

# Ovarian Drilling Efficacy, Estradiol Levels and Pregnancy Rate in Females With Polycystic Ovary Syndrome

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**Background:** Polycystic ovary syndrome (PCOS) is the most common cause of oligoovulation and anovulation in general population and in females with infertility.

**Objectives:** The purpose of this study was to compare the efficacy of ovarian laparoscopic drilling procedure (LOD) in females with PCOS, resistant to treatment with estradiol (E2) level less than 40 pg/mL versus more than 40 pg/mL.

**Materials and Methods:** Females with PCOS, resistant to drug for ovary stimulation, were grouped based on the Estradiol levels of  $\leq 40$  pg/mL (n=13) and  $> 40$  pg/mL (n=15). To survey the ovulation, continuing spontaneous ovulation and cumulative pregnancy rate, ovarian laparoscopic drilling was carried out after the analysis of serum E2.

**Results:** There was significant difference in the average starting time of ovulation and continuing spontaneous ovulation of cases with PCOS with E2 levels  $> 40$  pg/mL, compared with ones with  $E2 \leq 40$  pg/mL ( $P = 0.029$ ,  $P = 0.05$ , respectively). Significant differences were also found in pregnancy rates of cases with PCOS with E2 levels  $> 40$  pg/mL compared with ones with  $E2 \leq 40$  pg/mL ( $P = 0.05$ ).

**Conclusions:** This study revealed that LOD in females with PCOS with a serum  $E2 > 40$  pg/mL was sufficient and safe to trigger development of ovarian follicles followed by clinical pregnancy.

**Keywords:** Estradiol; Treatment; Pregnancy

## 1. Background

Polycystic ovary syndrome (PCOS) is the most common cause of oligoovulation and anovulation in the general population and in females with infertility (1). The diagnosis of PCOS can be confirmed by ruling out other medical disorders and it is based on two of the following disorders; 1- Oligoovulation or anovulation, manifested as oligomenorrhea or amenorrhea, 2- Hyperandrogenism, 3- Hyperandrogenism and its clinical complaints, 4- polycystic ovaries diagnosed by ultrasound (2-4). In other words, polycystic ovaries is a result of a functional disorder and does not occur due to central or local defects (4). In patients with persistent anovulation, the average daily level of estrogen and androgen is high which depends on the persistent stimulatory effect on secretion of the luteinizing hormone (LH) (5). This, in turn, has caused an increase in the average daily levels of testosterone, androstenedione, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone (17-OHP) and estrone (6). In addition, in cases with persistent anovulation, the ovaries do not secrete more estrogen and the estradiol concentration is permanently equivalent with its concentration in the early follicular phase (7). Indeed, despite a reduced secretion of estradiol, free estradiol levels increase, due to a significant decrease

in sex hormone-binding globulin (SHBG) secretion (7). Properly, an elevated LH-to-follicle-stimulating hormone (FSH) ratio is associated with the increase of free estradiol secretion (8). Appropriate selection of patients for treatment is an important factor in successful induction of ovulation in patients with PCOS. At first, PCOS treatments include weight loss, clomiphene citrate, gonadotropins administration and surgical treatment. Indeed, there is no fixed protocol for induction of ovulation in cases with anovulation (8). However, the rational method that must be used is first the least invasive and then the most aggressive method. Therefore, routinely, in patients with normal thyroid function, normal prolactin levels, no galactorrhea and with mean serum estradiol levels of more than 40 pg/mL or natural response of menstruation to progesterone concentration, clomiphene is the drug of choice for ovulation induction (9). However, for ovulation induction in cases with PCOS who are resistant to medical procedures, the surgical methods can be performed (10). The primary surgical methods for ovulation induction management of PCOS was ovarian wedge resection, taken place to reduce the size of the androgen-producing tissue, and thus, to decrease the disturbances of hyperandrogenism (10). In 91% of patients with PCOS treated by this method, it was as-

sociated with the resumption of menstruation. However, pelvic adhesion is the side-effect of this procedure which may lead to iatrogenic infertility, i.e. by uterine/tubal factors (11). As an alternative, laparoscopy techniques compared with this procedure are less associated with the formation of adhesions in the pelvis. Moreover, it was observed that in laparoscopic ovarian diathermy (LOD) (or puncture in the ovary), the ovulation rate increased and the resistant to induction by standard ovulating agents decreased (12). Additionally, surgical treatment resulted in a significant reduction in serum levels of LH, testosterone, DHEAS and androstenedione and the ratio of LH to FSH. In treatment of PCOS, different techniques for laparoscopic ovarian tissue destruction have been described, i.e. laser, monopolar and bipolar cautery (12). LOD appears to be an effective minimally invasive procedure and useful for the induction of ovulation in patients with PCOS, resistant to clomiphene citrate, seeking pregnancy (13). Moreover, LOD has been effective on assisted reproductive techniques (ART) outcomes (13). Although randomized trials have shown that no technique is superior to other methods, A number of recent reports have supported the effectiveness of diathermy or electrocautery to treat patients with PCOS resistant to medical methods, i.e. clomiphene citrate or gonadotropins (13, 14), given that ovulation in patients with PCOS with estradiol levels greater than 40 pg/mL occurs better.

## 2. Objectives

The purpose of this study was to investigate the effects of treatment with LOD on reproductivity in females with PCOS, resistant to treatment with estradiol levels of  $\leq$  or  $>$  40 pg/mL.

## 3. Materials and Methods

### 3.1. Study Design

A comparative, randomized, clinical trial was carried out in Fertility and Infertility Center of Imam Khomeini Teaching Hospitals in Ahvaz, Iran. This study was performed between April 2011 and January 2013 and targeted the infertility patients referred to the hospital with complaints of infertility, polycystic ovarian syndrome, resistance to ovulation induction, and candidate for laparoscopic ovarian drilling procedure. The Ethics Committee of Jundishapur Ahvaz University of Medical Sciences approved this study. Patients eligible to participation in this study during the 18 months in the hospital for elective infertility cauterization surgery were selected. The serum estradiol level was measured. Fifteen patients had serum estradiol levels more than 40 pg/mL and 13 had lower levels. Afterwards, the subjects underwent laparoscopic procedures for ovarian cauterization. Serial transvaginal ultrasounds were performed every month for monitoring the ovulation and pregnancy rate. The number of postoperative patients in which spontaneous ovulation and clinical pregnancy oc-

curred was also analyzed. The inclusion criteria were: irregular menstruation, clinical and biochemical evidences of hyperandrogenemia, sonographic evidence of PCOS, i.e. high rate of microcysts (0.5 - 0.8 inch) and resistance to treatment (failure of ovulation induction with clomiphene-letrozole-metformin-gonadotropins-tamoxifen after 6-3 months). Patients with the following criteria were not enrolled in the present study: FSH  $\geq$  12, family history of premature ovarian failure, smoking, and age over 40 years. The exclusion criteria also included medical conditions that precluded surgery or anesthesia, lack of patient cooperation, pregnancy, and dissatisfaction of patients from the operation or enrollment in the study.

### 3.2. Laparoscopic Ovarian Drilling Technique

Laparoscopic surgery for ovarian drilling (LOD) was performed under general anesthesia. One 10-mm port and two 5-mm ports were taken in the infraumbilical region and on either side of the lower abdomen, respectively. Four holes within four seconds, with a depth of 4-3 mm were created in both ovaries. By observation of the pelvic cavity, all other causes of infertility were investigated. During the laparoscopy, washing and suctioning was performed with 500 mL of Ringer's to prevent postoperative adhesions. Patients who underwent LOD were then treated with ovulation induction drugs after a following period of four months to control the spontaneous ovulation and clinical pregnancy. The first visit of the patients was carried out in the first cycle after cauterization, in which occurrence or non-occurrence of ovulation was confirmed by ultrasound and up to four months in each cycle, patients underwent ultrasound test.

### 3.3. End Points

The end point of the study was to see whether triggering the treatment with laparoscopic cauterization procedure had any effect on reproductive outcome of the patients with PCOS, resistant to drug treatment.

### 3.4. Statistics Analysis

All the analyses were carried out with the SPSS 16 statistical software. For comparison of the rates of ovulation and clinical pregnancy, chi-squared test was used. Categorical variables were used to compare the average times of ovulation and clinical pregnancy between the groups, using Independent t test,  $\chi^2$  tests or Fisher's exact test, where appropriate. For all other outcomes, a nominal P value  $<$  0.05 was considered significant.

## 4. Results

### 4.1. Maternal Demographic Characteristics Assessment

A total of 28 cases were randomized and available for investigation. The demographic characteristics are shown

in Table 1. None of the women refused to participate in the study. The mean age of all of the patients was  $25.5 \pm 4.4$  years with a range of 16 to 36 years. There was no significant relationship regarding the mean ages between the group with  $E2 < 40$  pg/mL versus  $E2 > 40$  pg/mL ( $P = 0.85$ ). Of 13 women with  $E2 < 40$  pg/mL, 10 (76.9%) were nulliparous and 3 (23.1%) were multiparous, whereas from 15 women with  $E2 > 40$  pg/mL, 11 (73.3%) were nulliparous and 4 (26.7%) were multiparous. However, the relation between parity and the amount of E2 was not significant ( $P = 0.99$ ). The two groups were identical in body mass index (BMI) and menstrual pattern (oligomenorrhea and regular menstrual cycle). We recorded no complications or difficulties in the performance of laparoscopy (none of the females had abdominal pain or nausea). In case of drug treatment before undergoing laparoscopy, from 13 patients with  $E2 < 40$  pg/mL, 12 (92.2%) were given clomiphene, 7 (53.8%) human menopausal gonadotropin (HMG), 13 (53.8%) tamoxifen, 1 (53.8%) letrozole, 9 (53.8%) metformin, 1 (53.8%) gonal F, and 1 (53.8%) menogan. From 15 patients with  $E2 > 40$  pg/mL, 12 (92.2%) were given clomiphene, 7 (53.8%) HMG, 13 (53.8%) tamoxifen, 1 (53.8%) letrozole, 9 (53.8%) metformin, 1 (53.8%) gonal F, and 1 (53.8%) menogan. Seventy percent of the cases with PCOS with  $E2 < 40$  pg/mL had primary infertility and the remaining had secondary infertility; eleven with  $E2 > 40$  pg/mL had primary infertility and the remaining had secondary infertility. The mean duration of infertility among the participants was at least two years, so that in the patients with  $E2 < 40$  pg/mL it was  $7.8 \pm 4.4$  and in cases with  $E2 > 40$  pg/mL it was  $6.2 \pm 4.4$ . Generally, The

most common cause of infertility in both groups ( $E2 > 40$  and  $E2 < 40$ ) was ovarian failure (100%); other causes along with ovarian failure were tubal failure (7.7% and 6.7%, respectively), male factor (46.2% and 40%, respectively), and uterine defects (15% and 6.4, respectively). The most common cause of infertility in the  $E2 < 40$  pg/mL group was ovarian failure (100%); other causes along with ovarian failure were tubal failure (16.7%), uterine defects, and uterine defects along with ovarian failure (15%). All the causes that were along with ovarian failure had been treated before performing the laparoscopic cauterization treatment.

#### 4.2. Clinical Parameters Assessment

The clinical parameters characteristics are shown in Tables 2 and 3. The average starting time of ovulation in patients after laparoscopic cauterization treatment in the  $E2 < 40$  pg/mL group was  $2.4 \pm 2$  months and in the other group was  $1.3 \pm 0.6$  months. Therefore, the relationship between the average starting time of ovulation and the amount of serum E2 was significant. Indeed, the average starting time of ovulation in patients with  $E2 < 40$  pg/mL was longer than the ones with  $E2 > 40$  pg/mL ( $P = 0.0002$ ). The mean percentage in the group with  $E2 > 40$  pg/mL was 100%, but in cases with  $E2 < 40$  pg/mL it was 84.6%. The cumulative pregnancy rate (60%) in the group with  $E2 < 40$  pg/mL was more pronounced than the group with  $E2 > 40$  pg/mL (15.4%). The mean duration of occurrence of clinical pregnancy after the laparoscopic cauterization treatment in cases with  $E2 < 40$  pg/mL was  $2 \pm 45/2$  months and in the group with  $E2 > 40$  pg/mL it was  $1.3 \pm 0.6$  months.

**Table 1.** Maternal Demographic and Clinical Characteristics in Females Admitted to the Department <sup>a</sup>

	Groups		P Value
	Estradiol < 40 pg/mL	Estradiol > 40 pg/mL	
Cases, No.	15	13	0.865
Age, y	$26.9 \pm 4.2$	$27.2 \pm 3.1$	0.85
BMI, kg/m <sup>2</sup>	$29.5 \pm 3.1$	$30.4 \pm 3.4$	0.486
Primary sterility	10 (76.9)	11 (73.3)	0.89
Secondary sterility	3 (23.1)	4 (26.7)	0.437
Duration of infertility	$6.2 \pm 4.4$	$7.8 \pm 4.2$	0.050
Clomiphene treatment	10	15	0.758
HMG treatment	7	9	0.396
Tamoxifen treatment	13	15	0.879
Letrozole treatment	1	15	0.0001
Metformin treatment	9	10	0.798
Gonal F treatment	1	4	0.09
Menogan treatment	1	2	0.978
Male factor of infertility	6	6	-
Ovarian factor of infertility	13	15	0.750
Oviduct tubal factor of infertility	1	1	-
Uterus factor of infertility	2	1	0.958
Idiopathic factor of infertility	0	0	-
Duration of Ovulation, mon	$2.54 \pm 1$	$1.33 \pm 0.6$	0.029
Duration of Pregnancy, mon	$6.19 \pm 1$	$3.25 \pm 0.6$	0.05
Ovulation rate, number	11	15	0.579

<sup>a</sup> Abbreviations: BMI, body mass index; HMG, human menopausal gonadotropin.

**Table 2.** Comparison of Serum Estradiol, Insulin, FSH, FBS, HDL, LH and GTT Between non- and Treated Cases

Duration of Ovulation	E2 < 40 pg/mL	E2 > 40 pg/mL	P Value
1 month	3	11	0.002
2 months	2	3	0.765
3 months	6	1	0.001
4 months and more	0	0	-
Total	11	15	0.624

**Table 3.** Comparison of Serum Estradiol, Insulin, FSH, FBS, HDL, LH and GTT Between non- and Treated Cases

Duration of Ovulation	E2 < 40 pg/mL	E2 > 40 pg/mL	P Value
1 month	0	1	0.89
2 months	0	1	0.89
3 months	0	1	0.89
4 months and more	2	6	0.024
Total	2	9	0.001

## 5. Discussion

PCOS is the most common cause of oligoovulation and anovulation in the general population and in infertile females. Properly, infertile females with anovulation are candidates for ovulation induction (2, 3). First choice of treatment for this problem, especially in patients with more 40 pg/mL serum E2 levels is using ovarian-stimulation drugs (4). However, clinicians are often faced with the problem of how to manage the induction of ovulation with a variety of drugs, which may lack specificity, low efficiency, or have potentially severe side-effects for the subjects or the ovarian function. For instance, one of the most commonly used drugs to stimulate the development of ovarian follicles is clomiphene citrate (15). Nevertheless, some patients do not respond to an adequate trial of this drug (13, 14). Therefore, proper steps should be taken to choose a new avenue, based on using the laparoscopy procedure, which can help the subjects with PCOS to overcome infertility. The results of the present study showed that after treatment with LOD, the females with anovulation resistant to drug treatment, especially the ones with E2 > 40 pg/mL, were better capable of inducing follicular maturation and ovulation. Indeed, the starting time of ovulation after laparoscopy in patients with PCOS with E2 ≤ 40 pg/mL was longer than the ones with E2 > 40 pg/mL. Therefore, it seems that there is a meaningful relationship between the average starting time of ovulation and the amount of serum E2. In addition, the mean rate of ovulation in the group with E2 > 40 pg/mL was more pronounced than the group with E2 < 40 pg/mL. However, whether the quality of the follicles released in these forms is optimal as well as the incidence of premature ovarian failure stays to be clarified. These findings were also in accordance with other three studies by Gjonnaess (16), Amer et al. (17) and Al-Ojaimi (18). Gjonnaess (16) showed that LOD was effective and well

tolerated for induction of ovulation in patients with PCOS undergoing assisted reproductive techniques (ART) treatment. Amer et al. (17) have also found similar clinical outcomes with LOD during ART treatment in abnormal responder patients. Balen et al. (9) obtained the same successes in inducing follicular maturation and ovulation rates in females treated with LOD before undergoing ART treatment. In contrast, Abdel Gadir et al. (19) reported that LOD was not more efficient to achieve optimal oocyte maturation than other treatment procedures. These observations strongly indicate that the effect of surgery is mediated via a central mechanism rather than a direct effect on the treated ovary (20). However, the pathophysiology of unusual ovarian blood supply in PCOS is not evidently understood. One probable reason is that E2 may play a role in the moderation of vascularity of ovary and uterine (21). Greenblatt and Casper (5) reported that the level of E2 at the first day after the LOD dropped, so that it reached the minimum concentration by day four and thereafter began to rise steadily to the end of the first menstruation period. Therefore, the suggestion of any relationship between the serum E2 levels and ovarian blood supply alters stays elusive. Alternatively, a noteworthy decline in vascular impedance to blood supply in the ovarian artery (22) and in the vessels around the follicles, in correlation with an increase in the number of follicles and serum E2 concentration (23), was observed after the ovarian stimulation with gonadotropins. Considering these observations and the data reported by Zaidi (24), it seems that some factors other than E2 could be the cause of increased ovarian stromal vascularity in PCOS. Primordial or smaller preantral follicles do not have any special vascular supply of their own and derive their blood supply from the stromal blood vessels (5). Subsequent growth of primary follicles leads to development of a vascular

network with increased follicular blood flow. Hence, the stromal blood flow velocity in an inactive or quiescent ovary may reflect the baseline blood flow perfusion. LOD may result in a reduction in the number of small and intermediate follicles usually seen in PCOS; it has the same effect on the ovarian stromal tissue (25, 26). Regarding these effects as well as the abovementioned mechanism by which ovarian stromal blood flow declined after the gonadotropin-releasing hormone agonist (GnRH) therapy (5), we can hypothesize that the decline in ovarian stromal blood flow velocity could be the result of the direct electrical and/or thermal effects of LOD. Taking into consideration the rise of ovarian stromal blood flow velocity in PCOS (27, 28) and its possible effects on ovarian steroidogenesis, there might be a possible beneficial effect of diminished ovarian stromal blood flow velocity on ovarian steroidogenesis in PCOS. In the present experiment, the difference was shown in terms of the cumulative ongoing pregnancy rate in patients with PCOS with E2 levels higher or lower than 40 pg/mL, undergoing LOD treatment. In patients with PCOS with E2 > 40 pg/mL, the pregnancy rate increased four times. Furthermore, other studies have been able to find the positive influence of LOD treatment on reproductive outcomes (28, 29). In contrast, other studies have reported that reproductive parameters such as clinical pregnancy, were not significant in patients with E2 levels both higher and lower than 40 pg/mL (30, 31). Considering this prospective randomized experiment, we can conclude that LOD, especially in females with PCOS with a serum E2 higher than 40 pg/mL is sufficient and safe to trigger ovulation followed by clinical pregnancy. However, well-designed, further studies are essential to say a final conclusion.

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