

OVULATION INDUCTION USING LAPAROSCOPIC OVARIAN DRILLING IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME : PREDICTORS OF SUCCESS

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ABSTRACT

Background: Anovulatory infertility is present in 75% of patients with polycystic ovarian syndrome (PCOS), in addition to oligomenorrhoea and signs and symptoms of hyperandrogenism.

Objective: This study was performed to find the role of laparoscopic ovarian drilling (LOD) in correcting anovulation, menstrual irregularities and failure of conception. Possible role of the factors as the predictors of success was also studied.

Method: This prospective cohort study included 49 women who were diagnosed with PCOS and anovulatory infertility. These patients had already tried various ovulation induction drugs for conception, and underwent LOD between January 1, 2006 until December 31, 2008 in the Department of Gynaecology and Obstetrics, at the Tertiary Care Hospital, Lahore. The major outcome measures spontaneous ovulation, menstrual regularity after LOD and influence of various pre-operative characteristics on pregnancy rates.

Results: Among 49 patients 33 (67.3%) started to menstruate regularly and ovulated spontaneously in 59.2%, of them 23 (46.9%) conceived. Younger age (less than 25 years), duration and infertility less than 5 years and higher LH (more than 12 IU/lit) emerged as clinically significant factors to have impact on successful outcome. BMI > 27 Kg / m², cycle pattern, morphology of ovary, LH / FSH ratios did not manifest significant role.

Conclusion: Women with PCOS respond favourably to LOD.

INTRODUCTION

The pathology of polycystic ovarian syndrome (PCOS) was described by Stein and Leventhal in 1935. It is characterised by infertility, oligomenorrhoea or amenorrhoea, hirsutism, acne and bilaterally enlarged cystic ovaries.¹ Polycystic ovarian syndrome is the most common cause of anovulatory infertility, being found in 75% of cases.²

There are several treatment options for PCOS related anovulatory infertility. First line of treatment is usually clomiphene citrate, but when it course fails to result in conception, gonadotrophins or laparoscopic ovarian drilling (LOD) may be used as a second line treatment. Gonadotrophin use requires extensive monitoring because of high sensitivity of polycystic ovaries to exogenous gonadotrophins, with the risk of multiple follicle development leading to termination of cycle, ovarian hyperstimulation syndrome or multiple pregnancies.³ Laparoscopic ovarian drilling, on the other hand, involves a single procedure that has minimal morbidity and can lead to consecutive ovulations with minimal risks of multiple pregnancies.⁴ Sensitivity to clomiphene citrate increases after this treatment.⁵

Many authors have reported high ovulation (80%) and pregnancy rates (60%) following LOD.⁶ However 20 – 30% of anovulatory PCOS women fail to respond to LOD. 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 only minimal amount of thermal injury is required. Another possible explanation for failure to respond is an inherent resistance of the ovary to the effect of drilling.⁷

The reasons for variation in pregnancy rate are not clear because there are multiple factors affecting the outcome. If it was possible to identify the factors that determine the response of PCOS patients to LOD, the fruitless treatments could be avoided and success rates improved for ovulation and pregnancy.

The aim of this study was to evaluate the efficacy of LOD in the treatment of anovulatory infer-

tility in PCOS. We also identified the demographic and clinical factors that can predict the successful outcome of LOD in PCOS.

METHODS

During the period from January 2006 through December 2008, fifty five patients of PCOS who underwent LOD using diathermy were included in this study.

Inclusion Criteria

Women between 20 – 35 years age and BMI between 20 – 30, treated with clomiphene citrate but failed to ovulate or get pregnant, were included in this study.

Exclusion Criteria

The following patients were excluded:

- Associated infertility factors such as bilateral tubal block, severe male factor (sperm density < 10 million / ml, motility < 30%, morphology < 10%) or moderate to severe endometriosis.

The diagnosis of PCOS was based on the Rotterdam criteria which necessitate two of the following three features to be present for diagnosis: i) oligomenorrhea and / or anovulation; ii) clinical and / or biochemical signs of hyperandrogenism; and iii) ultrasonic confirmation of polycystic ovaries.

The hormonal profile including FSH, LH, prolactin, thyroid levels were carried out in the Shalamar Hospital laboratory on 3rd day of menses or any indexed day in amenorrhoeic patients. In obese patients fasting serum insulin was also estimated. Abdominal / vaginal ultrasound was performed. Diagnosis was based on ultrasound evidence of stromal hypertrophy and more than 10 small follicles (2 – 9 mm) arranged peripherally. Ovarian volume more than 10 was considered as part of diagnosis.

Demographic features of each patient including age, BMI, duration of infertility, type of infertility (primary or secondary), and associated clinical features of hyperandrogenism such as acne and hirsutism were noticed. The technique of LOD used in this hospital is three puncture approach laparoscopy. Force 2 Vallylab electro-surgical units set at monopolar coagulation current at 30 watts was used. A laparoscopic ovarian diathermy needle made of stainless steel and measuring 8mm in length and 2mm in diameter produced by Wolf Germany was used. Duration of each penetration was 5 sec. About 3–10 punctures, 2mm in diameter and 7–8 mm in depth, were made in each ovary. At the end of each procedure, operative site was irrigated with 200ml Hartman's solution to cool the surrounding area.

Post – Operative Monitoring

Following ovarian drilling women were asked to keep a record of their menstrual cycle. If she started to

menstruate regularly serum progesterone was performed on day 21 to confirm the ovulation. Ovulation was diagnosed when the level was more than or equal to 30 nmol/l. If ovulation was not confirmed, clomiphene citrate was started as an adjuvant at 6 – 8 wks after surgery. If ovulation was achieved either spontaneously or with the help of clomiphene citrate, patients were followed up until they conceived or until 12 months after LOD. Some patients needed gonadotrophins as well.

Informed consent of the patients was taken. Hospital ethical committee approval was taken. Statistical analysis by SPSS (Student Version) 12 was carried out. Proportions were compared by chi-square method while continuous variables were presented as mean, standard deviation and percentages where applicable. A p value of <.05 was taken as statistically significant.

RESULTS

A of 55 women with the diagnosis of PCOS underwent laparoscopic ovarian drilling during the study period. Two women with blocked tubes and one with severe male factor were excluded from the study whereas 3 patients were lost to follow-up. Demographic features of the remaining 49 patients are presented in the Table I. Mean age of the patients was 25.35 ± 3.4 and BMI was 27.82 ± 3.5 Kg/m² (SD 3.5) that ranged between 18.8 to 35.7 Kg/m². Twenty seven (55.1%) patients had LH:FSH ratio > 2. Mean LH level was 11.32 IU/L (range 2.2 – 17.9). Forty four (89.8%) patients had ultrasound features typical of PCOS. In 10.2% of patients, ovaries were normal looking on ultrasonography.

Clinical features of hyperandrogenism i.e., hirsutism and acne were present in 37 (75.5%) and 16 (32.7%) respectively. Degree of hirsutism was only assessed as mild / moderate or severe. Objective assessment according to Ferriman Galway score was not applied. Most of these patients had either oligomenorrhoea (63.3%) or amenorrhoea (30%). Only 6.1% patients had regular menstrual cycle. Forty six (93.9%) patients had already tried clomiphene citrate in various doses but failed to conceive, whereas 6.1% used gonadotrophins for ovulation induction.

The table 2 depicts the outcome in terms of cycle regularity, ovulation and pregnancy. Thirty three patients (67.3%) resumed regular menstruation after LOD whereas 16 (32.7%) patients failed to do so. After LOD spontaneous ovulation occurred in 59.2% patients; whereas 30.6% did so after supplemental CC and 10.2% responded after gonadotrophin use. Total pregnancies achieved after LOD were 23 (46.9%), out of these 2 resulted in miscarriage. The patients were followed up for 1 year only and pregnancies achieved in second year or after

were not included. Table 3 shows the impact of various factors on the treatment outcome. Age played a significant role in achieving the pregnancy. Twenty three patients who conceived had average age of 24.35 years while patients who failed to achieve pregnancy had a mean age of 26.23 years ($p < .05$). BMI in both groups did not show any difference. Both groups had BMI above 25 kg / m₂. Patients in successful group had mean weight of 26.96 kg / m₂ and non-successful group had a mean of 28.59 kg / m₂. Patients who have been married for less than 4 years were significantly more successful in achieving pregnancy as compared to those married beyond 4 years ($p = 0.003$).

Higher value of LH more than 12 showed a clinical significance as compared to non-pregnant group with LH more than 12 mmol/ml. The LH / FSH ratio of more than 2 did not show any clinical significance. In non-pregnant patients mean LH / FSH ratio was 1.9 while in pregnant women mean was 2.4.

Other factors such as primary or secondary infertility or initial cycle pattern whether oligomenorrhoea or amenorrhoea did not show any clinical significance. Similarly ultrasonic features of polycystic ovaries failed to predict successful outcome of LOD.

DISCUSSION

This study analysed the impact of LOD on cycle regularity, ovulation and cumulative conception rates as well as factors affecting the successful outcome. Among 49 PCOS women, 67.3% resumed regular menstruation and 58.8% started to ovulate spontaneously after LOD in this study. Some studies have quoted higher ovulation rates i.e around 80%.⁹ Difference in response may be attributed to the use of other forms of energy modalities such as CO₂ laser and Argon in addition to the diathermy.

Successful outcome as pregnancy occurring within 12 months after LOD was defined for 2 reasons. First, 12 months period seems reasonable to wait for conception, beyond which patient might be advised to pursue alternative treatment such as gonadotrophin ovarian stimulation or IVF.⁶ Although pregnancies do occur after 12 months, in this series of

Table 1: The characteristics of 49 PCOS women who had LOD for anovulatory infertility.

Characteristic	n	Mean	SD	Range
Age (years)	49	25.35	3.4	22 – 32
BMI	49	27.82	3.5	18.8 – 35.7
Duration of Infertility (years)	49	3.47	2.76	1 – 14
Serum LH (IU/l)	49	11.32	6.04	2.2 – 17.9
Serum FSH (IU/l)	49	5.20	1.25	3.2 – 7.1
Serum LH:FSH	49			
	n	%		
Menstrual Cycle Pattern				
Regular	3	6.1		
Oligomenorrhoea	31	63.3		
Amenorrhoea	15	30		
Hirsutism				
Yes	37	75.5		
No	12	24.5		
Acne				
Yes	16	32.7		
No	33	67.3		
Infertility				
Primary	43	87.8		
Secondary	6	12.2		
Other mild sub-fertility factors				
Absent	41	83.7		
Male	2	4.1		
Tubal	3	6.1		
Endometriosis	3	6.1		
Ultrasound evidence of PCO				
Atypical of PCOS	5	10.2		
Typical of PCOS	44	89.8		
Previous Treatment				
Clomiphene	46	93.9		
Clomiphene +HMG	3	6.1		

LH = Luteinising Hormone; FSH = Follicle Stimulating Hormone; HMG = Human Menopausal Gonadotrophins

patients there were 4 additional pregnancies between 12 and 24 months but they were not included in the result.

The cumulative conception rate of this study was 46.9% which is comparable to other studies in the literature. Lei, et al in a study of 111 PCOS patients showed 51.1% overall pregnancy rate. The difference could be explained because of higher BMI in

our study with a mean of 27.8 kg/m² versus 25.5 Kg/m².⁶ BMI correlates with both increased rate of cycle disturbance and infertility,⁹ even moderate obesity (BMI > 27 Kg/m²) is associated with reduced chances of ovulation and pregnancy secondary to disturbances in insulin metabolism.¹⁰

All our subjects had anovulatory infertility of more than one year duration and had been unsuccessfully treated with clomiphene citrate of 150 mg / day in early follicular phase prior to LOD. In 46 patients, clomiphene citrate failed to induce ovulation due to clomiphene citrate resistance. Three patients had tried gonadotrophins without any success. Patients resistant to clomiphene citrate have the choice of gonadotrophin therapy or LOD. Patients who are hyperinsulinemic can be given insulin sensitising agents. Alternatively, LOD is useful in clomiphene citrate resistant anovulatory women with PCOS and it is as effective as gonadotrophins for ovulation induction in such patients.⁵ LOD has the advantage of inducing monofollicular stimulation and avoids the risk of multiple pregnancy and hyperstimulation. It is cost effective in a sense that it does not require intensive monitoring which is mandatory in Gonadotrophin therapy.⁶

In this study evaluation of impact of various clinical, biochemical and ultrasonographic features of PCOS on the clinical outcome of LOD was also done. Analysis of this study showed 3 main factors to have significant impact on efficacy of LOD i.e. age, duration of infertility, and preoperative LH levels more than 12 IU/L. Duration of infertility less than 5 years had the strongest impact as a predictor of success ($p < .003$). These results are in agreement with a study by Amar et al. A possible explanation for the role played by the duration of infertility may be the emergence of other subfertility factors as duration of infertility increases.¹¹ Patient's age also emerged as a significant factor ($p < .05$). The younger women less than 25 years were more successful as compared to those of more than 25 years old.

LOD responders with pretreatment serum LH concentration of ≥ 12 IU/L achieved higher pregnancy rates ($p < .05$) than those whose LH was < 12 IU/L. After LOD, with restoration of ovarian activity, serum concentrations of LH and testosterone fall. This increases the chances of conception and reduces the risk of miscarriage.^{11,12} On the other hand exact mechanism of ovulation induction by LOD remains uncertain, unilateral diathermy leads to bilateral ovarian activity, suggesting that LOD achieves its effect by correcting the disturbance of ovarian pituitary feed back.¹² Balen et al hypo-

Table 2: Outcome of LOD for PCOS.

Outcome Measure	n	%
<i>Menstrual Cycle Pattern</i>		
Regular	33	67.3
Irregular	16	32.7
<i>Ovulation</i>		
Spontaneous	29	59.2%
With help of CC	15	30.6%
HMG	5	10.2%
<i>Pregnancy</i>		
Take home baby	21	42.8%
Miscarriages	2	4.1%
Ectopic	nil	0%
Unsuccessful	26	53.1%

Table 3: Possible factors affecting the outcome of LOD for PCOS patients. Comparison between conception and non conception groups.

Characteristic	Within 12 Months		P
	Pregnant (n = 23)	Not Pregnant (n = 36)	
Age	24.35 (3.27)	26.23 (3.40)	.05
BMI	26.96 (3.05)	28.59 (3.82)	NS
Duration of Infertility	2.52 (2.17)	4.83 (2.82)	.003
Pretreatment			
Serum LH (IU/l)	13.18 (7.52)	9.67 (3.80)	.04
Serum LH:FSH	2.45 (1.3)	1.96 (0.77)	NS
<i>Menstrual Cycle Pattern</i>			
Regular	2	1	
Oligomenorrhoea	16	15	
Amenorrhoea	5	10	
<i>Infertility</i>			
Primary	22	21	
Secondary	1	5	
<i>Associated fertility factors</i>			
Endometriosis	2	1	
<i>Ultrasound of PCO</i>			
Typical of PCOS	21	23	
Atypical of PCOS	2	3	

Values are as mean (SD); duration in years

thesized that ovarian injury leads to release of local cascade of growth factors such as IGF₁ that interacts with FSH and leads to follicular growth and ovulation. In addition to this, ovarian injury causes change in intraovarian environment from androgen to oestrogen excess by destroying the androgen producing tissue and this promotes follicular growth and ovulation.⁷

Although, patients who responded to LOD were overweight with mean BMI of 26.9 Kg/m² but there was upward trend in achieving pregnancy as compared to women with higher BMI but clinical significance was not achieved. Three patients had gross obesity (35 kg/m²). These patients neither achieved regular menstruation nor they ovulated. It is the policy of the unit to encourage obese women to lose weight by lifestyle modification before undergoing LOD surgery. Loss of weight helps in a change in hormonal milieu as well as making surgery free of anaesthesia risk.¹⁴ In a study of 252 patients who underwent LOD for anovulatory infertility, it was concluded that marked obesity (BMI ≥ 36 Kg/m²) achieved significantly lower ovulation rates as compared to the women with normal and moderately elevated BMI.

This study did not show the significant impact of menstrual cycle irregularity, LH / FSH ratio > 2, presence or absence of hirsutism or acne and PCOS morphology of ovary on the LOD outcome. The co-existent mild to moderate male factor and non obstructive tuboperitoneal factors in a small subgroup of women did not appear to significantly influence the outcome of treatment.

This study has **concluded** that LOD is successful in PCOS patients who fail to ovulate on CC. The procedure is more effective in a subgroup of patients with age < 25, duration of infertility < 5 years and pretreatment serum LH concentration of ≥ 12 IU/L. These observations may help in selecting and counseling the patients for LOD.

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