

## Short-Term Effects of Laparoscopic Ovarian Drilling in Patients with Polycystic Ovarian Disease

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**Abstract:** About 15-40% of Polycystic ovarian Disease (PCOD) are considered clomiphene- resistant PCOD patients. One of the lines of management of those patients is laparoscopic ovarian drilling (LOD). **Aim of the study:** The aim of the present study was to evaluate effects of LOD in women with PCOD as regards ovulation induction, pregnancy rate, abortion rate, and hormonal profile changes. **Subjects and Methods:** Systematic review was done enrolling the randomized controlled studies as the gold standard during the period from 2000 to 2015. **Results:** Out of the selected 107/174 studies; after removal of repeated cases the true total number of cases was 5746. The mean age was 28.9 years and mean duration of infertility was 49.5 months. Ovulation was achieved in 68% and pregnancy in about 47% after LOD, but abortion occurred in about 19% of the pregnant cases. Patient age <25 years, obesity, duration of infertility <3 years, high LH, High LH/FSH, and high testosterone were favorable prognostic factors in 7 studies. On the other hand, patient age >30 years, BMI<30 kg/m<sup>2</sup>, duration of infertility >3 years, low LH, low LH/FSH, and low testosterone were unfavorable prognostic factors in 11 studies. Normalization of LH, LH/FSH and testosterone was achieved in 13 studies. **Conclusions:** LOD is considered a successful 2<sup>nd</sup> line treatment for patients with clomiphene- resistant PCO patients. **Recommendations:** LOD is recommended as a 2<sup>nd</sup> line therapy for patients with PCO after being clomiphene- resistant.

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**Key words:** PCO, PCOS, PSOD, ovarian drilling, and laparoscopic drilling.

### 1. Introduction

Polycystic ovary (PCO) is considered as one of the most common endocrine disorders. It occurs in 5 – 10 % of women in reproductive age group. It is the major cause of ovulation-related infertility, accounting for at least 75% of cases with an ovulatory in fertility<sup>(1)</sup>.

This major disorder is characterized by a marked increase in preantral follicular number arranged peripherally around a dense core of stroma or scattered throughout an increased amount of stroma<sup>(2)</sup>.

The first line of treatment of such disorder was induction of ovulation using clomiphene citrate and other members of selective estrogen receptor modulators (SERM)<sup>(3)</sup>. However, about 15 – 40 % of patients with PCO remain unresponsive to ovulation induction using clomiphene citrate and are considered as clomiphene citrate-resistant PCO patients<sup>(4)</sup>. Such patients can be managed either by using gonadotropins<sup>(5)</sup> or by minimal surgical procedure known as laparoscopic ovarian drilling (LOD)<sup>(6)</sup>. The mechanism of action of LOD is largely unexplained. In particular, it is not known whether LOD exerts its action through a direct effect on the ovary or through a systemic endocrine mechanism<sup>(7)</sup>.

One of the theories that explain the effect of LOD is the higher ovarian reserve presents in patients

with PCO. This proposed mechanism of exaggerated ovarian activity (at supra-physiological state) can be reduced to the physiological level by destruction or removal of some part of the ovary retaining the ovarian activity to physiological state<sup>(8)</sup>.

Although the available data in the literature is limited, there is no concrete evidence of a diminished ovarian reserve or premature ovarian failure due to LOD in patients with PCOS. Most of the changes in the ovarian reserve markers observed after LOD could be interpreted as normalization of ovarian function rather than reduction in ovarian reserve<sup>(8)</sup>. Adhesion formations related to pregnancy outcome is an important aspect of LOD. In the current practice, it is taken for granted that LOD causes abdomino-pelvic adhesions which results in further impairment in the reproductive performance of women with PCOS. This is based on a reportedly different amount and severity of adhesions seen in second look laparoscopy and leads to obvious conclusion that surgery is not the choice which expose women potentially to severe morbidity<sup>(9)</sup>.

The current Systematic Review was conducted to evaluate the effects of LOD in women with PCOD as regards ovulation induction rate, pregnancy rate, abortion rate, and the associated changes in hormonal profiles.

## 2. Patient and Methods

### Research Design:-

Systematic Review

### Setting

The study was conducted in the obstetrics and gynecology department of Sohag University Hospital, Sohag University, Egypt.

### Administrative and ethical considerations

The protocol was approved by the scientific research ethics committee of Sohag Faculty of Medicine. The study was conducted along one year during the period from the first of September 2014 to the end of August 2015.

### Selection criteria of the available researches:

#### A) Type of selected studies:

Randomized clinical trials (RCT) were the gold standard to obtain the evidence followed by non-randomized trials, available systematic reviews and meta-analysis were included whenever available.

#### B) Time and language of studies:

English language studies published during the period from 2000 till 2015

#### C) Sites visited:

- 1-Cochrane Library
- 2-Pubmed
- 3-Medline
- 4-Science Direct
- 6-E-Medicine
- 7-AidsLine
- 8-Google

#### D) Key words used:

PCO, PCOS, PSOD, ovarian drilling, and laparoscopic drilling.

#### E) The topic of interest:

Short term effects of laparoscopic ovarian drilling in (PCO) patients.

### Statistical analysis

After data collection, it was revised, coded and fed to statistical software SPSS version 22 IBM-Chicago. Chi-Square test ( $\chi^2$ ) was used for comparison between two or more groups as regards qualitative data. The statistical analysis used considered all tests to be T test with alpha error = 0.05. Microsoft office excel software was used to construct the needed graphs. After data coding the following data manipulations were done. After that all numeric data were expressed in the form of range (minimum to maximum), mean and standard deviation (SD). Categorical data were expressed in the form of frequencies and percentages.

## 3. Results

A total of 174 papers were obtained using the mentioned keywords in the search of all internet-based databases. Of these, 67 were excluded, due to non-relevance to our topic and/or poor studies' quality, and

107 papers were included in our study. The total number of cases in the selected studies was 6491 cases. After removal of repeated cases the true number of cases was found to be 5746 cases. The largest number of publications was in 2005 (11 papers), while the lowest number was in 2008 (2 papers only). There were two peaks of publication, one in 2005 (11 papers) and the other in 2010 and 2011 (10 papers for each).

The vast majority of papers (92/107; 86%) were prospective clinical trials, most of which were randomized controlled trials, 7/107 (6.5%) were systematic reviews, 4/107 (3.7%) were case reports, 2/107 (1.9%) papers were retrospective case-control studies, 1/107 (0.95%) was cross sectional study, and 1/107 (0.95%) was "correspondence" which is similar to "mini review article".

The mean age was recorded in 28 papers, and it was  $28.88 \pm 2.54$  (23.95-33.7) years. The mean duration of infertility was recorded in 8 papers, and it was  $49.45 \pm 9.7$  (37.2-62.4) months. Ovulation, as a sign of response to LOD, was recorded in 62 papers, and the number of cases succeeded to ovulate after LOD was 2763/4062 (68%) cases. Pregnancy, as a sign of response to LOD, was recorded in 70 papers, and the number of cases succeeded to get pregnant after LOD was 2303/4903 (47%) cases. Abortion, as a complication of pregnancy after LOD was recorded in 14 papers including 872 cases and the total number of abortions was 79/413 pregnancies (19.13%). Favorable prognostic factors for better response after LOD were reported in 7 studies in the form of infertility less than 3 years, younger age (less than 25 years), obesity (BMI more than 27 Kg / m<sup>2</sup>), LH more than 10 IU/L, LH/FHS ratio, initially low testosterone less than 50 ng/dL, and high androstenedione. On the other hand, unfavorable prognostic factors for worse response after LOD were reported in 11 studies in the form of infertility more than 3 years, older age (more than 25 years), BMI less than 27 Kg / m<sup>2</sup>, associated tubal or male factors, menarche at <13 years, LH less than 10 IU/L, LH/FHS ratio initially average, testosterone more than 50 ng/dL, and androstenedione <3.26 ng/ml, high triglycerides, total cholesterol and low density lipoprotein-cholesterol, low sex hormone binding globulin, high fasting insulin, low insulin resistance, and basal serum AMH >7.7 ng/ml.

Hormonal and chemical changes after LOD were reported in 13 studies. Testosterone, LH, FSH, LH/FSH ratio and serum inhibin B were significantly reduced. Also, Plasma AMH was significantly reduced. Among women with hyperinsulinemia, LOD decreases glucose and insulin responses to OGTT. Regardless of the insulin level, LOD does not influence adrenal steroid dynamics. LOD reduced serum VEGF, IGF-1, T, ovarian blood flow velocities,

which may explain the reduction of ovarian hyperstimulation syndrome in women with PCOS after LOD.

#### 4. Discussion

Polycystic ovary syndrome (PCOS) is a frustrating experience for women, often complex for managing clinicians and is a scientific challenge for researchers. It is the most common endocrine abnormality in reproductive-age women<sup>(10)</sup>. Its exact pathophysiology is complex and remains incompletely clear. The underlying hormonal imbalance created by a combination of increased androgens and/or insulin underpin PCOS<sup>(11)</sup>.

Laparoscopic ovarian drilling (LOD) was introduced as a second line treatment for ovulation induction in clomiphene citrate resistant PCOS. It was said that it is as effective as gonadotroph in treatment and is not associated with an increased risk of multiple pregnancy or OHSS<sup>(6, 12-14)</sup>.

The aim of this Systematic review was to evaluate effects of LOD in women with PCOD as regards ovulation induction rate, pregnancy rate, abortion rate, and the associated changes in hormonal profiles.

After exclusion of the non-relevant (67/174) ones; A total of 107/174 papers were included in this study, with their vast majority (92/107 paper) were prospective clinical trials.

Out of the 28 papers in which the mean age was recorded; it was 28.88±2.54 years. Only 7 studies had a population of patients with mean age older than 30 years<sup>(15-21)</sup>.

Also; out of the 8 papers in which the duration of infertility was recorded; it was 49.45±9.7 months. Only two studies had a mean duration of infertility of nearly 36 months<sup>(16, 22)</sup> while another 3 studies had a mean duration of infertility of 60 months or more<sup>(19, 23-24)</sup>.

Ovulation, as a sign of response to LOD, was recorded in 68% of the total number of treated cases in these studies. However, the percentages of ovulation varied greatly among studies. Some studies showed very low percentages (27-47%)<sup>(25-27)</sup> while others showed very high percentages of (90% or more)<sup>(28-33)</sup>.

Pregnancy, as a sign of response to LOD, was 47%. However, the percentages differed greatly among studies; with some studies showed percentages of lower than 30%<sup>(21-23, 25-27, 34-39)</sup> and others showed percentages of higher than 70%<sup>(29, 40-42)</sup>.

Abortion; as a complication of pregnancy after LOD; was 19.13% out of cases of pregnancy. However, the percentage of abortion varied greatly, from 0%<sup>(38)</sup>, 9.68%<sup>(12)</sup> and up to 70%<sup>(26)</sup>.

Analysis of 7 studies revealed some favorable prognostic factors, which when present, predict better response to LOD, as higher preoperative hormones

(LH, FSH, testosterone and/or androstenedione), shorter period of infertility<sup>(43-46)</sup>, as well as younger age<sup>(47-48)</sup>. Regarding weight of the patients, there was a great variability among different studies; as while one study stated that average weight gives best results<sup>(47)</sup>, others said that better results were obtained among thin patients<sup>(49)</sup>, and a third one stated that LOD was better among obese patients<sup>(50)</sup>.

Analysis of 11 studies revealed some unfavorable prognostic factors, which when present, predict worse response after LOD. Older age<sup>(35, 47, 50)</sup> and Low basal hormonal level<sup>(43, 50-54)</sup> were mentioned as bad prognostic factors; while the opposite was mentioned for basal hormonal level<sup>(35-36, 55)</sup>. Obesity, impaired lipogram profile and/or impaired insulin metabolism were recorded as bad prognostic factors<sup>(47, 51, 54, 56)</sup>. Contrary to this, average built with BMI <30 was detected by Al-Ojaim *et al.*,<sup>(17)</sup>. Duration of infertility >3 years was stated as bad prognostic factor<sup>(51, 54)</sup>. Also, early menarche, along with hypoglycemia were bad prognostic factors<sup>(52)</sup>.

Analysis of 13 studies revealed the following hormonal and chemical changes after LOD: reduction of sex hormones (LH, FSH, LH/FSH ratio and/or testosterone) which is in fact, restoration of these sex hormones to the normal or near normal levels<sup>(15, 22-23, 31, 57-58)</sup>. Other chemical changes recorded were normalization of initially high VEGF after LOD<sup>(59)</sup> or the failure of this normalization<sup>(60)</sup>; improvement of insulin resistance<sup>(61)</sup> and reduction of serum inhibin B<sup>(18)</sup>.

#### Conclusion

LOD is considered a successful 2<sup>nd</sup> line treatment for patients with clomiphene-resistant PCO patients.

#### Recommendations

LOD is recommended as a 2<sup>nd</sup> line therapy for patients with PCO after being clomiphene-resistant.

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