Original Article

Laparoscopic Ovarian Drilling Reduces Testosterone and Luteinizing Hormone/Follicle-Stimulating Hormone Ratio and Improves Clinical Outcome in Women with Polycystic Ovary Syndrome

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Abstract

Background: Laparoscopic ovarian drilling (LOD) is one of the common modes of treatment for women with polycystic ovary syndrome (PCOS) who are resistant to clomiphene citrate. The data related to the effect of LOD on sex hormones are limited. **Aim:** The objective of the study was to investigate the effect of LOD on hormonal parameters and clinical outcomes in women with PCOS. **Settings and Design:** This study was conducted in a tertiary care hospital. **Materials and Methods:** Fifty PCOS patients who were admitted for LOD were enrolled in the study. Serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels were estimated in all the patients before and after LOD. **Statistical Analysis:** Paired *t*-test was used to assess the differences in hormonal parameters before and after LOD. **Results:** LOD reduces testosterone ($P < 0.001$), LH ($P < 0.001$), and LH/FSH ratio ($P < 0.001$), increases FSH ($P < 0.001$) levels, and improves the rate of ovulation (38/50) and clinical pregnancy (21/50) in PCOS. When subgroup analysis was done, LOD significantly reduced testosterone and LH/FSH ratio in ovulatory and conceived groups. Furthermore, the menstrual cycle became regular, and hirsutism and acne were reduced after LOD in women with PCOS. **Conclusions:** LOD reduces testosterone and LH/FSH ratio and improves clinical outcome in PCOS.

Keywords: *Follicle-stimulating hormone, laparoscopic ovarian drilling, luteinizing hormone, polycystic ovary syndrome, testosterone*

Introduction

The prevalence of polycystic ovary syndrome (PCOS) is increasing in India, and a recent community-based study undertaken in Mumbai has reported a prevalence of 22.5% by Rotterdam and 10.7% by Androgen Excess Society criteria.[1] Although clomiphene citrate (CC) is considered as initial treatment for inducing ovulation in infertile PCOS women, around 20%–40% were reported to be resistant to CC.[2] Although the cause for CC resistance is unclear, previous studies have linked factors such as insulin resistance, hyperandrogenism, and obesity.[3]

Hyperandrogenism is the most important diagnostic component of PCOS. High concentration of circulating testosterone is demonstrated in 60%–80% of women with PCOS.[4] High androgen levels are reported to be associated with adverse pregnancy outcomes including reducing fetal weight.[5] Previous studies have demonstrated an association between elevated testosterone levels and increased metabolic risk factors in women with PCOS.[6]

Several studies have reported inappropriate gonadotropin secretion in PCOS.[7] Abnormal gonadotropin pulsatility

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seen in PCOS is characterized by excessive secretion of luteinizing hormone (LH) with normal secretion of follicle-stimulating hormone (FSH), and it has been attributed to reduced progesterone-mediated feedback inhibition of the gonadotropic-releasing hormone pulse generator.[8,9] A recent study has concluded that LH/FSH ratio could be used to predict the development of dominant follicle (DF) during ovulation induction with letrozole.[10] A previous study has hypothesized that FSH levels are reduced in PCOS women undergoing *in vitro* fertilization (IVF) and demonstrated the need for tailoring of FSH starting dose during controlled ovarian stimulation for intrauterine insemination cycles.[11,12]

Laparoscopic ovarian drilling (LOD) has been widely used as an effective treatment of anovulatory women with PCOS.[13] LOD is preferred in patients with PCOS, as it reduces the risk of OHSS and the multiple pregnancy rate induced by gonadotropin therapy.[14] Since there are limited data available about the effect of LOD on hormonal parameters, the present study was designed to analyze the testosterone, FSH, and LH levels before and after LOD.

Materials and Methods

This was a cross-sectional study with follow-up for 6 months. The study was approved by the Institute Ethics Committee for Human Studies (No. JIP/IEC/2014/14/260). Written informed consent was obtained from all the patients before the study. This manuscript conforms EQUATOR Network guidelines. LOD is a routine procedure done in our hospital to treat CC-resistant PCOS cases. Since this is an observational study, we did not register this study at Clinical Trials Registry-India.

Sample size calculation

The sample size was calculated presuming ovulation rate of 77% after LOD, for a power of 80%, a relative precision of 15%, and α error of 0.05. Based on these findings, the total sample size calculated was 50.[15]

Fifty infertile women who were diagnosed as PCOS and those who were resistant to CC (women who fail to ovulate or conceive with a minimum of three cycles of CC) were included in the study. Patients with other causes of infertility such as tubal factors and azoospermia were excluded from the study. Since the pregnancy rate is less in patients with tubal factors and male partners having azoospermia even after LOD, we excluded patients with these conditions from the study.

Blood sample collection

The blood samples for hormonal assays were collected by peripheral venipuncture after an overnight fast in the early follicular phase of menstrual bleeding (days 2–5) or progesterone-induced bleeding in all patients undergoing LOD. The induction of withdrawal bleeding with progestins has been considered a common procedure in patients with PCOS. A recent study has compared the effects of progesterone used to induce withdrawal bleeding on hormonal parameters in patients with PCOS and concluded that the administration of oral progesterone for withdrawal bleeding in PCOS patients did not significantly alter circulating androgen or 17-hydroxyprogesterone levels and suggested that it could be used to time blood sampling in these patients.[16]

LOD was done under general anesthesia by treating physician according to the standard protocol (4–5 punctures on each ovary using electrical diathermy needle, employing 40W coagulation current for 4–5 s) after noting all the findings regarding uterus, tubes, and ovaries. Peritoneal saline wash was given after the procedure. Following LOD, women were asked to keep a record of their menstrual cycle. The second blood sample was collected in the early follicular phase of the menstrual cycle or progesterone-induced bleeding after 3 months. For biochemical parameters, serum was separated and stored at −80°C until assayed. Testosterone, LH, and FSH levels were estimated by chemiluminescence (ADVIA Centaur CP, Siemens Diagnostics, Germany) using reagent kits from Siemens Diagnostics.

Improvement in menstrual cyclicity and hyperandrogenic symptoms was noted. Ovulation was confirmed by the development of follicle on transvaginal ultrasound. The ultrasound helps in monitoring the development of DF in the follicular phase and also helps in increasing the dose of the drug if DF is not formed. The presumptive evidence of ovulation is the disappearance of DF and the presence of free fluid in the Pouch of Douglas. Follicular monitoring was done for three cycles, and spontaneous conception was awaited. Twenty-five women who did not conceive at the end of 3 months were treated with metformin and CC combination regimen and four women were referred to assisted reproductive technology (ART). All patients were followed up to the end of the study (6 months).

Statistical analysis

The results were expressed as mean and standard deviation. Testosterone, LH, and FSH levels were compared between before and after LOD using paired *t*-test. $P < 0.05$ was considered statistically significant.

Results

The effect of LOD on hormonal parameters and clinical symptoms is shown in Table 1. Testosterone, LH, and LH/FSH ratio were significantly reduced, and FSH was

significantly increased in PCOS women after LOD when compared with baseline values. The menstrual cycle became regular in 82% (n = 41); hirsutism (n = 37) and acne (n = 49) were reduced after LOD in women with PCOS.

Table 2 shows the effect of LOD on hormonal parameters in ovulatory and nonovulatory groups. Testosterone, LH, and LH/FSH ratio were significantly reduced, and FSH was significantly increased in PCOS women after LOD in both ovulatory and nonovulatory groups.

Table 3 shows the effect of LOD on hormonal parameters in conceived and nonconceived groups. Testosterone, LH, and LH/FSH ratio were significantly reduced, and FSH was significantly increased in PCOS women after LOD in both conceived and nonconceived groups.

In the present study, 21 (55.3%) patients were conceived within 6 months after LOD. Of the 21 patients, 10 patients were conceived spontaneously within 3 months of LOD and 11 women were conceived with ovulation induction within 6 months after LOD. After 1½ months of gestation, one patient had a spontaneous abortion and one had a ruptured ectopic pregnancy. Eleven delivered at term of which five patients underwent cesarean section and six had normal vaginal delivery. Eight patients are ongoing pregnancies with no comorbidities and have good fetal well-being. Only one twin pregnancy was noted in the conceived group who had conceived in the first cycle of ovulation induction with CC along with gonadotropin after 3 months of LOD. The data related to exact outcome in different treatment groups (metformin/CC or ART) were not available as those women did not come for regular follow-up.

Table 1: Effect of laparoscopic ovarian drilling on hormonal parameters and clinical symptoms in polycystic ovary syndrome (n=50)

Parameter	Before LOD	After LOD	*P*
Age (years)	27±4	-	
Body mass index (kg/m^2)	26.3±4.5	-	
LH (mIU/ml)	13.95±4.44	8.30±2.73	<0.001
FSH (mIU/ml)	5.55±1.56	6.62±1.61	<0.001
LH/FSH ratio	2.60±0.77	1.27±0.35	<0.001
Testosterone (mg/L)	80.66±34.83	47.56±20.37	<0.001
Menstrual cycle (irregular/regular)	40/10	9/41	
Hirsutism (yes/no)	18/32	13/37	
Acne (yes/no)	10/40	1/49	

LOD=Laparoscopic ovarian drilling, LH=Luteinizing hormone, FSH=Follicle-stimulating hormone

Discussion

Several investigators have revealed insulin resistance as one of the factors which play a crucial role in the pathogenesis of PCOS. Insulin resistance has been found to associate with hyperandrogenism in PCOS. Insulin sensitizers such as inositols are reported to be effective in the treatment of PCOS. It was demonstrated previously that inositol isoforms improve ovarian stimulation parameters and hormonal and metabolic parameters, thereby inducing ovulation.[17-19] Furthermore, it has been shown that different fasting regimens reduce insulin resistance and hyperandrogenism and improve ovarian function and infertility in PCOS women.[20,21]

LH hypersecretion is considered as a hallmark of PCOS, and women with PCOS having high LH levels were reported to have significantly lower rates of ovulation, fertilization, and pregnancy when compared with normal

Table 2: Effect of laparoscopic ovarian drilling on hormonal parameters in the ovulatory and nonovulatory groups in polycystic ovary syndrome

Biochemical parameters	Ovulatory group (n=38)			Nonovulatory group (n=12)		
	Pre-LOD	Post-LOD	*P*	Pre-LOD	Post-LOD	*P*
LH (mIU/ml)	13.74±4.26	7.66±2.09	<0.001	14.62±5.11	10.32±3.55	0.001
FSH (mIU/ml)	5.46±1.53	6.59±1.62	<0.001	5.83±1.71	6.70±1.63	0.003
LH/FSH ratio	2.61±0.78	1.18±0.27	<0.001	2.57±0.79	1.57±0.41	<0.001
Testosterone (mg/L)	78.50±37.92	43.40±19.02	<0.001	87.53±22.37	60.73±19.56	<0.001

LOD=Laparoscopic ovarian drilling, LH=Luteinizing hormone, FSH=Follicle-stimulating hormone

Table 3: Effect of laparoscopic ovarian drilling on hormonal parameters in conceived and nonconceived groups

Biochemical parameter	Conceived group (n=21)			Nonconceived group (n=29)		
	Pre-LOD	Post-LOD	*P*	Pre-LOD	Post-LOD	*P*
LH (mIU/ml)	13.95±3.77	7.47±2.00	<0.001	13.95±4.94	8.90±3.04	<0.001
FSH (mIU/ml)	5.72±1.37	6.85±1.65	<0.001	5.43±1.70	6.45±1.59	<0.001
LH/FSH ratio	2.49±0.59	1.09±0.18	<0.001	2.68±0.88	1.40±0.38	<0.001
Testosterone (mg/L)	67.17±20.04	35.72±15.80	<0.001	90.44±40.01	56.14±19.15	<0.001

LH=Luteinizing hormone, FSH=Follicle-stimulating hormone, LOD=Laparoscopic ovarian drilling

LH levels of PCOS patients.[22,23] Previous studies have documented elevated LH/FSH ratio in PCOS and demonstrated that LH/FSH ratio predicts ovulation induction in PCOS women.[10,24] At cutoff value of 11.5 IU/L, LH has been shown to predict spontaneous ovulation after LOD in CC-resistant PCOS women with 88% sensitivity and 79% specificity.[25] Laganà *et al*. have demonstrated that myoinositol supplementation reduces gonadotropin levels and the length of controlled ovarian hyperstimulation (SL) in PCOS women undergoing IVF.[19] In the present study, LH was significantly reduced, FSH was significantly increased, and LH/FSH ratio was reduced in PCOS women after LOD. These findings were supported by earlier studies which reported a reduction in LH/FSH ratio after LOD.[26,27]

Several studies have reported a high prevalence of hyperandrogenemia in women with PCOS.[28] Hyperandrogenism is considered to be responsible for ovarian morphology and ovulatory dysfunction in animal models as well as in women with PCOS.[29] Hyperandrogenism has been attributed by earlier investigators to thecal cell dysfunction of polycystic ovaries.[30] Previous investigators have demonstrated a reduction in testosterone levels after ovarian drilling.[26,27] In agreement with these findings, the present study also showed a significant reduction in testosterone levels after LOD.

When subgroup analysis was done in PCOS patients between ovulatory, nonovulatory, conceived, and nonconceived groups before and after LOD, we observed a significant reduction in LH/FSH ratio and testosterone levels in both ovulatory and conceived groups after LOD, indicating that LOD improves clinical pregnancy and ovulation rate in PCOS patients. Furthermore, there was an improvement in clinical symptoms such as regularization of the menstrual cycle and reduction in hirsutism and acne after LOD.

Even though the mechanism through which LOD improves ovulation rate is not clear, earlier studies have suggested that LOD causes destruction of ovarian stroma which is the primary source of androgen and hence decreases the amount of substrate available for peripheral aromatization to estrogens.[31] A reduction in circulating estrogen helps in restoring the feedback mechanism to hypothalamus and pituitary leading to pulsatile gonadotropin secretion required for follicular growth and development.[31] LOD also leads to decrease in inhibin production along with a subsequent rise in FSH production.[15] All the above factors may potentiate follicular growth and hence improve ovulation in PCOS patients.

The main limitation of the study was only testosterone, and LH and FSH were estimated in the study. Prolactin and metabolites of testosterone were not estimated due to financial constraints.

Conclusions

The finding from the present study concludes that LOD reduces testosterone and LH/FSH ratio in women with PCOS and improves clinical symptoms, ovulation rate, and pregnancy rate in these women.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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