] aromatase inhibitors,[23] exogenous gonadotropins, pulsatile GnRH, and ultimately surgery.[24] Gonadotropin-releasing hormone therapy is effective but cumbersome, and the chance of pregnancy is lower compared with gonadotropin alone.[25,26] Although ovulation induction with gonadotropin is successful in CC-resistant patients, it is expensive and extensive monitoring is necessary because of the high sensitivity of polycystic ovaries to exogenous gonadotropin, with a high risk of ovarian hyperstimulation, multiple pregnancy, cycle termination, and abortion.[27] Although promising results have been obtained in initial studies of new alternative treatment options, including first-line treatment with insulin sensitizers or aromatase inhibitors, their place in routine clinical practice will remain uncertain until randomized controlled trials are done in large series of patients.[28,29]

Meanwhile, an alternative to medical treatment is the surgical approach.[3] Surgical therapy with laparoscopic ovarian drilling (LOD) may avoid or reduce the need, or facilitate the use, of gonadotropins to induce ovulation. The procedure can be done on an outpatient basis with less trauma and fewer postoperative adhesions. Many studies have shown that LOD is followed by a high rate of spontaneous postoperative ovulation and conception, or that subsequent medical induction of ovulation become easier.

Ovarian Surgery

Ovarian wedge resection, multiple ovarian biopsies, laser vaporization and electrocautery have been introduced as surgical treatments for PCOS. Wedge resection of the ovaries was first described by Stein and Leventhal in 1935.[30] They observed restoration of regular menstruation in approximately 80% and spontaneous conception in about 50% of the patients who were treated.[31] However, the procedure, whether performed by laparotomy or laparoscopy, is associated with a high percentage of ovarian and peri-adnexal adhesions,[32] that may lead to mechanical-factor infertility. It is also associated with substantial tissue loss, and it may cause premature ovarian failure if the vascular supply to the ovary is compromised.[33] For these reasons this procedure has been abandoned.

In 1984 LOD was first described by Gjonnaess and colleagues in women with PCOS. These authors used a monopolar electrode at 300-400 W for 2-4 seconds and reported an ovulation rate of 90% and a pregnancy rate of 80% among 35 patients.[34] Laparoscopic ovarian drilling has replaced ovarian wedge resection as surgical treatment for CC-resistance in women with PCOS. It is free of the risks of multiple pregnancy and ovarian hyperstimulation, and does not require intensive ultrasound monitoring.[35] Its disadvantages are the need for surgery under general anesthesia, the unknown long-term effects on ovarian function, and possible adhesion formation.[19] Methods of LOD include monopolar or bipolar electrocautery and laser vaporization (CO_2, argon, Nd:YaG, KTP).[35,36]

Laparoscopic ovarian drilling is performed using a two-puncture technique, with an optic that equipped with an operative channel. The laparoscope is introduced through a subumbilical incision and a grasping forceps is introduced suprapubically to stabilize the ovary by grasping the utero-ovarian ligament. After assessment of the pelvic structures and tubal

patency, an insulated needle connected to a unipolar electrocautery unit is inserted through the operative channel of the optic. Eight to ten cautery points 3-4 mm in diameter and 4-6 mm in depth are created in each ovary with a current of 40 W applied through the insulated needle perpendicular to the ovary for 2-4 seconds at each point.[37] During the procedure it is important to hold the ovary away from the bowel to avoid thermal injury. Care must be taken to avoid the hilum of the ovary and ovarian blood supply. At the end of operation, the ovarian surface is lavaged and 500-1000 mL of crystalloid solution is left in the peritoneal cavity.

Laser vaporization including CO_2, KTP, and Nd:YaG have also been used for LOD. The technique is similar to electrocauterization.[38]

The exact mechanism through which endocrine dysfunction is reversed and the menstrual cycle re-established after ovarian surgery for PCOS is unclear. Destruction of a mechanical barrier has been postulated by Katz and colleagues,[39] and Ben Shlomo and coworkers.[40] Katz and colleagues believed that the reduction in ovarian size after surgery allows gonadotropin to act more effectively.[39] Increased ovarian blood flow is another theory to explain the increased delivery of gonadotropin.[41,42] Our group has proposed that LOD modifies ovarian stromal and ovarian artery blood flow.[43]

The reduction in androgen after ovarian surgery lowers the peripheral aromatization of estrogens and could theoretically result in the restoration of feedback to the hypothalamus and pituitary.[36,42-45] Gonadotropin surge-attenuating factor (GnSAF), as suggested by Messinis and others,[46] is produced by the ovaries and is responsible for the regulation and suppression of LH.[47] A deficiency in GnSAF in patients with PCOS has been hypothesized as the cause of elevated LH levels.[48,49] Laparoscopic ovarian drilling can cause follicular growth, which theoretically increases the production of GnSAF, which in turn suppresses LH secretion.[50] Reduced inhibin levels leading to an increase in FSH concentration was suggested as another mechanism of LOD.[51] The role of antimüllerian hormone (AMH) after LOD is not well established.[52,53]

This is the first systematic literature review to evaluate hormonal change in addition to ovulation, pregnancy rates, androgenic symptoms, and ovarian blood flow after LOD. Our ultimate aim was to determine the effectiveness and safety of LOD compared with ovulation induction in subfertile women with clomiphene-resistant PCOS.

Materials and Methods

To evaluate the effect of LOD on hormonal status, ovulation, pregnancy rate and ovarian artery blood flow and complications of LOD, a systematic search was performed of the PubMed (1966 to August 2007) Ovid Medline (1966 to August 2007) and EMBASE (1974-2007) databases. The search strategy was based on three sets of terms:

PCOS: surgical intervention, electrocautery, electrocoagulation, diathermy, drilling, and laparoscopic ovarian drilling.

Hormones: LH, FSH, testosterone, gonadotropin, gonadotropin releasing hormone, prolactin, androgens, androstenedione, dihydrotestosterone (sulfate), dihydrotestosterone (DHT), sex hormone-binding globulin, estrogen, progesterone, antimüllerian hormone (AMH), gonadotropin surge inhibitory factor, gonadotropin surge attenuating factor.

Clinical outcomes: ovulation, pregnancy rate, adhesion, ovarian blood flow

Since there is not any relation between the post LOD behavior and geographic setting, we did not consider specific geographic criteria.

The primary outcomes measured were hormonal changes, ovulation and pregnancy rate as well as ovarian artery blood flow and the secondary outcome was rate of pelvic organ adhesion.

We included all articles that had been published in English, and that reported treatment consisting of an ovarian surgery procedure to induce or facilitate ovulation in subfertile women with PCOS, together with endocrine hormone values before and after the operation, and that also reported data for ovulation rate, pregnancy, complications and ovarian artery blood flow.

Results

Hormonal changes after LOD

Luteinizing hormone

Ovarian androgen (androstenedione) is produced by LH stimulation of theca cells. Luteinizing hormone is also stimulates ovulation and luteinization.[54] Patients with PCOS have a chronically high LH level, which is responsible for the problems associated with the syndrome.[55] In most studies, LH concentration in patients with PCOS increased on the day after ovarian surgery,[56-61] but some studies reported no significant changes.[62-67] We reported a decrease in the LH level the day after surgery,[37] although many authors found that LH level remained low for a long time after surgery with exception of peri-ovulatory peak.[37,51,56,59,61,64,68-97]

A few studies reported no change in LH level weeks to months after surgery.[60,62,63,65,67,98-102] Luteinizing hormone levels were higher before LOD in non-obese women and in women who responded to the procedure.[51,103,104] but some authors found no differences and others reported lower LH levels in responders.[91,95] In comparison to non-responders, patients who ovulated or conceived after LOD showed a more significant decrease in LH levels after surgery.[37,51,66,69,93,95,103,105,106] Weiden and Sumioki found that LH amplitude decreased but LH frequently remain stable after surgery.[70,64]

On the basis of these results we conclude that LH concentration transiently increased on the day after LOD, and then gradually decreases, remaining low thereafter for weeks to years after surgery except for peri-ovulatory peaks (figure 1).

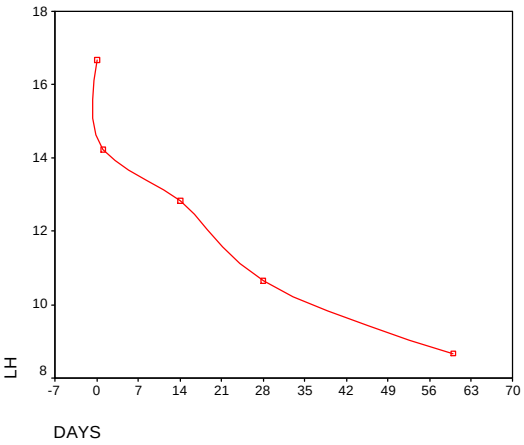

Figure 1: Mean serum LH levels in women with polycystic ovary syndrome before ovarian surgery, on days 0, the first 60 days after laparoscopic ovarian drilling, and the subsequent early follicular phase. PCOS values are derived from 38 publications comprising a maximum of 1148 patients.

Follicle Stimulating Hormone (FSH)

Follicle stimulating hormone is secreted by the pituitary and stimulates granulosa cells to produce estradiol, inhibin B and GnSAF.[46,107,108] During the early follicular phase, increasing serum FSH concentrations cause follicular cohort growth. Follicle stimulating hormone interacts with the granulosa cell FSH receptor to cause granulosa cell growth and differentiation. These steps massively expand the inherently limited capacity of granulosa cell for estrogen synthesis. Relative intrinsic inhibition of the action of FSH is one of the causes of anovulatory state in patients with PCOS, and is reversed by FSH supplementation or stimulation of endogenous FSH production with CC.

Although we and some other authors found no significant change in FSH level the day after LOD in patients with PCOS,[37,56,62,65,67,109] in a randomized study we found a significant increase in FSH concentration on the first days after surgery.[43] Others also reported the same result.[57,61,93] In our randomized clinical trial FSH level was significantly higher in responders on the first postoperative day in comparison to non-responders,[43] a finding also reported by other authors.[66,67,69,71] Many studies showed a decline in FSH level to the baseline value 1 week after the operation.[37,56,63,67,71,76,79,81,83,85,87,89,91,97,96,100,110] However, others found an increase,[51,64,66,72,74,80,90,93,95,111] or decrease in FSH levels during the same period.[82,86,98,112]

Follicle stimulating hormone pulse frequency and amplitude did not change after LOD.[70,74] Some articles reported similar values for responders and non-responders one week after LOD,[51,95,105,106] whereas in our two studies responders had higher FSH values.[43,109] However, Hayashi and colleagues,[103] found high FSH level weeks after the operation in non-responders.

Overall, FSH concentrations increased on the first days after ovarian surgery (figure 2). Following this initial elevation, levels gradually returned to pre-operative values (figure 2). Follicle stimulating hormone pulse did not change after surgery. Figure 2 summarizes the data for pre-operative and postoperative FSH concentrations.

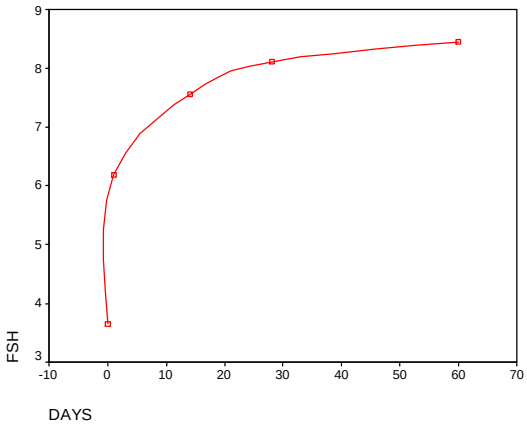

Figure 2: Mean serum FSH levels in women with polycystic ovary syndrome before ovarian surgery, on days 0, the first 60 days after laparoscopic ovarian drilling, and the subsequent early follicular phase. PCOS values are derived from 38 publications comprising a maximum of 1148 patients.

Testosterone

In our two clinical trials we showed that testosterone concentration decreased in the day after LOD in women with OCOD.[43,109] Many clinical trials also reported the same values,[37,56,57,59,61,64,65,67,69,73,99,113] with only one study

showing no significant decrease one day after surgery.[63] An increase in testosterone level followed by a rapid decrease during the first postoperative day was also reported.[62]

Three days after surgery, testosterone level reached a nadir,[57,61,67] followed by a small increase, but failed to reach pretreatment values.

In our studies testosterone level remained low in the first days, weeks, and months after surgery, whereas most articles that reported long-term follow-up results noted that testosterone values decreased over the years.[37,51,57,59,64,65,69,72,80,87,89,93,95,97,99,102,112-116]

A few studies reported no significant change in testosterone concentration after ovarian surgery.[63,78,79,98,117-118]

Responders had significantly lower testosterone levels in our studies,[109,43] and in some other articles,[69,95,96,103,106] whereas many studies found no difference in baseline and post-treatment testosterone values between responders and non responders, or between obese and lean patients.[37,51,66,67,91,104] Only one report noted higher testosterone values post-operatively.[78]

Some studies found no change in testosterone in regularly ovulating women in a control group who underwent diagnostic laparotomy and laparoscopic tubal ligation,[57-61] but other studies found a decrease in testosterone levels after surgery in the control group, although the decrease was less marked than in women with PCO.[37,56,65]

Overall, a substantial reduction of testosterone was seen from the first day after ovarian surgery. Testosterone levels reached a nadir around the third postoperative day and increased gradually thereafter, but without reaching pre-operative values (figure 3).

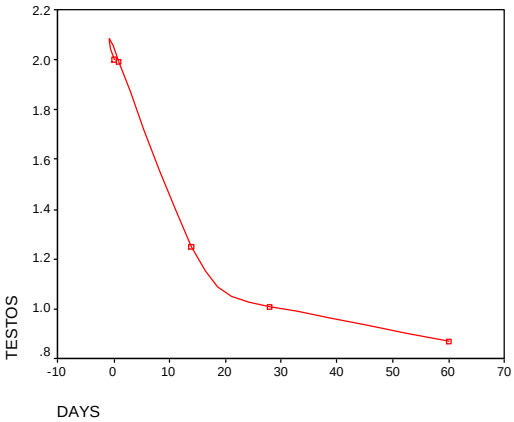

Figure 3: Mean serum testosterone levels in women with polycystic ovary syndrome before ovarian surgery, on days 0, the first 60 days after laparoscopic ovarian drilling, and in the subsequent early follicular phase. PCOS values are derived from 38 publications comprising a maximum of 1148 patients.

Androstenedione

Androstenedione is derived from dehydroepiandrosterone. Its final product is estrogen and progesterone. Serum androstenedione level was significantly higher in women with PCOD than in normally ovulating women. Serum androstenedione decreased significantly on first postoperative day in most studies,[56,58,61,64,67,69,71,85,98] although some of the articles we reviewed reported no significant reduction after surgery.[65,113] Two studies reported an increase in androstenedione during the surgical procedure,[62,71] and one also reported an increase during laparoscopy in the control group.[62]

Many authors found that androstenedione concentration reached a nadir 2-4 days after ovarian surgery,[57,58,61,62,67,71] or weeks to years after surgery. However, there was a tendency for this hormone to increase slightly over time.[57,58,62,64,67,69,71,74,76,80,82,84,87,88,92,97,100,112-115]

A few studies reported no change in androstenedione following ovarian surgery.[65,99,101] Androstenedione concentration was lower on day 0 and after surgery in responders compared with non-responders.[69]

We concluded that a reduction in androstenedione in women with PCOS occurred from the first day after ovarian surgery, but during surgery serum concentration of this hormone was elevated. Androstenedione levels reached a nadir around the fourth postoperative day, and thereafter androgen values increased gradually (figure 4).

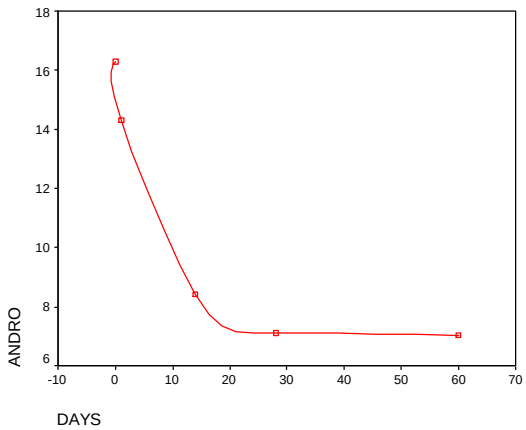

Figure 4: Mean serum levels of androstenedione in women with polycystic ovary syndrome before ovarian surgery, on days 0, the first 60 days after laparoscopic ovarian drilling, and in the subsequent early follicular phase. PCOS values are derived from 38 publications comprising a maximum of 1148 patients

Dehydroepiandrosterone Sulfate

Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) are derived from pregnenolone.

They are secreted predominantly by the adrenal glands and are frequently elevated in PCOS.[8] Both hormones act as an inactive precursor steroid for peripheral conversion into more potent androgens.[119-120] DHEAS concentrations are elevated in some women with PCOD but not in all of them.[20] We,[43,109] and others,[5,56,61,65,98] found a decrease in the DHEAS level the day after surgery, whereas others found no significant changes.[37,60,69,101]

While some authors found a steady decrease in DHEAS values weeks to months post-operatively,[60,61,86,92,97,112] we and many others found no significant difference between pre- and postoperative levels.[37,56,60,65,69,71,74,76,82,84,89,91,95,96,98,101,104,114,117] Some articles showed no difference in DHEAS levels before or after surgery in responders compared with non-responders.[37,69,91,95,121]

In control groups with normal ovulation who underwent laparoscopic surgery, DHEAS levels varied from a decrease on the first day after surgery,[56,65] to no change for up to months after the operation.[37]

In summary, DHEAS decreased significantly from the first day after surgery, followed by an increase during three weeks approximately after treatment (figure 5).

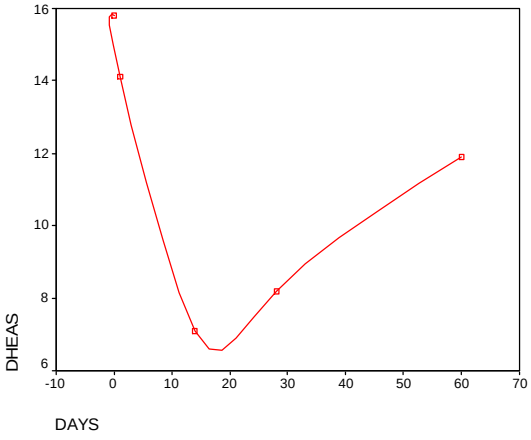

Figure 5: Mean serum levels of DHEAS in women with polycystic ovary syndrome before ovarian surgery, on days 0, the first 60 days after laparoscopic ovarian drilling, and in the subsequent early follicular phase. PCOS values are derived from 38 publications comprising, a maximum of 1148 patients.

17-Hydroxy Progesterone

17-OH progesterone decreased on the first day after LOD in women with PCOS and in regularly ovulating women,[50,69] and subsequently returned to pretreatment levels in patients with PCOS.[69,92,97,100] Only one study in 1988 reported an increase in 17-OH progesterone after surgery.[82]

Estradiol

Estradiol is produced by granulosa cells of the ovary under FSH stimulation. In women with PCOD the level of estradiol remains stable. Estradiol levels also remained stable during the first days after LOD in most studies,[56,58,63,66,69,70,98] but some studies reported a decrease.[57,62,68]

Early and mid-follicular estradiol concentrations during the weeks after LOD were similar to pretreatment levels,[58,59,64,72,96,100,104,110] or were decreased.[74,75]

Late follicular, peri-ovulatory, and luteal estrogen levels were higher than pre-operative levels, especially in responders.[63,69,82,90] No changes in estradiol were reported in regularly ovulating women after laparoscopy.[56]

We conclude that estradiol levels decreased slightly during the first 2 days after LOD and then increased significantly from the fifth day postoperatively and remained high for 2 cycles of follow-up (figure 6).

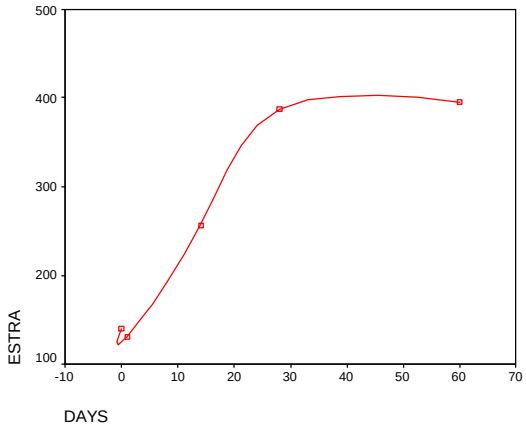

Figure 6: Mean serum levels of estradiol in women with polycystic ovary syndrome before ovarian surgery, on days 0, the first 60 days after laparoscopic ovarian drilling, and in the subsequent early follicular phase. PCOS values are derived from 38 publications comprising a maximum of 1148 patients.

Prolactin

Although many authors reported that prolactin concentration was not altered weeks to years after surgery,[64,51,72,82,86,91,96,98,100,104] we showed that prolactin levels increased on the first postoperative day.[37] Few of the articles we reviewed reported the same result.[37,56-64] Only one article noted a decrease in prolactin level on the first day post-surgery.[77] In our randomized clinical trial, prolactin level remained elevated up to 10 weeks after surgery in women with PCOD who were still anovulatory.[37]

Overall, prolactin level declined dramatically from the first day of LOD and rose again from the second week, and remained at the normal preoperative level thereafter (figure 7).

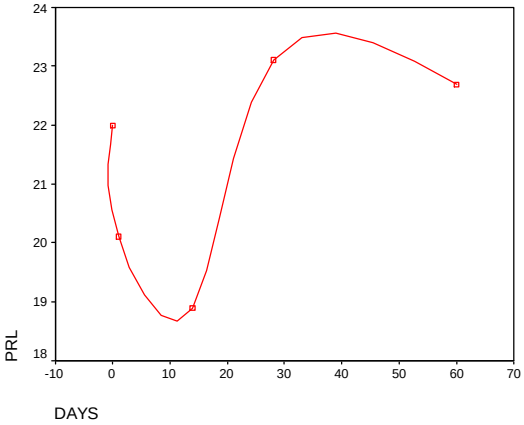

Figure 7: Mean serum levels of prolactin in women with polycystic ovary syndrome before ovarian surgery, on days 0, the first 60 days after laparoscopic ovarian drilling, and in the subsequent early follicular phase. PCOS values are derived from 38 publications comprising a maximum of 1148 patients.

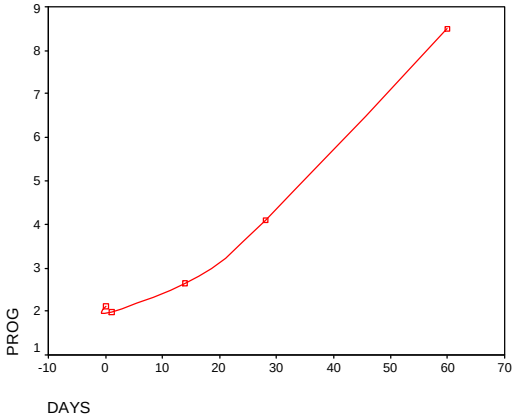

Figure 8: Mean serum levels of progesterone in women with polycystic ovary syndrome before ovarian surgery, on days 0, the first 60 days after laparoscopic ovarian drilling, and in the subsequent early follicular phase. PCOS values are derived from 38 publications comprising a maximum of 1148 patients.

Dihydrotestosterone

On the first day after LOD, dihydrotestosterone (DHT) levels decreased in women with PCOS and in ovulating women in the control group in the follicular phase (56,69), but no change in DHT level was reported by Gjonnaes and Aakvaag weeks to years after surgery.[69,112]

Pretreatment DHT values were lower in responders than non-responders.[69]

Progesterone

The major source for progesterone secretion is the corpus luteum, so the best time for progesterone assay is the mid-luteal phase of the postoperative cycle. Progesterone concentration remained stable for up to 2 weeks after ovarian surgery and in the subsequent follicular phase.[56,69,100,104]

Ovulatory women showed a decline in progesterone level 8 days after surgery.[71] Three weeks after surgery and during the subsequent luteal phase, progesterone levels rose to above pretreatment values.[69,82,100,112]

To summarize, progesterone levels increased from the luteal phase of postoperative cycles in ovulating women (figure 8).

Antimüllerian Hormone

Antimüllerian hormone is expressed in pre- and small antral follicles and acts as a marker of ovarian reserve. High serum levels are found in women with polycystic ovaries, consistent with their increased number of small follicles. Serum antimüllerian hormone is strongly correlated with the number of antral follicles, and is more strongly related to ovarian reserve than other known markers such as day-3 FSH, inhibin-B, or estradiol.

No studies have examined the effect of LOD on serum Antimüllerian hormone levels in women with PCOD.

Ovulation and Conception after Ovarian Drilling

Numerous published case studies have shown that most women with PCOS who are clomiphene-resistant ovulated after LOD (table1).[35,45,57,59,61,65,67,69,71,72,87,92,95,97,99,118,121,133-135] However, 20-30% of anovulatory women with PCOS failed to respond to LOD.[44] As depicted in table 1, the overall ovulation rate was 79.2 (74.9%-83.5% 95% CI) (figure 9). Of all women who ovulated only 66.6 % (60.8 % -72.4% 95% CI) conceived (table 1, figure 10).

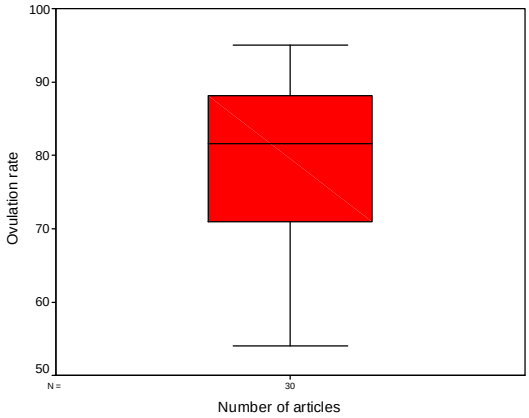

Figure 9: Ovulation rate in women with polycystic ovary syndrome treated with laparoscopic ovarian drilling. The median is marked by a horizontal line in the box. The height of the box indicates the interquartile range. The two lines outside the box indicate the lowest and highest reported values.

Table 1: Ovulation and pregnancy rate after laparoscopic ovarian drilling in different studies

Authors	Year	Number	Ovulation	Pregnancy
Gjonnuess,[34]	1984	62	92%	80%
Aakvag and Gjanness,[69]	1985	58	72%	NA
Choen and Au Debret,[122]	1988	778	NA	31.8%
Green and,[57]	1987	6	83%	66%
Daniell and Miller,[123]	1989	85	71%	56%
Armar et al,[71]	1990	21	81%	52%
Utsunomiya et al,[65]	1990	16	94%	50%
Gurgan et al,[124]	1991	7	71%	57%
Neather et al,[60]	1993	104	86%	70%
Campo et al,[67]	1993	23	56%	43%
Gjonnaess,[125]	1994	252	92%	84%
Kriplani et al,[126]	2001	66	82%	55%
Merchant,[127]	1996	74	88%	84%
Juledi et al,[128]	1997	34	88.2%	70%
Pelosi and Pelossi,[129]	1996	30	83.3%	NA
Felemban,[45]	2000	112	73%	58%
Li et al,[130]	1998	111	97%	56%
Gadir et al,[72]	1990	29	26.5%	43.8%
Tasaka,[59]	1990	11	91%	36%
Kovacs et al,[99]	1991	10	70%	20%
Armar and Iachelin,[131]	1993	50	86%	66%
Gjoannaess,[125]	1994	252	92%	84%
Naether et al,[132]	1994	145	86%	70%
Farquhar et al,[118]	2002	29	54%	28%
Amer et al,[87]	2002	30	80%	47%
Malkawi et al,[92]	2003	97	83.5%	59.8%
Parsanezhad et al,[43]	2003	52	73.1%	NA
Amer et al,[133]	2004	200	78%	50%
Cleemann et al,[121]	2004	57	NA	61%
Bayram,[134]	2004	83	70%	78%
Palomba,[135]	2005	55	76.4%	56.4%
Malkawi and Qublam,[97]	2005	63	57%	59.8%
Kucuk and Kilic-Okmen,[96]	2005	22	95%	54.5%
Api,[95]	2005	45	NA	64.4%
Parsanezhad et al,[109]	2005	36	55.6%	NA

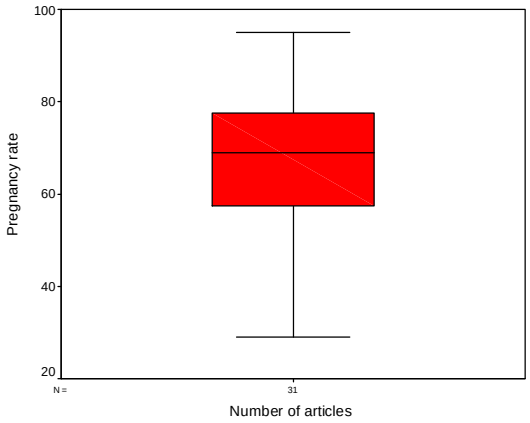

Figure 10: Pregnancy rate in women with polycystic ovary syndrome treated with laparoscopic ovarian drilling. The median is marked by a horizontal line in the box. The height of the box indicates the interquartile range. The two lines outside the box indicate the lowest and highest reported values.

Considerable variation in the reported outcome of LOD is caused by both variations in techniques and—to a large extent—heterogeneity in the patients samples. Although the diagnostic criteria were recently revised, the criteria that have been used to diagnose the syndrome varied from continent to continent. Whereas in Europe and England (England is a part of Europe) the diagnosis was primarily based on ovarian morphology as assessed by transvaginal ultrasound scan, in North America it was based on biochemical features, especially hyperandrogenemia and chronic anovulation.

In our two randomized clinical trials we concluded that ovulation and pregnancy rates after LOD were highly correlated with postsurgical prolactin levels, presurgical LH/FSH ratio, pre-operative androgen level, and post-operative ovarian stromal blood flow.[43,109]

Recently, Amer and colleagues,[133] studied the clinical response to LOD in 200 patients with PCOS. They found that women with marked obesity, marked hyperandrogenemia or a history of infertility longer than 3 years seemed to be resistant to LOD.

Although pretreatment luteinizing hormone levels did not seem to influence the ovulation rates of LOD once ovulation was achieved, luteinizing hormone levels appear to have a significant impact on pregnancy rates.

Van Welly and others,[136] did not find any correlation between either androgen level or body mass index (BMI) with ovarian response following LOD, but they showed that women

with low LH/FSH ratios and low glucose level before the operation were more likely to have persistent anovulation.[136] In their study LH/ FSH level was found to be the strongest predictor of ovarian response after electrocautery.[136]

It was shown,[136] that women with an LH/ FSH ratio below 2 were more likely to be anovulatory after operation.

Using life table analysis, Duleba and Stegmann reported that younger age and lower body mass index are predictive factors for pregnancy after LOD.[91,137]

Using life table analysis, Li and co-workers in a series of 111 patients, reported cumulative pregnancy rates of 54%, 62%, and 68% respectively at 12, 18, and 24 months follow-up.[130] Felemban and others in 112 CC-resistant women, reported cumulative pregnancy rates of 36%, 54%, 68%, and 82% respectively at 6, 12, 18, and 24 months following the procedure.[45]

Some studies have elucidated additional advantages of LOD. Patients who were resistant to CC may respond to the medication after the operation.[71,99] Sensitivity to exogenous gonadotropin treatment is increased,[35,78,87,125,131] and associated with a lower duration of stimulation, lower total dose of gonodotropins and higher pregnancy rates.

Laparoscopic ovarian drilling has been reported to decrease serum concentration of vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1), which are typically increased in patients with PCOS.[90]

Ovarian Blood Flow after LOD

Women with PCOS have significant increases in intra-ovarian and uterine artery hemodynamics compared with women with normal ovaries.[138-141] The difference in ovarian stromal blood flow is likely to be resulted from a primary disorder within the polycystic ovary or it may cause PCOS.[142] These women have increased ovarian stromal blood flow velocity in the early follicular phase of the normal menstrual cycle.[142-143] The pathophysiology of abnormal ovarian blood flow in PCOS is not clearly understood.[93]

In a clinical trial,[93] we showed that Doppler indices of ovarian stromal blood flow decreased significantly after LOD, and these changes were significantly correlated with hormonal changes and subsequent ovulation. We therefore hypothesized that a decline in ovarian stromal blood flow velocity could be the result of a direct electrical or thermal effect of LOD.

On the other hand Wu, Amin and their colleagues also concluded that ovarian blood flow velocity was reduced after LOD,[90,104] but Vizer and co-workers showed increased intra-ovarian blood flow after the procedure.[144] More studies should be done to investigate the correlation between LOD, ovarian blood flow, and ovarian steroidogenesis.

Complications of LOD

Complications associated with LOD include those associated with anesthesia, surgical access (laparoscopic surgery) and ovarian drilling procedures which include the use of electrical or laser energy. The patients may experience bleeding from drilling sites or laceration of the utero-ovarian ligament, and the use of excessive energy will destroy large numbers of follicles, resulting in decreased ovarian reserve. Introduction of energy through the electrode deep into the ovary may destroy hilar blood vessels, resulting in premature ovarian failure caused by necrosis.

The most likely risk of LOD may be postoperative adhesions. In our unpublished study of cesarean section and second-look laparoscopy, we found that approximately 40% of women with PCOD who underwent LOD had adnexal adhesions, although they were too filmy? to interfere with their future fertility. During cesarean section, Gjonnaess and colleagues found no adhesions in women with PCOD who underwent LOD.[35]

Reported rates of adhesion vary widely from 0% to 85% (table 2),[32,45,132,145-149] with a mean rate of 22.7% (95% CI 21.4%-24%) (figure11).

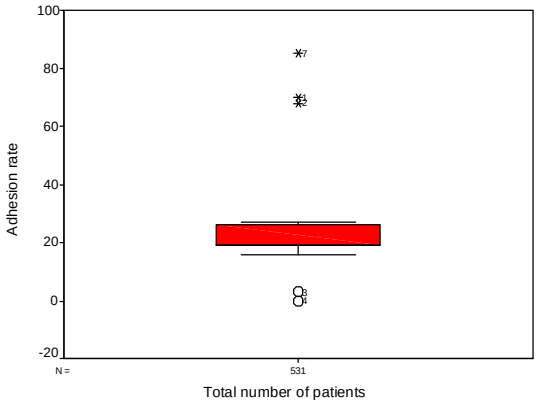

Figure 11: Adhesion rate in women with polycystic ovary syndrome treated with laparoscopic ovarian drilling. The median is marked by a horizontal line in the box. The height of the box indicates the interquartile range. The two lines outside the box indicate the lowest and highest reported values.

The diversity of the rates of adhesion formation may be due in part to variations in techniques. Differences in the interpretation of the findings of second-look surgery to assess

Table 2: Adhesion formation after laparoscopic ovarian drilling in different studies

Authors	Year	Number	Adhesion (% of Patients)
Weise et al,[145]	1991	10	70
Gurgan et al,[146]	1992	20	68
Corson and Grochmal,[147]	1990	30	3
Portuondo et al,[32]	1987	24	0
Naether et al,[132]	1994	62	19
Felemban et al,[45]	2000	15	27
Gurgan et al,[124]	1991	7	85
Naether et al,[60]	1993	133	26
Naether and Fischer,[148]	1993	199	19
Dabirachrafi et al,[149]	1991	31	16

adhesion formation seem to be more frequent with laser than electrocautery techniques, and the use of adhesion barriers has not reduced the incidence. Abdominal lavage and the use of insulated needle electrocautery may help to reduce its occurrence.[45,60]

Greenblatt and Casper (1993) observed peri-ovarian adhesions of varying severity in eight women after LOD. The use of an "interceed" barrier to prevent adhesions had no protection effect.[150]

Ovarian Surgery for Androgenic Symptoms

In clinical practice, patients with PCOS also need medical therapy for excessive hair-growth, hair loss, and acne. Some women do not respond to conservative medical treatment for androgenic symptoms, and many women are reluctant to accept long-term medical treatment because of potential side-effects. Therefore the surgical approach has been proposed as a safe long-term treatment strategy. Johnson and Wang,[151] evaluated 19 reports of improvements in androgenic symptoms after LOD. They concluded that in spite of the decrease in androgen level in most studies, LOD had no effect on androgenic symptoms.

Does it Need to Repeat Sx?

The endocrine changes after LOD persist for a long time. Gjonnaess et al.[82] reported that over 50% of those who underwent LOD continued to ovulate for more than 10 years.

Amer and co-workers,[87] also reported the long-term effects of LOD in 116 anovulatory infertile women. They found that 67% of these patients had regular menstruation during the first year after LOD, and 50% of the total group continued to have regular menstruation 7 years later. They also reported a decrease in androgen and LH levels, and also in LH/FSH ratio, which remained low for 3 years after procedure.

Recently, Lunde and colleagues,[152] presented a follow-up study on fertility and menstrual pattern in 149 patients 15-25 years after ovarian wedge resection, done between 1970 and 1980. Of the 129 patients who attempted pregnancy, 54% had one or more live births resulting from spontaneous pregnancies, and 74% of the women who used ovarian stimulation after LOD had one or more live birth. Regarding menstrual pattern, 82 of 103 premenstrual women menstruated regularly for more than 15 year after the operation.

Conclusion

Compared with medical induction of ovulation, additional advantages of LOD are; just needs to be done only once, no need to do intensive follicular and hormonal monitoring, and there is no danger of multiple ovulation or ovarian hyperstimulation. Laparoscopic ovarian drilling is a useful treatment for anovulatory women with PCOS who fail to respond to CC, hypersecrete LH, or need laparoscopic assessment of their pelvis, or who live too far away from the hospital to be able to attend for intensive monitoring required for gonadotropin therapy.

Surgery has its own risks and must be performed only by expert laparoscopic surgeons. The main complications of LOD are postoperative adhesion formation and the potential risk of reduction in viable ovarian tissue (Ovarian reserve), with the possibility of inducing premature ovarian failure. The chance of achieving successful pregnancy within 6 months is lower than with carefully conducted ovulation induction with gonadotropin, but adjuvant ovulation-inducing agents are given for women who do not initially respond. The 12-month pregnancy rate can consequently approach that obtained with gonadotropin therapy as long as patients are carefully selected on the basis of indication. Meticulous technique is used to establish surgical access and perform drilling in order to avoid the complications mentioned earlier. In the future, lifestyle modification (diet and exercise) and metformin, which is currently being investigated, may well reduce the need for LOD.

Conflict of Interest: None declared

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