

## Effect of laparoscopic ovarian drilling (LOD) in treatment of polycystic ovarian syndrome (PCOS)

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### Abstract:

**Background:** Laparoscopic ovarian drilling (LOD) has been widely used to induce ovulation in women with polycystic ovarian syndrome (PCOS), but still there is considerable controversy about its effect.

**Objective:** To evaluate the effectiveness of laparoscopic ovarian drilling in women with polycystic ovarian syndrome and to note clinical outcome.

**Methods:** A prospective study has been carried out in AL-Yarmouk teaching hospital, Abu-Greab General hospital and Private hospitals. From August 2011 to April 2015, 95 women with polycystic ovarian syndrome were diagnosed and treated by LOD after failure of medical treatment and compared the result before and after LOD.

**Results:** After LOD, 58 out of 95 patients were ovulated with overall ovulation rate was 61%. Twenty (34.48%) out of 58 women had a conception without additional treatment. The LH: FSH ratio, mean serum concentration of LH and testosterone and free androgen index decreased significantly after LOD and remained low during the follow-up periods.

**Conclusions** Laparoscopic ovarian drilling was a safe, effective surgical technique, and widely accepted as the preferred second line of treatment in PCOS.

**Keywords:** Polycystic ovary, Laparoscopic drilling

### Introduction

Laparoscopic ovarian drilling (LOD) is

Surgical technique dedicated for the treatment of polycystic ovary syndrome. It consists of performing micro-perforations in ovaries in order to induce ovulation. Polycystic ovary syndrome PCOS is a common endocrine disorder affecting 6-8% of women of reproductive age, and the most common cause (75%) of anovulatory infertility.<sup>[1]</sup> PCOS is defined as a syndrome of ovarian dysfunction along with the cardinal features of hyperandrogenism and polycystic ovary morphology. It is characterized by a varied combination of clinical oligomenorrhoea, hirsutism and obesity, biochemical (increased serum levels of luteinizing hormone and androgens), and sonographic (enlarged polycystic ovaries) features. In women with PCOS presenting with anovulatory infertility, clomiphene citrate is the standard first-line treatment for induction of ovulation. Patients who either remain anovulatory (clomifene citrate resistant) or fail to conceive despite ovulation on clomifene citrate, can be offered laparoscopic LOD is treatment that result in a dramatic lowering of male hormones within days and is often performed in women who have polycystic ovary syndrome PCOS. Studies have shown that up to 80% of patients will benefit from such treatment. Many women who fail to ovulate with clomiphene or metformin therapy will respond when these medications are reintroduced to the system after ovarian drilling.<sup>[3]</sup>

In female ovary follicles are sacs within the ovaries that contain eggs. Normally, a number of eggs are released during each menstrual period. This is called ovulation. In PCOS, instead, they are able to form really small cysts within the ovary. These changes

can contribute to infertility. Another sign of this issue are due to the hormonal imbalance.<sup>[4]</sup>

Women are often diagnosed much more in their twenty or thirty years, but PCOS could also affect teenage girls. The symptoms often begin whenever a girl's periods start. Women with this particular disorder usually have a mother or a sister that has symptoms similar to those of PCOS symptom.<sup>[5]</sup>

Increase LH reduces the chances of conception and increase miscarriage. The preferred treatment has been ovulation induction with clomiphene citrate, with rate of ovulation reported at 70% after first treatment, if no response, treated with gonadotrophins. In 1935, Stein Leventhal proposed wedge resection of the ovaries as treatment option for clomiphene resistant polycystic ovarian syndrome. This treatment was abandoned because of postoperative peri-ovarian adhesion. So that trends towards minimally invasive laparoscopic surgery which established as second line of treatment.<sup>[6]</sup>

Laparoscopic ovarian drilling is really a surgical treatment that may trigger ovulation in females with polycystic ovary syndrome who have not responded to weight reduction and fertility medication. Electrocautery or laser can be used to eliminate servings of the ovaries.<sup>[7]</sup>

LOD has been widely used in many reproductive centers as treatment of choice in clomiphene-citrate resistant PCOS patients. More recently, the efficacy of LOD in inducing ovulation and generating pregnancies has been confirmed in large randomized clinical trials.<sup>[8]</sup> Many authors have reported high ovulation (80%) and pregnancy rates (60%) following LOD.<sup>[9]</sup>

### Patients and Methods

A prospective study has been carried in AL-Yarmouk teaching hospital/department of

Surgery, Abu-Greab General hospital and private hospitals. From August 2011 to April 2015, 110 women with PCOS were treated by laparoscopic ovarian drilling after failure of medical treatment for 6 months. 15 out of 110 patients were excluded from the study, because of their lost from reliable follow-up period and declined to participate and 95 women included in this study. The diagnosis of those women with PCOS was based on two out of three of the following criteria:

- 1-Amenorrhea, oligomenorrhea and anovulation.
- 2-Clinical and biochemical evidence of elevated serum androgen levels [testosterone  $\geq 2.5$  nmol/l, androstenedione  $\geq 10$  nmol/l or free androgen index (FAI)  $> 4$ ]. LH, LH:FSH ratio was greater than two.
- 3-Ultrasound evidence of PCOS: ovarian stromal hypertrophy and multiple small (2-8mm) more than 10 follicles arranged in the periphery.

All patients have been followed up by usual investigations such as complete blood picture, hormonal assay, u/s, with routine investigation of operation such as CXR, ECG and patient consent. All women had anovulatory infertility of more than 1 year duration, based on U/s finding and hormonal assay, and assessment of tubal patency by hysterosalpingography and exclusion of male factor by seminal fluid analysis, had been unsuccessfully treated with clomiphene citrate (CC) at up to 150 mg/day for 5 days in the early follicular phase of the menstrual cycle and/or FSH injection prior to LOD. Some of those patients ovulated, but failed to conceive after CC treatment for 6-9 months. In addition, other patients had received HCG therapy for trigger ovulation and failed to conceive.

Ovarian drilling, done during laparoscopy, is a procedure in which an electrosurgical needle punctures the ovary 5 to 10 times in each ovary depending on its size, each measuring 4mm in diameter and 7-8 mm in depth. This procedure is done under short general anesthesia. Patient can leave the hospital on the same day of surgery. Ovarian drilling is usually done through a laparoscope (small incision). The surgeon makes a small cut (incision) in the abdomen with inflation of carbon dioxide gas so that he or she can insert the viewing instrument without damage to the internal organs. The surgeon looks through the laparoscope at the internal organs were found to have enlarged ovaries with a smooth pearly white appearance. This appearance was presumed to be due to the lack of sites of ovulation that typically would leave scars. Surgical instruments may be inserted through the small incision. The ovaries are identified

and 5-10 holes made in each ovary with a fine hot diathermy probe. Patients were observed in a ward for any possible complications and then discharge home.

Following ovarian drilling, women were asked to keep a record of their menstrual cycle. If the patient started a menstrual period within 6 weeks of the surgery, a blood sample was taken on day 2 of that cycle for measurement of serum concentrations of LH, FSH, Testosterone, androstenedione and FAI. Another sample was taken on day 21 of the same cycle for measurement of progesterone. Ovulation was diagnosed when the progesterone level was  $\geq 30$  nmol/l. If spontaneous menstruation did not occur, a random blood sample was taken to measure all the above hormones at 6 weeks following surgery.

If ovulation was achieved either spontaneously or with help of CC, patients were followed-up until they conceived or for up to 12 months after LOD.

Serum hormonal concentrations were measured using well-established assays, which have been validated in our laboratory at the department of clinical chemistry.

The endocrinological & ultrasonographic data before and at different intervals (1-3 years) after LOD were documented.

Our study was carried out to evaluate the effectiveness of laparoscopic ovarian drilling in PCOS and to note the clinical outcomes like ovulation and pregnancy rates.

#### **Statistical analysis:**

Statistical analysis was performed using the soft-ware SPSS and chi-square test. A p-value of  $< 0.05$  was considered significant.

#### **Results:**

A very rapid response has been reported following LOD in our study, with ovulation occurring within 2-4 weeks and menstruation within 4-6 weeks in the responders. During the period of this study, 43(45.26%) out of 95 patients ovulated spontaneously after LOD and a further 15(15.78%) patients ovulated after the addition of CC treatment, giving an overall ovulation rate of 58(61.04%) for about 3 years. Restoration of regular ovulatory cycle occurs in about two-thirds of cases. 30(51.72%) out of 58 women, had a conception leading to live birth without additional treatment, whereas 20(34.48%) women needed further medical treatment to do so, 10 needed FSH and IUI, 9 needed CC, 1 needed IVF treatment and 8 women had no conception. Thus LOD, resulted in a significant lower need for stimulated cycles to reach a live birth. After surgery, ovulation occurs spontaneously in 70-90% of women and the probability of

pregnancy after one year is in the region of 40-60%. There is no increased risk of multiple pregnancy or induction.

The serum concentration of LH and the LH:FSH ratio decrease significantly after LOD and remained low during the follow-up period. Comparison of the proportion of women with high LH concentration ( $\geq 10$  IU/l) before and after LOD showed a significant (p-value less than 0.01). There was no significant change in the serum concentrations of FSH after LOD

While the main serum testosterone concentration and FAI (free androgen index) decreases significantly after LOD and remained low throughout the follow-up periods. With p-value less than 0.05 at that time. The percentage of women with FAI  $\geq 4$  showed a significant p-value less than 0.01 decreases shortly after LOD. And the value remains low during follow-up period.

The result show that women with marked obesity (BMI $\geq 35$ kg/m<sup>2</sup>) achieved significantly (p<0.05) lower ovulation and pregnancy rate while women with normal or slightly elevated BMI (<29kg/l) achieved better ovulation and pregnancy rate in response to LOD.

The possible impact of age and BMI on the follow-up was analysed as age at the time of follow-up had a significant impact on serum concentration of LH after LOD. Women  $\geq 36$  years old had significant lower levels of LH (7.5IU/l) than those (10.4IU/l) of younger

women ( $\leq 35$  years) with p-value 0.0347. Age at the time of long-term follow-up did not have a significant impact on the serum concentration of FSH. With p-value 0.0134 As far as androgen levels are concerned, age did not have a significant impact on FAI and the serum concentration of testosterone and androgen at the time of long-term follow-up. There was an inverse relationship between the duration of infertility and the chances of success of LOD. Indeed the duration of infertility has been found to be the most important independent predictor of success of LOD. 72% chance of conception in women with infertility of <3 years while only 18% chance of conception in women with infertility of >6 years with p-value 0.0132.

Intraoperative complications of LOD are rare and include damage to the utero-ovarian ligament, bleeding from ovary at the cautery points and thermal injury to the bowel. Postoperatively, the main drawback of LOD is iatrogenic adhesion formation, which does not seem to affect the pregnancy rate after LOD. Nevertheless, all precautions should be taken to minimize adhesion formation. This can be achieved by minimizing thermal injury to the ovarian surface, irrigation and instillation of crystalloid solution at the end of the procedure and minimize the number of punctures made and deliver the energy away from the ovarian hilum.

**Table 1 The characteristic of 95 women with PCOS who had LOD for anovulatory infertility**

Characteristic	No. of cases	Mean $\pm$ SD	Range	P- value
Age( years)	95	33.3 $\pm$ 4.4	21-45	0.0134
Body mass index(Kg/m)	93	26.7 $\pm$ 4.9	19-41	0.0347
Duration of infertility (years)	93	3.1 $\pm$ 2.1	1-12	0.0132
Serum LH(IU/L)	75	14.4 $\pm$ 7.5	1.8 -49.0	0.01
Serum FSH(IU/L)	75	5.4 $\pm$ 1.5	1.2 -10.4	0.05
Serum LH:FSH ratio	75	2.7 $\pm$ 1.2	0.4 5.7	0.05
Serum testosterone(nmol/l)	78	2.6 $\pm$ 1.3	0.8-6.1	0.05
Serum androgen(IU/l)	78	9.8 $\pm$ 4.0	1.7- 27.1	0.05
Free androgen index	79	8.6 $\pm$ 8.2	1.0- 36.9	0.01

**Table 2: ovulation and pregnancy rates in 95 patients after LOD.**

parameter	category	No.	Ovul.rate%	Preg.rate%	p-value
Age (years)	≤35	85	78	50	
	35 >	10	70	50	
BMI(Kg/m <sup>2</sup> )	29 >	80	80	55	0.05
	29-34	10	75	40	
	34>	5	40	10	
Menstrual pattern	Regular	15	85	30	0.01
	Oligomen	70	70	50	
	Amenorrhea	10	65	40	
LH(IU/L)	10<	30	80	40	0.05
	10-19.9	50	70	50	
	≥20	15	75	55	
LH/FSH	2>	30	78	40	0.01
	2-3.9	60	75	50	
	≥4	5	80	50	
Testosterone	2.6 <	60	85	50	0.001
	2.6-4.4	30	75	45	
	≥4.5	5	30	10	
FAI	4<	40	90	60	0.01
	4-14.9	50	80	40	
	15 >	5	30	10	
Duration of infertility (years)	3<	70	80	75	0.0132
	3-6	20	75	30	
	6>	5	40	10	

## Discussion

In this study, we have evaluated the impact of various clinical, biochemical and ultrasonographic features of PCOS on clinical outcome of LOD. Our data showed three main factors to have a significant impact on the efficacy of LOD, namely BMI, hyperandrogenism and duration of infertility. Women with marked obesity (BMI  $\geq 35$  kg/m<sup>2</sup>), marked hyperandrogenism (testosterone  $\geq 4.5$  nmol/l, FAI  $\geq 15$ ) and /or with duration of infertility longer than 3 years seem to be resistant to LOD. We confirm the previously reported endocrine changes shortly after LOD, including lowering of the LH:FSH ratio and the serum concentrations of LH and androgens and these endocrine changes are produced by ovarian drilling rather than age, since the serum concentrations of LH and androgens in women who underwent LOD were significantly low at the period of follow-up (1-3 years).<sup>[10]</sup>

The proportion of women with high LH concentrations (>10 IU/l) decreased significantly from 70 to 33% shortly after LOD, but increase back to 45% during the medium-term follow-up (1-3 years). This decreased may be explained by a phenomenon related to the natural history of the disease, in that the clinical and endocrine features of PCOS become less pronounced with advancing

age. This is further supported by the observation that older women ( $\geq 36$  years) at the time of follow-up had significantly lower serum LH concentrations compared with younger (<36 years) women.<sup>[11]</sup>

This observation is comparable with an earlier report by Gjonnaess who demonstrated that the endocrine changes after LOD were stable for long follow-up period. However, we confirm in this study that these long-term endocrine changes are produced by ovarian drilling rather than the effect of advancing age, since the serum concentration of LH and androgens in women who underwent LOD were significantly lower than those of the comparison group at corresponding periods of follow-up.<sup>[12]</sup> Our data showed that increasing serum levels of testosterone and/or increasing FAI are associated with a statistically significant reduction of the chances of success of LOD. Furthermore, a subgroup of PCOS women with marked hyperandrogenism (testosterone  $\geq 4.5$  nmol/l, FAI  $\geq 15$ ) appeared to be resistant to LOD. This is in disagreement with the result of Abdel-Gadir et al which showed that androgen levels had no impact on the success of LOD.<sup>[13]</sup>

PCOS women with BMI  $\geq 35$ kg/m<sup>2</sup> achieved significantly lower ovulation and pregnancy rates after LOD compared with moderately overweight and normal weight

women. More recently, in accordance with our observations, Duleba et al.(2003) reported that lean PCOS women ( $BMI \leq 25$  kg/m<sup>2</sup>) achieved higher conception rates than overweight women ( $BMI > 25$  kg/m<sup>2</sup>) after LOD.<sup>[14]</sup> There was an inverse relationship between the duration of infertility and the chances of success of LOD. Indeed the duration of infertility has been found to be the most important independent predictor of success of LOD. Whilst ovulation rates did not show a significant decrease in women with infertility  $\geq 3$  year, conception rates showed a marked decrease. These findings are consistent with our results which showed that women with duration of infertility more than 3 years were less likely to respond to LOD. A possible explanation for this is that women with longer duration of infertility are more likely to have other subtle subfertility factors.<sup>[15]</sup>

Although laparoscopic electrocautery of the ovaries has been shown to be more cost-effective than ovulation induction with gonadotrophin (Bayram et al.2004)<sup>[16]</sup>, fear for possible long-term side effects have been made many clinicians reluctant to offer this treatment. None of women in our study had perioperative complications or an early menopause, which may indicate that electrocautery is a safe technique and that it is unlikely that menopause before 40 years should occur as a consequence of destroying ovarian tissue.<sup>[17]</sup>

Pretreatment LH levels did not seem to influence the ovulation rates of LOD. However, once ovulation is achieved, LH levels appear to have a significant impact on pregnancy rate. LOD responders with higher LH levels ( $\geq 10$  IU/l) have a significantly higher chance of conception than those with lower LH levels. This is agreement with report of S.A.K.Amer<sup>[18]</sup> The importance of this study is that it provides solid evidence for its long-term safety and effectiveness and should thereby convince professionals caring for CC resistant women to offer laparoscopic electrocautery as a safe and effective second line treatment. The importance of this study is that it provides solid evidence for its long-term safety and effectiveness and should thereby convince professionals caring for CC resistant women to offer laparoscopic electrocautery as a safe and effective second line treatment.

### Conclusions

Laparoscopic ovarian drilling is a safe and effective procedure. No need of continuous monitoring as seen with hormonal treatment. No fear of multiple births and ovarian hyperstimulation. LOD increase the sensitivity to gonadotrophins and because of

ease of the procedure and safety it can be used as second line of treatment in PCOS

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