

Hope for clomiphene citrate resistant ovaries

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ABSTRACT

Objectives: To assess the presentation, different surgical modalities and their outcome in the treatment of polycystic ovarian disease.

Methods: A retrospective study was carried out on 66 patients with polycystic ovarian disease. The majority of the cases had a history of infertility for at least 2 years and were known to be clomiphene citrate resistant in the Saudi German Hospital, Jeddah between 1994 and 1998 undergoing laparoscopic ovarian drilling.

Results: More than 80% of the patients were below 30 years of age. The majority of cases below 30 years had primary infertility. Irregular cycle was the main clinical presentation in 75% of cases; ovarian volume was more

than 5.5cm³ in all of the cases. Diathermy drilling was carried out for 50 patients, laser for 12 patients and wedge resection for 4 patients. The follow-up treatment showed that pregnancy rate was 23%, 38% and 0% in the 3 groups. Cases that failed to conceive had significantly higher luteinizing hormone level.

Conclusion: Laparoscopic ovarian drilling using diathermy or laser is effective during the induction of ovulation and increases the pregnancy rate in cases of polycystic ovarian disease resistant to clomiphene citrate.

Keywords: Polycystic ovarian disease, laparoscopy, drilling.

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Polycystic ovarian disease (PCO) is the most common endocrine disorder in women of reproductive age. The clinical presentations are those of hyperandrogenemia like hirsutism, acne, together with anovulation, infertility and oligomenorrhea.¹ Anovulatory infertility is a common presenting symptom of PCO.² There are several treatment options. The first line is clomiphene citrate, but its usage for more than 12 months has been associated with ovarian cancer.³ Human menopausal gonadotrophins or laparoscopic ovarian drilling may be used as a 2nd line of treatment.⁴ When gonadotrophins are used, there are health risks associated with ovarian hyperstimulation syndrome as well as those of multiple pregnancy.³

Methods. Sixty-six cases of polycystic ovarian disease with a history of infertility and resistance to clomiphene therapy for at least 2 years were presented to the Saudi German Hospital, Jeddah between January 1994 and December 1998. The following parameters were recorded: age, duration and type of infertility, obesity, acne, hirsutism (using Gallway scoring),⁵ details of menstrual history (amenorrhea, oligomenorrhea, irregular cycles), past medical induction of ovulation and its duration. The diagnosis of PCO was primarily based on the clinical presentation of oligomenorrhea, obesity or hirsutism or both in the presence of typical ultrasound appearance of polycystic ovarian transvaginal ultrasound examination.^{6,7} In addition to

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Table 1 - Relation between the age of patients and their complaints.

Complaints	AGE (YEARS)									
	<25 n=22		25-29 n=32		30-35 n=8		>36 n=4		Total n=66	
	No.	%	No.	%	No.	%	No.	%	No.	%
Infertility (64)	22	100	32	100	7	87.5	3	75	64	96
*primary (42)	18	82	22	69	2	29	0	0	42	66
*secondary (22)	4	18	10	31	5	71	3	100	22	34
Irregular Cycles (50)	19	86	26	81	4	50	1	25	50	76
Hirsutism (35)	7	32	17	53	7	87.5	4	100	35	53
Obesity (30)	5	23	14	44	7	87.5	4	100	30	46

the estimation of ovarian volume via ultrasound, hormonal profile for follicle-stimulating hormone (FSH), luteinizing hormone (LH) and FSH/LH ratio was performed in all patients pre-operatively. Testosterone and prolactin and other hormonal assays were not carried out for economical reasons. Tubal patency was documented by hysterosalpingogram (HSG) and male factor was excluded by semen analysis. The laparoscopic findings were recorded as well as the procedure whether electrocautery, laser drilling or wedge resection.

Statistical Methods. The statistical analysis was carried out using Fisher exact test SPSS software. The statistical tests used were Chi Square for association between categorical variable, Yates corrected X^2 was carried out when suitable and t-test to assess the significance between the 2 means. The P value of <0.05 was used as the cut off level for significance.

Results. Table 1 shows that of the 66 patients with PCO disease included in the study, 54 patients

(82%) were from the young group (<30 years). Infertility was the main presenting symptom in 96% of the patients (64 patients). The only 2 patients who did not complain of infertility were unmarried. Out of the 64 infertile cases studied 65% (42 patients) had primary infertility while 34% (22 patients) had secondary infertility (Table 1). Irregular cycles and hirsutism were combined symptoms in most patients. Irregular cycle was the main clinical presentation in three-quarters of patients with PCO (76%) while hirsutism was seen in more than half the patients (Table 1). Out of the 35 hirsute patients, only 17% (6 patients) became pregnant after surgery, 5 of whom had mild hirsutism and only one had moderate hirsutism.

FSH/LH ratio and ovarian volume in PCO. Table 2 shows that 49 patients (75%) with polycystic ovaries had reversed FSH/LH ratio. A significantly higher percentage of patients with ovarian volume of 7-10 cm³ (88%) and 75% of those with ovarian volume >10cm³ had reversed FSH/LH ratio compared to 60% of patients with smaller ovarian volume (P=0.0467).

Table 2 - Relation between FSH/LH ratio and ovarian volume.

FSH/LH Ratio	< 7cm ³		7-10 cm ³		> 10 cm ³		Test of significance
	No.	%	No.	%	No.	%	
Normal (n=17)	12	40	4	12.5	1	25	$X^2 = 6.12$ P = 0.0467
Reversed (n=49)	18	60	28	87.5	3	75	
Total	30	100	32	100	4	100	

FSH=follicle-stimulating hormone, LH=luteinizing hormone, P=test of significance

Table 3 -Relation between type of surgery and level of luteinizing hormone and occurrence of pregnancy after surgery during follow up period.

Variables	Got pregnant (n=10)		Failed to get pregnant (n=30)		Total (n=40)		Test of significance
	No.	%	No.	%	No.	%	
Type of surgery							# Yates' corrected $\chi^2 = 0.35$ P = 0.556
- Diathermy	7	23	23	77	30	75	
- Laser	3	37.5	5	62.5	8	20	
- Wedge resection	0	0	2	100	2	5	
Luteinizing hormone							T = 6.33 P < 0.0019
Min-Max	6.8 - 10.2		10.2 - 16.3		6.8 - 16.3		
X ± S	8.56 ± 1.02		12.5 ± 1.9		11.52 ± 41		
X=mean, S=standard deviation							

Mode of Surgery Diathermy ovarian drilling was carried out for 50 patients (76%), laser drilling for 12 (18%) and 4 patients with ovarian volume of >10cm³ underwent wedge resection. The number of patients studied was 66 and only 40 patients returned for follow-up after surgery. The reversed FSH/LH ratio was demonstrated in 49 out of the 66 patients with PCO before the follow-up, and out of the 40 patients who came for follow-up the LH level was higher in those who failed to become pregnant (Table 3). Table 3 also shows that out of the 30 patients that underwent diathermy and continued follow-up, only 23% became pregnant. This is compared to 38% of those who underwent laser drilling and became pregnant. None of those with wedge resection became pregnant in the follow-up period.

Discussion. Polycystic ovarian disease is a heterogeneous group of conditions. It ranges from individuals with normal body weight, regular menstrual cycles with ultrasonic findings of polycystic ovaries to those of the full clinical picture of oligomenorrhea, obesity, hirsutism and hyperandrogenemia.⁸ Management of PCO is also heterogeneous ranging from medical hormonal treatment to surgical laparoscopy alone or medical and surgical modalities.⁸ Doneski et al⁹ and Adashi et al,¹⁰ reported successful induction of ovulation following laparoscopic ovarian drilling using diathermy or various forms of laser and the success rate varies from 20 to 88%. In the present study, 66 cases underwent surgical laparoscopy after failed medical treatment. Sixty-four patients were infertile and 2 were unmarried. So 96% of our patients were

infertile, which is in agreement with Goldzieher and Young.¹¹ Most of our patients (82%) were below 30 years of age. The immediate post-pubertal onset of symptoms remains an important criterion in the pathogenesis of disorder.¹² Hypersecretion of LH occurs in approximately 40% of women ultrasonographically diagnosed with PCO.³ Conway et al,¹³ in a study of 556 patients found that those complaining of infertility had significantly high LH concentration (11.3 IU/L) and those not complaining of infertility had a mean of 6.7 IU/L. Our results show that resistant cases that failed to conceive had a high mean of LH (12.5). They also demonstrate reversed FSH/LH ratio in 75% of cases (49 patients out of the total 66). Hyperinsulinemia encountered in PCO caused a direct increase in testosterone secretion by the ovary, which reduces synthesis of sex hormone binding globulin by the liver leading to increased free testosterone and hirsutism.^{13,14} Hence our results show 35 hirsute patients, out of whom 17% (6 patients) became pregnant after surgery: 5 with mild hirsutism and only one with moderate hirsutism.^{15,16} Obesity was also manifest in 30 patients with PCO. Obesity is associated with insulin resistance and the body mass index correlates with an increased rate of hirsutism. Achieving regular ovulatory cycles should remain a main concern in managing PCO, as chronic anovulation results in infertility and a greater risk of developing endometrial carcinoma and perhaps breast cancer.^{17,18} Surgery for PCO helps to achieve regular ovulatory cycles. The results of our study showed that laparoscopic drilling by electrocautery or laser, led to pregnancy in 23% and 38% compared to none in those that underwent wedge resection. Our results match with those of Soliman et al, which reveal a

pregnancy rate of 38% after ovarian cautery.¹⁹ Gjonnaes found that after ovarian electrocautery there was a significant decrease in androgen and gonadotrophins, a clear shift from anovulation to ovulatory cycles and an increase in sex hormone binding globulin. These effects continued for many years and two thirds of the women were still ovulating after 18-21 years.²⁰ Laparoscopic ovarian drilling remains the hope for clomiphene resistant ovaries. Moreover, the long lasting hormonal changes that take place after ovarian electrocautery improves the general health of the patient and thus reduces the risk of developing diseases such as diabetes mellitus, endometrial carcinoma, ovarian cancer, myocardial infarction and hypertension, all of which are associated with PCO.²¹

In conclusion, laparoscopic ovarian drilling using diathermy or laser is effective in the induction of ovulation and increasing the pregnancy rate in cases of PCO resistant to clomiphene citrate.

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