

# Laparoscopic ovarian drilling for infertile PCOS women who are resistant to oral ovulation-inducing drugs

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## ABSTRACT

**Background:** Gonadotrophin treatment to achieve pregnancy in infertile individuals with polycystic ovarian syndrome (PCOS) who are resistant to ovulation induction drugs is costly, time consuming and associated with hyperstimulation and multiple pregnancy. **Aim:** The aim was to determine the pregnancy rate after laparoscopic ovarian drilling (LOD) in infertile PCOS cases resistant to oral ovulation-inducing drugs. **Setting and Design:** The setting was a tertiary care center without assisted reproductive techniques (ART) facilities catering to patients with general gynecological problems from all socioeconomic strata. This was a prospective observational study involving women resistant to oral ovulation induction drugs. **Period of Study:** The period of the study was from 2008 to 2012. **Materials and Methods:** Forty-eight infertile PCOS cases who did not achieve pregnancy after three or more cycles of clomiphene citrate (CC)/CC and metformin combination and letrozole. LOD was carried out by electrical diathermy. **Results:** The overall pregnancy rate was 66%. Thirteen percent conceived in the same cycle, 11% in the second cycle, and 6% in the third cycle. Spontaneous abortion occurred in 10% and the live birth rate was 90%. **Conclusion:** Ovarian drilling may be considered as a good option for oral drug-resistant PCOS cases, as 66% achieved pregnancy with this procedure.

**Keywords:** Laparoscopic ovarian drilling (LOD), polycystic ovarian syndrome (PCOS), pregnancy rate, resistance

## INTRODUCTION

Clomiphene citrate (CC) is the first-line drug for ovulation induction for infertile polycystic ovarian syndrome (PCOS)-affected women. The ovulatory rate with CC is 70-80% but the pregnancy rate is only 20-40%.<sup>[1]</sup> The cumulative conception rates with incremental doses are 50%, 45%, and 33% with 50 mg, 100 mg, and 150 mg at 3 months and 62%, 66%, and 38% at 6 months, respectively.<sup>[2]</sup> Thus, a significant proportion of women fail to conceive even after six cycles. The reasons may be a high intraovarian androgen environment affecting the oocyte quality as well as ovulation,

tenacious cervical mucus, and unfavorable endometrium. PCOS resistant to CC was designated variously by various authors, and there is no consistency when considering resistance/failure to ovulation induction drugs. Some authors consider three cycles of increasing doses of CC and others consider a dose of 150 mg or 200 mg, with which there is no pregnancy and or ovulation.<sup>[3]</sup> Other ovulation induction drugs such as letrozole and metformin are also used when CC fails to enable pregnancy. At our Institute we encounter infertile women who have undergone ovulation induction with various ovulogens and approach us for further advice.

The options for those who fail to conceive with oral ovulation drugs include gonadotropins with or without intrauterine insemination (IUI), ovarian drilling, and *in vitro* fertilization (IVF). Gonadotropin treatment is costly, time-consuming, and

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associated with hyperstimulation and multiple pregnancy.<sup>[4]</sup> Ovarian drilling is a cost-effective procedure that brings about a decrease in intraovarian androgens and facilitates ovulation. It also corrects the metabolic and hormonal abnormalities associated with PCOS. IVF is costly and the pregnancy rate is comparatively low, and many of the women who attend our Institute cannot afford the cost of gonadotropins. Hence this study was aimed to determine the pregnancy rate after laparoscopic ovarian drilling (LOD) in infertile PCOS women who were resistant to oral ovulation-inducing drugs.

### Setting and design

The setting was a tertiary care center without assisted reproductive techniques (ART) facilities, catering to patients with general gynecological problems from all socioeconomic strata. This was a prospective observational study involving women resistant to oral ovulation induction drugs. The period of study was from 2008 to 2012.

## MATERIALS AND METHODS

Forty-eight infertile PCOS (diagnosed as per Rotterdam criteria) cases who did not achieve pregnancy after three or more cycles of CC/CC and metformin combination and leterozole. All women were screened for endocrine abnormalities. Day 2 follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, and prolactin levels were done; glucose tolerance test (GTT) and thyroid profile were done. Hyperandrogenic PCOS (hyperandrogenemia) cases were treated with six cycles of Krimson 35 and a repeat serum testosterone was obtained and when it was normal, they were given ovulation induction with CC and those who did not conceive after three cycles were recruited for LOD. Similarly, hypothyroidism and diabetes were treated and when the values were within normal limits they were recruited. LOD was carried out as an outpatient procedure under general anesthesia. Three-port technique was used. After stabilizing the ovary with a nontoothed forceps (Maryland), four to five punctures were made using the drilling needle (8 mm in length and 2 mm in diameter) with 40 watts monopolar current. The duration of cauterization was for 10 s, unlike what was described as 4-5 s in previous studies. Saline irrigation was done with 500 mL of normal saline after doing chromotubation. All women received single-dose ceftriaxone and the procedure was carried out by the author (single investigator). They were advised to cohabit normally and return after 3 months if pregnancy did not occur. Ovulation induction with 150 mg of CC and 500 mg of metformin three times daily was initiated after 3 months. The pregnancy rate was calculated after 3 months and 6 months. Those who achieved pregnancy with metformin and CC continued metformin throughout pregnancy. All women with type 2 diabetes mellitus (T2DM) were also on metformin during pregnancy.

## RESULTS

Of the 48 women recruited, 3 were lost for follow-up as they were from far-off places. Hence, they were excluded. The clinical profile of the women is shown in Table 1. The mean age was 28 years and the mean duration of infertility was 4.3 years (range 2-10 years). Eight percent had hyperandrogenism and 4% had hyperprolactinemia. Six percent suffered from hypothyroidism and 4% from T2DM. Six percent had hypothyroidism as well

as T2DM. Outcome is represented in Table 2. At 3 months the pregnancy rate was 30.7% with 13% conceiving in the same cycle, 11% in the next cycle and 6.7% in the third cycle. After 3 months and within 6 months, 35.5% conceived with ovulation induction employing metformin and CC. Ten percent suffered from early pregnancy loss and 90% had live births. Two patients experienced bleeding from ovarian ligament during the procedure and 1 of them needed laparotomy to control hemorrhage due to technical difficulties. The woman who underwent laparotomy conceived in the third month and had normal delivery.

## DISCUSSION

The problem of nonresponse to CC is common in practice and is reported to be 15-40%. CC resistance can be tackled medically or surgically. The NICE guideline for CC-resistant PCOS advice in offering women LOD or combined treatment with CC and metformin or gonadotropin therapy depending on the clinical circumstances and preferences of women.<sup>[5]</sup> A prospective study done by Malkawi *et al.*, which compared metformin therapy with ovarian drilling in CC-resistant infertile PCOS women, concluded that there was no significant difference in ovulatory rate and pregnancy rates, and hence women with CC resistance could be offered either of these. The pregnancy rates with metformin and ovarian drilling were 64.1% and 59.8%, respectively.<sup>[1]</sup> In our population, the pregnancy rates were much lower when metformin and CC combination was employed for CC-resistant infertile PCOS.<sup>[6]</sup> Hence, there was a need for an alternative therapy.

Kaya *et al.* randomized 35 CC-resistant infertile PCOS women to laparoscopic multineedle intervention and ovulation induction with gonadotropins followed by IUI. They did not find any significant difference in pregnancy rates between the two groups (35.3% vs 33.3%), and the pregnancy rate in this study was low.<sup>[3]</sup> The Cochrane review in 2010, which analyzed five eligible randomized controlled trials (RCTs), concluded that the cumulative conception rate at 6 to 12 months after ovarian drilling is equal to three to six cycles of gonadotropin therapy with the advantages reduced incidence of OHSS and multiple pregnancy.

**Table 1: Clinical profile**

| Characteristic               | Number (%) N = 45 |
|------------------------------|-------------------|
| Mean age in years            | 28                |
| Mean duration of infertility | 4.3 years         |
| Hyperandrogenic PCOS         | 4 (8%)            |
| Hyperprolactinemia           | 2 (4%)            |
| Hypothyroidism               | 3 (6%)            |
| T2DM                         | 2 (4%)            |
| Hypothyroidism and T2DM      | 3 (6%)            |

**Table 2: Conception after ovarian drilling**

| Duration to conception            | Pregnancy (%) rate |
|-----------------------------------|--------------------|
| ≤3 months                         | 14 (30.7)          |
| Same cycle                        | 6 (13)             |
| Second cycle                      | 5 (11)             |
| Third cycle                       | 3 (6.7)            |
| >3 to 6 months (metformin and CC) | 16 (35.5)          |
| 6 months                          | 66                 |

The ovarian response after administration of either metformin or ovarian drilling to CC in CC resistant PCOS was studied by Palomba *et al.* CC was given at a dose of 150 mg for 5 days for 6 months. There was no significant statistical difference in ovulatory and pregnancy rates between the two groups and the pregnancy rate was only 16% with a sample size of 28 women.<sup>[4]</sup> In an effort to examine whether the ovulatory and pregnancy rates could improve with laser used for drilling, Takeuchi *et al.* conducted a prospective study using two types of lasers: Harmonic scalpel and ND-YAG. The cumulative pregnancy rate after 2 years of follow-up was 77% with harmonic scalpel and 60% with neodymium-doped yttrium aluminium garnet laser (ND-YAG).<sup>[7]</sup> A pregnancy rate of 47.8% at 2 years was reported in a study involving 69 infertile PCOS women who failed to conceive with CC. A monopolar current of 35 watts was used and electrical diathermy was carried out for 2-4 s only.<sup>[8]</sup> Gjonnaess, who invented LOD, used 200-300 watt current for 2-4 s and made three to eight punctures on each ovary. He reported a pregnancy rate of 69% and an abortion rate of 15%.<sup>[9]</sup> In the present study, a 40-watt current was used but the duration was for 10 s and a maximum of five punctures and a minimum of two punctures were made depending on the size of the ovaries. This is to ensure adequate cauterization of stroma. With this modification the pregnancy rate was 30% at 3 months, the total pregnancy rate was 66% at 6 months, and 10% aborted. Most of the studies in the literature followed the rule of 4, i.e., using 40-watt current for 4 s and making four punctures on each ovary. It was our observation (prior to this study) that women who underwent LOD employing cautery for 2-4 s did not achieve pregnancy (unpublished thesis done by different authors at our Institute). Hence, it was thought to increase the duration of cauterization for 10 s without increasing the amount (in watt) of current to the ovary.

The ovulatory and pregnancy rates are supposed to be dependent on the dose of the actual current delivered and increasing rates reported with increasing doses up to 600 J per ovary. The lowest effective recommended dose was 600 J per ovary irrespective of ovarian volume or size.<sup>[10]</sup> Adjusting the dose of thermal energy depending on the ovarian volume was also found to give better outcomes.<sup>[11]</sup> To investigate the optimum number of punctures and dose/response relationship, a retrospective analysis of 161 women who underwent drilling was analyzed by stratification of number of punctures. They concluded that two punctures per ovary had poor results, three punctures had plateau results, and seven or more punctures resulted in damage to ovary without increasing the results.<sup>[12]</sup> Following the initial work of Gjonnaess, different investigators have used various numbers of punctures varying 3-25 per ovary and there was no consensus regarding the amount of thermal energy used. Increase in thermal energy damages and increases the chance of ovarian atrophy; however, the dose of thermal energy that causes ovarian atrophy is not known. Armar *et al.* concluded that four punctures per ovary were sufficient to give good results and no improvement could be expected by increasing the number of punctures.<sup>[13]</sup> The total amount of electrical energy delivered to each ovary was calculated to be more than 3700 J in the Gjonnaess study and 640 J by Armar *et al.*<sup>[12]</sup> In the present study, the amount of thermal energy delivered varied 800-1600 per ovary. In the retrospective study, Amer *et al.* found 450 J per ovary at plateau results and recommended prospective studies to find the optimum dose of thermal energy required.

The theoretical problem of concern with diathermy of the ovaries is decreased ovarian reserve, which is detrimental for infertile women. Anti-Müllerian hormone (AMH), a marker of ovarian reserve, is found to be increased by two- to threefold in women with PCOS. A study to address the issue of decreased ovarian reserve after ovarian diathermy assessed serum AMH prior to and after LOD. The cutoff level of AMH was 7.7 ng/mL, above which the chances of pregnancy were reduced. Following LOD, the median plasma AMH level significantly decreased to 4.6 ng/mL ( $P = 0.003$ ) and remained low at 3 months and 6 months of follow-up. Women who ovulated subsequent to LOD had significantly low pretreatment AMH levels than those who did not ovulate. AMH was found to be a good predictor of no ovulation following LOD with a sensitivity of 78% and specificity of 76%. Women who failed to ovulate after LOD had high pretreatment AMH values and in these women the follicle destruction by LOD may not have been sufficient to reduce intraovarian AMH levels.<sup>[14]</sup>

The pregnancy rate and outcome reported by various authors and the present study are shown in Table 3. The amount of thermal energy used varied with each other and the follow-up also varied, though the pregnancy rate was more than 50% in all the studies.. A pregnancy rate of 55% and a miscarriage rate of 6% was reported as early as 1998 in women with PCOS with anovulatory infertility.<sup>[15]</sup> The follow-up of women who underwent laparoscopic ovarian diathermy for 4-5 years at All India Institute of Medical Sciences (AIIMS) reported a pregnancy rate of 54.5%.<sup>[16]</sup> High LH levels, duration of infertility, and preexisting tubal disease were the factors that affected the outcome after ovarian drilling.<sup>[15,16]</sup>

The consensus on infertility treatment of PCOS recommends six cycles of CC with or without metformin as first-line therapy, laparoscopic ovarian surgery or gonadotropin stimulation as second-line treatment, and IVF as third-line therapy.<sup>[17]</sup> An economic evaluation of laparoscopic ovarian diathermy versus gonadotropin therapy for women with CC-resistant PCOS concluded showing reduced direct and indirect costs (20% lower) with ovarian drilling, with the added advantage of reduction in multiple pregnancy.<sup>[18]</sup> A recent large review addressed the role of LOD as an alternative therapy for young PCOS women with raised LH levels, those needing laparoscopic assessment, nonfeasibility for follow-up of intensive monitoring, noncompliance, and for those who showed exaggerated response to gonadotropins.<sup>[19]</sup>

## CONCLUSION

The pregnancy rate following LOD is >50% in CC-resistant PCOS, hence it can be concluded that LOD reduces the need for

**Table 3: LOD: Pregnancy rate and outcome**

| Author                           | Year | Number of subjects | Pregnancy (%) rate | Miscarriage (%) rate |
|----------------------------------|------|--------------------|--------------------|----------------------|
| Gjonaess <sup>[9]</sup>          | 1984 | 62                 | 69                 | 15                   |
| Li <i>et al.</i> <sup>[14]</sup> | 1998 | 118                | 55                 | 6                    |
| Kriplani <sup>[15]</sup>         | 2001 | 66                 | 55                 | —                    |
| Amer <i>et al.</i>               | 2004 | 200                | 50                 | 9                    |
| Kucuk <i>et al.</i>              | 2005 | 22                 | 54                 | 8                    |
| Amer <i>et al.</i>               | 2009 | 29                 | 66                 | 12                   |
| Present study                    | 2014 | 45                 | 66                 | 10                   |

ART by 50% in CC-resistant PCOS and is a safe option, especially for women who cannot afford the cost of ART.

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#### Conflicts of interest

There are no conflicts of interest.

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