

## Unilateral Versus Bilateral Laparoscopic Ovarian Drilling in Clomiphene Citrate Resistant Polycystic Ovary Syndrome

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**Abstract: Objective:** The aim of the current trial was to compare the efficacy of unilateral versus bilateral LOD in women with CC-resistant PCOS as regard regularity of menses and successful ovulation within 3 months following laparoscopy. **Methods:** The study included women who had a diagnosis of clomiphene-citrate-resistant polycystic ovarian syndrome (CC-resistant PCOS) and planned for laparoscopic ovarian drilling (LOD). In all included cases, a three-puncture laparoscopy was performed under general anesthesia. Ovarian drilling was performed using unipolar diathermy needle. The primary outcome was documented ovulation through a midluteal serum progesterone > 3 ng/ml three months after laparoscopy. **Results:** A total of 60 women were included in the study; and randomized equally into one of the two groups: unilateral versus bilateral ovarian drilling. There was no significant difference between women of both groups regarding regularity of menses within 3 months following LOD. In each group, individually, there was a significant rise in basal serum FSH, a significant reduction in basal serum LH and a significant rise in midluteal serum progesterone when 3-month post-LOD levels were compared to pre-LOD levels. These significant changes were comparable in both groups. **Conclusion:** Unilateral LOD seems to be as effective as bilateral LOD in terms of restoration of regular menstrual pattern and ovulation, as evident by the midluteal serum progesterone.

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### 1. Introduction:

Polycystic ovary Syndrome (PCOS) is the most common cause of anovular infertility being responsible for almost 70% of such cases<sup>[1]</sup>. Medical induction of ovulation with clomiphene citrate (CC), despite being the drug of choice in induction of ovulation in those cases, is not always successful, with an approximate 20% rate of the so-called CC resistance. One treatment option for women who are CC-resistant is induction of ovulation using gonadotropins. Gonadotropin therapy is often characterized by over-production of follicles and is, therefore, associated with higher risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies<sup>[2]</sup>. The second alternative to gonadotropin therapy is the laparoscopic ovarian drilling (LOD)<sup>[3]</sup>. A recent study<sup>[4]</sup> even suggested that LOD could be recommended as a first line if laparoscopy is indicated for other reasons in these women and as an adjunct to CC treatment. It has been shown that LOD both induces ovulation and remarkably improves responsiveness of the ovaries to the CC in previously-labeled CC-resistant women<sup>[5,6]</sup>. Benefits of LOD include the eliminated need for cycle monitoring and the low risk of multiple pregnancies and OHSS<sup>[3]</sup>. LOD is not without hazards, however. Tubo-ovarian adhesions and theoretical risk of premature ovarian failure (POF) following LOD are of concern. The

standard LOD includes drilling of both ovaries. It has been suggested by some authors that unilateral rather than bilateral ovarian drilling would have similar benefits, with lower risk of adhesions and POF<sup>[7]</sup>. The aim of the current trial was to compare the efficacy of unilateral versus bilateral LOD in women with CC-resistant PCOS as regard regularity of menses and successful ovulation within 3 months following laparoscopy.

### 2. Patient and Methods:

The current study was conducted at Ain Shams University Maternity Hospital during the period between February 2010 and September 2010. The study included women attending the outpatient infertility clinic with a diagnosis of clomiphene-citrate-resistant polycystic ovarian syndrome (CC-resistant PCOS) and planned for laparoscopic ovarian drilling (LOD). PCOS was diagnosed according to the Rotterdam criteria<sup>[8]</sup>, by presence of two of the following three criteria (after exclusion of related disorders of hyperandrogenism like congenital adrenal hyperplasia): oligomenorrhea and/or anovulation; clinical and/or biochemical signs of hyperandrogenism; and transvaginal sonographic appearance of polycystic ovaries. Oligomenorrhea was defined as cycle intervals of more than 35 days. Anovulation was defined if mid-luteal serum progesterone was less than 3 ng/ml. The

presence of polycystic ovaries is established when at least one ovary has either  $\geq 12$  follicles measuring 2–9 mm in diameter tightly spaced along the periphery of the ovary and/or an ovarian volume of  $>10 \text{ cm}^3$  by transvaginal ultrasonography<sup>[9]</sup>. CC resistance was identified when the patient failed to respond in terms of ovulation to an incremental dose of clomiphene citrate up to 150 mg per day<sup>[7]</sup>. Basal serum levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) and midluteal serum progesterone were assayed in included women prior to laparoscopy. In all included cases, a three-puncture laparoscopy was performed under general anesthesia. Ovarian drilling was performed using unipolar diathermy needle (Karl Storz®, ND, Germany). The drilling needle was used to penetrate the ovarian capsule at right angle to a standard depth of 8 mm at 4 points with an initial 60-W cutting current to allow penetration of the ovarian surface followed by a 40-W coagulation current for 4 seconds. The included 60 women were randomized into one of two groups: group I, in who unilateral ovarian drilling was performed; and group-II, in whom bilateral ovarian drilling was performed. The primary outcome was documented ovulation through a midluteal serum progesterone  $> 3 \text{ ng/ml}$  three months after laparoscopy. Secondary outcomes included regularity of menstrual cycles and basal levels of serum FSH and LH within three months after laparoscopy.

#### Statistical Analysis

Statistical analysis was performed using Microsoft® Excel® version 2010 and Statistical Package for Social Sciences (SPSS®, Inc., Chicago, IL, USA) for Windows version 15.0. Data were described as range, mean and standard deviation (for numeric variables); or number and percentage (for categorical variables). Difference between two unrelated groups was estimated using independent student's t-test (for numeric variables) or chi-squared test (for categorical variables). Difference between two related numeric

groups was estimated using paired student's t-test. Significance level was set at 0.05.

#### 3. Results

A total of 60 women were included in the study; and randomized equally into one of the two groups: unilateral versus bilateral ovarian drilling. The mean age of included women was  $27.23 \pm 2.11$  years (range: 24 – 32 years). The mean duration of infertility was  $3.01 \pm 0.94$  years (range: 2 – 5 years). Of the included 60 women, 14 (23.3%) had amenorrhea, while 46 (76.7%) had oligomenorrhea. The mean body mass index (BMI) was  $29.8 \pm 2.8 \text{ Kg/m}^2$  (range: 26 – 40  $\text{Kg/m}^2$ ). There were no significant differences between women of both groups regarding age, duration of infertility, irregularity of menses and BMI. There were no significant differences between women of both groups regarding initial (pre-laparoscopy) serum levels of basal FSH, basal LH and midluteal progesterone (Table-1). There was no significant difference between women of both groups regarding regularity of menses within 3 months following LOD [21/30 (70%) vs. 23/30 (76.7%), respectively,  $p=0.826$ ] (Table-2). The rate of documented ovulation (through a midluteal progesterone  $> 3 \text{ ng/ml}$ ) 3 months following LOD was slightly lower in women who had unilateral LOD when compared to those who had bilateral LOD [20/30 (66.7%) vs. 22/30 (73.3%), respectively]; this difference was, however, not significant ( $p=0.573$ ) (Figure-1). There were no significant differences between women of both groups regarding serum levels of basal FSH, basal LH and midluteal progesterone measured 3 months post-LOD (Table-2). In each group, individually, there was a significant rise in basal serum FSH, a significant reduction in basal serum LH and a significant rise in midluteal serum progesterone when 3-month post-LOD levels were compared to pre-LOD levels. These significant changes were comparable in both groups (Table-2).

**Table-1 Post-Laparoscopic Ovarian Drilling Hormonal Profile in Included Women**

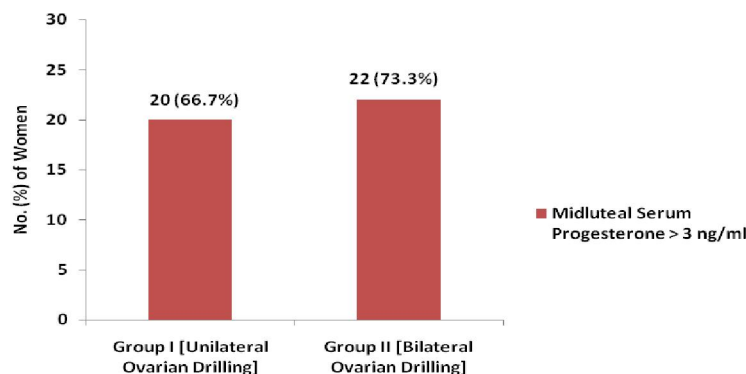
		Group I [Unilateral Ovarian Drilling] (n=30)	Group II [Bilateral Ovarian Drilling] (n=30)	P*
Basal serum FSH (mIU/ml)	Pre-LOD	2.6 – 11 6.02 ± 2.35	2.8 – 9.4 6.2 ± 1.4	0.719 NS
	Post-LOD	4.8 – 10.8 6.89 ± 1.3	3.8 – 9.9 7.01 ± 1.6	0.751 NS
	P**	0.032 S	0.008 S	
Basal Serum LH (mIU/ml)	Pre-LOD	3.3 – 10.1 7.2 ± 1.92	3.7 – 10.3 7.01 ± 1.5	0.671 NS
	Post-LOD	3.1 – 8.4 5.8 ± 1.69	2.8 – 8.1 5.7 ± 1.7	0.820 NS
	P**	<0.001 HS	<0.001 HS	
Midluteal Serum Progesterone (ng/ml)	Pre-LOD	0.58 – 1.8 1.1 ± 0.33	0.65 – 1.79 1.2 ± 0.35	0.259 NS
	Post-LOD	1.1 – 5.9 4.6 ± 1.2	1.5 – 5.9 4.3 ± 1.16	0.329 NS
	P**	<0.001 HS	<0.001 HS	

Data presented as range, mean  $\pm$  SD \* Difference between Groups I and II – Analysis using independent student's t-test  
 \*\* Difference between Pre-LOD and Post-LOD Levels – Analysis using paired student's t-test  
 FSH follicle stimulating hormone LH luteinizing hormone LOD laparoscopic ovarian drilling NS non-significant – S significant – HS highly significant

**Table-2 Post-Laparoscopic Ovarian Drilling Menstrual Regularity in Included Women**

Post-LOD	Group I [Unilateral Ovarian Drilling] (n=30)	Group II [Bilateral Ovarian Drilling] (n=30)	P
<b>Menstrual Pattern</b>			
Regular	21 (70%)	23 (76.7%)	0.826 NS
Oligomenorrhea	6 (20%)	5 (16.7%)	
Amenorrhea	3 (10%)	2 (6.7%)	

Analysis using chi-squared test  
 LOD laparoscopic ovarian drilling  
 NS non-significant



**Figure-1 Bar-Chart showing Difference between Groups regarding Documented Ovulation through Midluteal Serum Progesterone**

#### 4. Discussion

In the current trial, 21 (70%) women of those who had unilateral LOD restored their regular menstrual cycles after unilateral ovarian drilling, in contrast to 23 (76.7%) women of those who had bilateral LOD; an obviously non-significant difference. LOD has been evidently shown to clinically improve outcomes in women with PCOS in terms of regular menstrual cycles. In a study conducted on 66 women with oligo/amenorrhea due to PCOS, 53 (80.3%) showed a regular menstrual cycle post-laparoscopy<sup>[10]</sup>. In a study similar to the current one, Roy et al. randomized 44 women into either unilateral or bilateral ovarian drilling. The rates of regular menstrual cycles following LOD were 72.7% and 81.8%, respectively ( $p=0.760$ )<sup>[7]</sup>. Restoration of regular menstrual cycles is a good clinical indicator of resumption of normal ovulatory function. This has been biochemically proven through a significant rise in midluteal serum progesterone 3 months post-LOD in both women who underwent unilateral or bilateral drilling. The difference between both groups regarding the midluteal serum progesterone was not significant, denoting, along with the close rates of regular menstrual cycles following LOD, a comparable efficacy of unilateral and bilateral drilling regarding induction of ovulation.

Similar conclusions were reached by similar previous studies<sup>[7,11-13]</sup>. LOD has been associated with reduction in basal serum LH level in women with PCOS; a finding of the previous and current studies<sup>[7,11,13-14]</sup>. High basal serum LH has been linked to CC resistance in women with PCOS. Reduction in basal serum LH was known to be a marker of good response to LOD<sup>[7,13,15]</sup>. One of the possible major drawbacks of LOD is the risk of diminished ovarian reserve and premature ovarian failure (POF)<sup>[16]</sup>. In the current study, despite being short-term, LOD was associated with significant rise in basal serum FSH; the rise was no significantly different between women who underwent unilateral and those who underwent bilateral ovarian drilling. However, again, the results regarding ovarian reserve cannot be deduced from such short-term evaluation. Longer follow-up over years is needed to explore such a risk. Indeed, the impact of LOD on ovarian reserve has been revised by more recent work and was found to be just theoretical. Api conducted a systematic review in 2009 on this issue and concluded that no solid evidence of a diminished ovarian reserve or POF was associated with LOD over years<sup>[17]</sup>. In conclusion, unilateral LOD seems to be as effective as bilateral LOD in terms of restoration of regular menstrual pattern and ovulation, as evident by the midluteal

serum progesterone. Nevertheless, impact on ongoing pregnancy rates is needed to be explored. Moreover, long-term follow-up is needed to explore the difference between both approaches regarding the risks of tubo-ovarian adhesions and diminished ovarian reserve.

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