# Predicting Factors for The Efficacy of Laparoscopic Ovarian Drilling for Ovulation Induction in Polycystic Ovary Disease

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## Abstract

**Background:** Laparoscopic ovarian drilling has been widely used to induce ovulation in women with polycystic ovarian syndrome. There are factors that affect the outcome of this procedure like age of the patient, duration of infertility, body mass index, hormonal changes and menstrual irregularities. Laparoscopic ovarian drilling may avoid or decrease the need for gonadotrophins or may facilitate their effectiveness. The procedure can be done with less trauma and fewer postoperative adhesions than with traditional surgical procedures.

**Objective**: To evaluate the effectiveness and safety of laparoscopic ovarian drilling for ovulation induction in polycystic ovary patients and to identify which of the mentioned factors help to predict the outcome of the procedure.

**Patients And Methods:** This prospective clinical study included 80 patients with failure of 12 weeks clomiphene citrate treatment for an ovulatory infertility due to (PCOS) who underwent (LOD) in Alhindiya general hospital between January 2008 and September 2011. The effect of various patients' pre-operative characteristics on the ovulation rate after (LOD) was assessed. The success rates were compared between these categories of each factor to identify the predictors of success of laparoscopic ovarian drilling.

**Results**: Women with marked obesity (BMI 35 kg/m2) achieved significantly ($P < 0.05$) lower ovulation rate (40%) compared with those (61.5%) of moderately overweight (BMI 29–34 kg/m2) women and those (75%) of women with normal and slightly elevated BMI (<29 kg/m2). women with testosterone levels ≥4.5 nmol/l, the rate was 30 %, which was significantly ($P < 0.05$) lower than those (57%) of women with moderately elevated testosterone (2.6–4.4 nmol/l). Patients with normal serum testosterone levels (<2.6 nmol/l) showed significantly ($P < 0.05$) higher success rates (80%) than the other groups

**Conclusion:** Marked obesity, marked hyperandrogenism and/or long duration of infertility in women with (PCOS) seem to predict resistance to (LOD). Ovarian drilling by laparoscopy is safe but should be used on selective scale.

**Keywords:** Polycystic ovary, Laparoscopic ovarian drilling, laparoscopic electrocautery, ovulation induction, infertility.

## الخلاصة

**خلفية:** حفر المبيض بالمنظار تستخدم على نطاق واسع للحث على التبويض في النساء مع متلازمة المبيض المتعدد الكيسات. هناك عوامل تؤثر على نتائج هذا الإجراء مثل عمر المريض، ومدة العقم ومؤشر كتلة الجسم، والتغيرات الهرمونية واضطرابات الحيض

حفر المبيض بالمنظار قد يجنب او يقلل الحاجة الى العلاج بالهرمونات او قد تسهل فعاليتها ويمكن اجراء العملية باقل الصدمات وأقل الالتصاقات بعد العملية الجراحية من العمليات الجراحية التقليدية.

**الهدف:** تقييم فعالية وسلامة حفرالمبيض بالمنظار لتحريض الإباضة لدى مرضى المبيض المتعدد الكيسات والتعرف على اي العوامل المذكورة قد تساعد إلى التنبؤ بنتيجة هذا الإجراء.

**المرضى والطرق:** شملت هذه الدراسة السريرية الارتقابية ٨٠ مريضة اللات يعانين من فشل ١٢ أسبوعا عقار كلوميفين سترات علاج لعقم التبويض بسبب متلازمة تكيس المبايض اللاتي خضعن لعملية حفر المبايض بالمنظار في مستشفى الهندية العام بين يناير ٢٠٠٨ وسبتمبر ٢٠١١. تم تقييم

تأثير الخصائص المختلفة للمرضى قبل الجراحة على معدل التبويض بعد عملية حفر المبايض بالمنظار . وتمت مقارنة معدلات النجاح بين هذه الفئات من كل عامل لتحديد تنبؤ نجاح حفر المبيض بالمنظار.

**النتائج:** النساء ذوات السمنة المفرطة(معامل كتلة الجسم ٣٥ كغم\م) حصلت بصورة مهمة(قيمة P أقل من ٠.٠٥) على نسبة اباضة اقل(٤٠%) مقارنة مع تلك (٦١.٥٪) من زيادة الوزن بشكل معتدل (معامل كتلة الجسم ٢٩-٣٤ كغم\م) وتلك (٧٥٪ ) من النساء ذوات مؤشر كتلة الجسم طبيعية الى مرتفعة قليلا. النساء مع مستويات هرمون تستوستيرون ٤.٥ نانومول / لتر، كانت نسبة ٣٠٪ والذي كان معنويا مهم (قيمة P أقل من ٠.٠٥) أقل من تلك (٥٧٪) من النساء مع هرمون تستوستيرون مرتفعة باعتدال (٢.٦-٤.٤ نانومول / لتر) أظهرت معنويا مهم (قيمة P أقل من ٠.٠٥) أعلى معدلات النجاح (٨٠٪) من المجموعات الأخرى .

**الأستنتاجات:** فرط السمنة, فرط الأندروجين و / أو مدة طويلة من العقم في النساء ذوات متلازمة تكيس المبايض تشير ال مقاومة الأستجابة للعملية ,حفر المبيض بواسطة المنظار هو آمن ولكن ينبغي أن يستخدم على نطاق انتقائي

**كلمات البحث:** تكيس المبيض،حفر المبيض بالمنظار ، كهربي بالمنظار، تحريض الإباضة، والعقم.

## Introduction

Polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory infertility, being found in 75% of cases [1] . Laparoscopic ovarian drilling (LOD) has been widely used to induce ovulation in (PCOS) women after failure of treatment with clomiphene citrate (CC).Of course, not all the patients will respond to this type of intervention, so we should know how to select the cases that will get the benefit from the operation. Many authors have reported high ovulation (80%) and pregnancy (60%) rates following (LOD). However, 20–30% of anovulatory (PCOS) women fail to respond to (LOD)[2]. The mechanism of action of (LOD) is not fully understood and therefore it is not exactly clear why some PCOS patients do not respond to this treatment. A possible explanation is that the amount of ovarian tissue destroyed during (LOD) is not sufficient to produce an effect in some patients. However, others believe that ovarian diathermy works by increasing the sensitivity of the ovaries to endogenous (FSH), and that only a minimal amount of thermal injury is required . Hence another possible explanation of failure to respond is an inherent resistance of the ovary to the effects of drilling [3].

Ovulation induction with gonadotrophins is well-established in patients resistant to clomiphene citrate, but extensive monitoring is necessary because of the high sensitivity of polycystic ovaries to exogenous gonadotrophins [4], Laparoscopic drilling of the ovaries is an alternative treatment for patients with clomiphene citrate resistant polycystic ovary syndrome. Patients may respond to clomiphene citrate after this treatment. Disadvantages are the need for surgery under general anesthesia, the unknown long term effects on ovarian function. Patients who fail to ovulate after laparoscopic ovarian drilling and clomiphene citrate can still be treated with gonadotrophins, before proceeding to in vitro fertilization.

The success rates for laparoscopic ovarian drilling appear to be better for patients at or near their ideal body weight, as opposed to those with obesity. Most studies have been published with success rates for ovulation between (53% and 92%) for patients with ideal body weight. Patients with decreases in hormone production (testosterone and luteinizing hormone) are more likely to ovulate and achieve pregnancy than those without hormonal improvement[5]. Patients not ovulating after the procedure have been found in many cases to become responsive to clomiphene citrate if they were previously resistant and their pregnancy rates have ranged from 37% to 86%. Overall these success rates are similar to the use of clomiphene citrate (80% chance of ovulation and 40% chance of pregnancy). Frequently, the surgical approach is chosen when a patient has already failed to ovulate on clomiphene citrate at maximal doses and has not responded to insulin sensitizing agents.

## The Technique of Ovarian Drilling

The technique of ovarian drilling is to destroy (cauterize) the testosterone producing

tissue of the ovary. Usually the small follicles visible on the surface of the ovary are chosen as the spots to direct the electrical energy, because presumably this is where hormone production is maximal. From 4-20 "holes" can be made in each ovary, usually 3 millimeters wide and 3 millimeters deep (see figure I). Treatment of both ovaries is usually preformed, but reports that treatment of only one ovary can be successful have been published[5]. Many surgeons try to make the areas of cautery as far as possible from the fallopian tube to try to limit the chance of tubal scarring.

## Materials and Methods

Eighty patients with an ovulatory infertility due to PCOS for more than 1 year were admitted to Alhindiya general hospital after failure of 12 weeks clomiphene citrate treatment and underwent (LOD) between January 2008 and September 2011.

Each patient has been examined for symptoms & signs of (PCOD) and the height and weight was measured and sent for serum concentrations of LH, FSH and testosterone.

Ultrasound examination was done for all patients and the ovarian volume was calculated using the formula for a prolate ellipsoid: 0.523 x length x width x thickness, according to the method of Kovacs *et al.* (1991). The mean volume of the right and left ovary was calculated for each subject.

Certain criteria for diagnosing (PCOD) were considered:

-Severe oligomenorrhoea or amenorrhoea

-Serum LH/FSH ratio was ⩾2 and/or raised serum testosterone ⩾2.5 nmol/l

-There was ultrasonographic evidence of ovarian stromal hypertrophy and multiple (⩾10), small (6- mm) follicles arranged in the periphery.

The influence of patients' pre-operative characteristics including age, body mass index (BMI), duration of infertility, menstrual pattern, LH/FSH ratio, serum concentrations of LH and testosterone and ovarian volume on the outcome of (LOD) was evaluated. For BMI, LH, LH/FSH ratio, and testosterone, women were divided into three categories: normal or slightly elevated, moderately elevated and markedly elevated. With regard to ovarian volume, women were divided into two categories: patients with ovarian volume <14 ml and those with ⩾14 ml. Ovulation rate after (LOD) was compared between the different categories of each factor. $P > 0.10$ was used as a cut-off level for exclusion of non-significant individual parameters from the prognostic model.

## Post-operative Follow up

If the patient started a menstrual period within 6 weeks of the surgery, a blood sample is taken on day 2 of that cycle for measurement of serum concentrations of LH, FSH and testosterone.

Another blood sample is taken on day 21 of the same cycle for measurement of serum concentration of progesterone.Ovulation is diagnosed when the progesterone level was 30 nmol/l.

If spontaneous menstruation did not occur, a random blood sample is taken to measure all the above hormones at 6 weeks following surgery.

If the patient does not ovulate as evidenced by the low progesterone levels or lack of menstruation, clomiphene citrate would be started 6–8 weeks after surgery. If ovulation was achieved either spontaneously or with the help of clomiphene citrate, patients are followed-up until they conceive.

## Results

A total of 80 patients with anovulatory infertility associated with (PCOS) who underwent (LOD) were included in this study. The characteristics of this group of women are shown in Table I.

| Characteristic | Mean | Standard deviation | Range |
|---|---|---|---|
| Age (years) | 28.5 | 3.8 | 18–36 |
| BMI ($kg/m^2$) | 27 | 4.7 | 18.5–40 |
| Duration of infertility (years) | 3.1 | 2.2 | 1–10 |

| | | | |
|---|---|---|---|
| Serum LH (IU/l) | 13.7 | 6.3 | 1.5–36.5 |
| Serum FSH (IU/l) | 4.9 | 1.4 | 1.2–8.1 |
| Serum LH/FSH ratio | 2.7 | 1.2 | 0.5–6.1 |
| Serum testosterone (nmol/l) | 2.6 | 1.3 | 0.7–6.3 |
| Ovarian volume(ml) | 11.2 | 3.6 | 4-18 |

**Table I.** The characteristics of 80 (PCOS) women who had (LOD) for an ovulatory infertility

Amongst the 80 patients included in the study, 40 (50%) ovulated spontaneously after (LOD) and a further 13 patients ovulated after the addition of (CC), giving an overall ovulation rate of 53 out of 80 (66.25%).

**Factors Affecting the Success Rates**

Table II illustrates the ovulation rate following( LOD) in (PCOS) patients with different categories of age, BMI, serum testosterone and LH concentrations, LH/FSH ratio, ovarian volume, duration of infertility and menstrual pattern.

The results show that the age, menstrual pattern, LH/FSH ratio and ovarian volume did not seem to influence the outcome of( LOD).

Women with marked obesity (BMI ≥35 kg/m$^2$) achieved significantly ($P < 0.05$) lower ovulation rate (40%) compared with those (61.5%) of moderately overweight (BMI 29–34 kg/m$^2$) women and those (75%) of women with normal and slightly elevated BMI (<29 kg/m$^2$).

| | Category | *n* | *n ovulate* | Ovulation rate (%) |
|---|---|---|---|---|
| Age (years) | ≤35 | 72 | 50 | 69% |
| | >35 | 8 | 3 | 37% |
| BMI (kg/m$^2$) | <29 | 44 | 33 | 75% |
| | 29–34 | 26 | 16 | 61.5% |
| | ≥35 | 10 | 4 | 40% |
| Menestrual pattern | Regular | 8 | 6 | 75% |
| | Oligomenorrhoea | 60 | 34 | 54% |
| | Amenorrhoea | 18 | 5 | 27% |
| LH (IU/l) | <10 | 29 | 20 | 68% |
| | 10–19.9 | 30 | 20 | 66% |
| | ≥20 | 21 | 13 | 61% |
| LH/FSH | >2 | 30 | 21 | 70% |
| | 2–3.9 | 30 | 20 | 66% |
| | ≥4 | 20 | 12 | 60% |
| Testosterone (nmol/l) | <2.6 | 42 | 34 | 80% |
| | 2.6–4.4 | 28 | 16 | 57% |
| | ≥4.5 | 10 | 3 | 30% |

| | | | | |
|---|---|---|---|---|
| Ovarian volume (ml) | <14 | 52 | 35 | 67% |
| | ≥14 | 28 | 18 | 64% |
| Duration of infertility (years) | <3 | 40 | 32 | 80% |
| | 3–6 | 25 | 15 | 60% |
| | >6 | 15 | 6 | 40% |

**Table II** Ovulation rate in 80 PCOS patients after (LOD) related to different categories of age, body mass index (BMI), serum concentrations of LH and testosterone, LH/FSH ratio, duration of infertility and ovarian volume.

As far as the androgens are concerned, ovulation rate showed significant reduction with increasing androgen levels: in women with testosterone levels ≥4.5 nmol/l, the rate was 30 %, which was significantly ($P$ < 0.05) lower than those (57%) of women with moderately elevated testosterone (2.6–4.4 nmol/l). Patients with normal serum testosterone levels (<2.6 nmol/l) showed significantly ($P$ < 0.05) higher success rates (80%) than the other groups (Table II).

A significant drop in the ovulation rates was observed in patients with >6 years of infertility, with only 40% chance of ovulation compared with 80% in women with infertility of <3 years.

## Discussion

Laparoscopic ovarian drilling was effective strategy for inducing ovulation in patients with clomiphene citrate resistant polycystic ovary syndrome. Treatment with clomiphene citrate remains the first line treatment for polycystic ovarian syndrome.For those with clomiphene resistant disease, laparoscopic ovarian drilling should be the second line treatment[6].

Disadvantages of the electrocautery strategy are the potential risks from surgery carried out under general anesthesia. Because ovulation induction with gonadotrophins is a non-invasive procedure it does represent a safer alternative[7]. In this study, we have evaluated the impact of various clinical, biochemical and ultrasonographic features of (PCOS) on the outcome of (LOD) in eighty (PCOS) women.

Only 10% percent of (PCOS) women in our study had regular menstrual cycles. Although chronic an ovulation in women with (PCOS) is usually associated with menstrual irregularities[13] , several authors have reported that 16–24% of these women do have apparently 'regular' menstrual cycles[7, 8]. Our data showed three main factors to have a significant impact on the efficacy of (LOD), these were: body mass index, hyperandrogenism and duration of infertility.

Patients with (BMI) ≥35 kg/m$^2$ achieved significantly lower ovulation rates after (LOD) compared with moderately overweight and normal weight women. (Table II). The findings in the present study are in agreement with a previous report by Gjonnaes[5] (1994) who reviewed 252 patients who underwent ( LOD) and found that women with marked obesity (BMI ≥36 kg/m$^2$) have lower ovulation rate compared with women with normal and moderately elevated (BMI). It is not clear why obese (PCOS) women are refractory to( LOD). Several previous studies have shown an inverse relationship between (BMI) and the response to medical ovulation induction by (CC) [9, 10].

Our results showed that increasing serum level of testosterone is associated with a significant reduction of the chances of success of ( LOD). This is in disagreement with report of Abdel-Gadir *et al.* (1993)

which showed that androgen levels had no impact on the success of (LOD)1. The results of the present study were consistent with those of Naether (1993) who found that women with high levels of free testosterone, whether they were of normal weight or overweight, were less likely to respond to( LOD) 11. It is difficult to explain the relative resistance of hyperandrogenic (PCOS) patients to (LOD) since the exact mechanism of action of this treatment is yet to be determined. A possible explanation could be that the amount of destruction of androgen-producing ovarian tissue during (LOD) is relatively insufficient in women with marked hyperandrogenism12. It remains to be elucidated whether an increased number of punctures or increased total power used during (LOD) in women with marked hyperandrogenism could result in reduction of the androgen levels, which may in turn result in an improvement of the outcome.

We found that the duration of infertility is the most important independent predictor of success of (LOD). A significant drop in the ovulation rate was observed in patients with >6 years of infertility, with only 40% chance of ovulation compared with 80% in women with infertility of <3 years. These findings are consistent with Shiraaz *et al.* which showed that women with a duration of infertility >3 years were less likely to respond to (LOD) 14. A possible explanation for this is that women with longer duration of infertility are more likely to have other subtle sub fertility factors.

LH levels did not seem to influence the ovulation rate of (LOD) (Table II). Interestingly, some studies have reported that patients receiving (CC) had a significantly higher probability of conception once ovulation had been achieved by( CC) if their pre-treatment LH levels were elevated15.

With regard to age, menstrual pattern, LH/FSH ratio and ovarian volume, they did not influence the outcome of( LOD). Only a small number (8) of patients in our study were aged ≥35 years, and therefore the effect of age on the success of( LOD) cannot be determined conclusively in this study.

## Conclusions

The three main factors which have significant role in success of( LOD) are:
(BMI), androgen level and the duration of infertility, all have inverse relationship with the ovulation rate.
The age, menstrual irregularity, LH/FSH ratio and ovarian volume, have no significant effect on the ovulation rate.
Ovarian drilling by laparoscopy should be used on selective scale

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