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Clinical outcome and hormone profile of laparoscopic ovarian drilling in women with polycystic ovarian syndrome

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Abstract

Background. *Although laparoscopic ovarian drilling (LOD) has been widely used to induce ovulation in women with polycystic ovarian syndrome (PCOS), predicting the clinical response to this treatment remains to be elucidated. The study was carried out to identify factors that may help to predict the outcome and hormone profile of LOD.* ***Methods.*** *This retrospective study included 40 patients with anovulatory infertility due to PCOS who underwent LOD between 2009 and 2012. The influence of the various patient characteristics on the ovulation and pregnancy rates after LOD was achieved. The patient's characteristics including age, body mass index (BMI), menstrual pattern, serum concentration of luteinizing hormone (LH), LH/follicle-stimulating hormone ratio, testosterone, and duration of infertility on the outcome of LOD was evaluated.* ***Results.*** *Women with BMI ≥35 kg/m^2, serum testosterone concentration ≥5 nmol/l, and duration of infertility >3 years seem to be poor responders to LOD. In LOD responders, serum LH levels >10 IU/l appeared to be associated with higher pregnancy rates.* ***Conclusion.*** *Obesity, hyperandrogenism and long duration of infertility in women with PCOS seem to predict resistance to LOD. The ovulation and pregnancy rates in women with infertility duration of <3 years, treated with diathermy, reached 85 and 80%, respectively.*

Keywords: *polycystyc ovary syndrome, hyperandrogenism, infertility, laparoscopy*

Introduction

The pathology of polycystic ovarian syndrome (PCOS) was first described in 1935. It is characterized by infertility, oligomenorrhoea and/or amenorrhoea, and bilaterally enlarged cystic ovaries[(1)]. PCOS is the most common cause of anovulatory infertility, being found globally in 75% of cases[(2)].

There are several treatment options for PCOS related anovulatory infertility. First line of treatment is usually clomiphene citrate (CC), 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 having in the view the higher 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)]. LOD, 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)] and sensitivity to CC should increase after this treatment[(5)].

There is an extensive body of literature related to defining the problems and potential complications associated to higher ovulation (80%) and pregnancy rates (60%) following LOD[(6)]. However, only 20-30% of anovulatory PCOS women fail to respond to LOD. The mechanism of action of LOD is not yet fully understood and therefore it is not exactly clear why some PCOS patients do not respond to this treatment. A plausible explanation could be the amount of ovarian tissue destroyed during LOD is not sufficient to produce an effect in some patients or the presence of inherent resistance of the ovary to the effect of drilling[(7)].

The reasons for variation in pregnancy rate are not clear in respect with multiple factors affecting the outcome. If it was possible to identify the factors that determine the response of PCOS patients to LOD, the beneficial treatments could be avoided and success rates improved for both, ovulation and pregnancy. In a previous study, our group reported that the LOD in CC-resistant patients with PCOS could reduce the risk of ovarian hyperstimulation syndrome in which the spontaneous pregnancy rate was found to be 36.6%[(8)].

Although laparoscopic ovarian drilling (LOD) has been widely used to induce ovulation in women with polycystic ovarian syndrome (PCOS), predicting the clinical outcome and hormone profile remain to be discovered. The present study was carried out to identify factors that may help to predict the outcome and hormone profile of LOD.

Methods

Between 2009 and 2012, 78 patients with anovulatory infertility due to PCOS underwent LOD at the Clinical Emergency Hospital 'Sf. Spiridon', Iasi, from Romania.

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Twenty-four women had laser ovarian drilling and were excluded from analysis. Fourteen patients underwent ovarian drilling using diathermy but received only two or three punctures per ovary and were also excluded from the analysis, being known the fact that two or three punctures per ovary are associated with poor outcome[9].

The hospital clinical records of the remaining 40 patients were reviewed and the biochemical data were documented. All the women had anovulatory infertility of >1 year's duration, and had been treated unsuccessfully with CC (between 3 and 6 months, 3cp/day for 5 days starting from day 5 of their menstrual cycle) prior to LOD.

Of the 30 patients from our earlier report, only 6 (20%) were included in this study based on unregulated cycles[8]. The diagnosis of PCOS was based on the early follicular phase (defined as days 2-5 of the menstrual cycle) serum luteinizing hormone (LH)/ follicle-stimulating hormone (FSH) ratio ≥2 and/or testosterone ≥2.5 nmol/l[10].

Hormonal analysis

Serum hormonal concentrations (serum concentration of LH and FSH, LH/FSH ratio and testosterone) were measured using well-established assays, which have been validated in our laboratory from Clinical Emergency Hospital "Sf. Spiridon", Iasi, from Romania.

Laparoscopic ovarian drilling

The technique of LOD used in our hospital has been previously described[8]. Briefly, a specially designed diathermy probe was used to penetrate the ovarian capsule at a number of points with the aid of a short burst of diathermy (Figure 1). The diathermy needle was 7-8 mm long and reached 0.5 mm in diameter, the coagulation current being set to 30 W and the duration of each penetration of the ovarian tissue was of approximately 1 s. Ten to 15 punctures were made in each ovary depending on its size, each measuring 3 mm in diameter and 4-6 mm in depth. After the diathermy puncture, a solution of 0.9% NaCl was used to wash the peritoneal cavity.

Post-operative monitoring

Following ovarian drilling, women were asked to keep a record of their menstrual cycle. If the patient started a menstrual period within 6 weeks of the surgery, a blood sample was taken on day 3 of that cycle for serum concentrations of LH, FSH, and testosterone analysis. Another blood sample was taken on day 21 of the same cycle for measurement of serum concentration of progesterone. Ovulation was diagnosed when the progesterone level was ≥30 nmol/l. If spontaneous menstruation did not occur, a random blood sample was taken to measure all the above hormones at 6 weeks following surgery. If the patient did not ovulate as evidenced by the low progesterone levels or lack of menstruation, CC would be started 6-8 weeks after surgery. If ovulation was achieved either spontaneously or with the help of CC, patients were followed-up until they conceived or for up to 12 months after LOD.

Figure 1. Laparoscopic incision of the ovary

Analysis of data

The data were entered into the Statistical Package for Social Science (SPSS) for Windows version 11.

For BMI, LH, LH/FSH ratio, and testosterone, women were divided into three categories: normal or slightly raised, moderately and markedly raised (Table 1). Ovulation and pregnancy rates after LOD were compared between the different categories of each factor. For ordered categorical data including age, BMI, menstrual pattern, LH levels, LH/FSH ratio, testosterone levels and duration of infertility statistical comparisons were performed by one-way analysis of variance (ANOVA). In the case of the identification of statistical differences using ANOVA, the Student Newmal-Keuls test was used to compare ovulation

Table 1 Categories according to each factor

	Normal	Moderate raised	Markedly raised
BMI (kg/m^2)	<28	28-35	≥35
LH (IU/l)	<9	9-20	≥20
LH/FSH	<3	3-4	≥4
Testosterone (nmol/l)	<3	3-5	≥5

and pregnancy rates between the categories of each factor. Probability values <0.05 were considered to indicate significant difference.

Results

A total of 40 patients with anovulatory infertility associated with PCOS who underwent LOD were included in this study. Table 2 illustrates the ovulation and pregnancy rates following LOD in PCOS patients with different categories of age, BMI, menstrual pattern, LH concentration, LH/FSH ratio, testosterone concentration and duration of infertility. The results showed that women with marked obesity (BMI ≥35 kg/m^2) achieved significantly (p <0.05) lower ovulation and pregnancy rates (32 and 10%, respectively) compared with those (70 and 23%) of moderately overweight (BMI 29-34 kg/m^2) and those (75 and 24%) of women with normal and slightly raised BMI (<29 kg/m^2). However, in women who ovulated in response to LOD, BMI had no impact on the pregnancy rate. Responders with BMI <29 kg/m^2 achieved a 24% pregnancy rate which was not significantly different from those of women with moderately raised BMI (23%). As far as the androgens are concerned, ovulation and pregnancy rates showed significant reduction with increasing androgen levels: in women with testosterone levels ≥5 nmol/l, the rates were 29 and 8%, respectively, which were significantly lower (p <0.05) than those (52 and 15%) of women with moderately elevated testosterone (2.6-4.4 nmol/l). Patients with normal serum testosterone levels (<2.6 nmol/l) showed significantly higher (p <0.01) success rates (62 and 31%) than the other groups (Table 2).

There was a trend towards higher conception rates with increasing levels of LH, although statistical significance was not reached (Table 2). Further analysis revealed that once ovulation was achieved, serum LH levels had a statistically significant impact on the pregnancy rate: LOD responders with pre-treatment serum LH concentrations ≥10 IU/l achieved a significantly (p<0.05) higher pregnancy rate than that of responders with serum LH concentrations <10 IU/l.

On the other hand, age, menstrual pattern and LH/FSH ratio did not have any significant impact on the ovulation or pregnancy rates after LOD (Table 2). In a subgroup of PCOS women with duration of infertility <3 years, ovulation and pregnancy rates of 85 and 80%, respectively, were observed. When patients with duration of infertility ≥3 years were excluded, the ovulation and pregnancy rates in the remaining 28 women showed statistical significance difference (p <0.001), (i.e. 36 and 45% respectively).

Discussion

In this study, we have evaluated the impact of various clinical and biochemical features on the clinical outcome of LOD in 40 PCOS women. Although chronic anovulation in women with PCOS is usually associated with menstrual irregularities[11], several authors have reported that 16-24% of these women do have apparently regular menstrual cycles[12,13,14]. Furthermore, many anovulatory PCOS

Table 2 Ovulation and pregnancy ratesw in 40 PCOS after LOD

	Category	n	Ovulation rate (%)	Pregnancy rate (%)
Age (years)	≤32	32	80	45
	>32	5	65	43
BMI (kg/m^2)	<29	32	75	24
	29-34	38	70	23
	≥35	12	32*	10*
Menstrual pattern[a]	Regular	12	86	57
	Oligomenorrhoea	39	76	58
	Amenorroea	28	67	45
LH(IU/l)	<10	37	48	34
	10-20	33	58	46
	≥20	35	70*	87*
LH/FSH	>2	31	57	47
	2-4	38	45	78
Testosterone (nmol/l)	<2.6	34	62**	31**
	2.6-4.4	29	52	15
	≥ 5	7	29*	8*
Duration of infertility (years)	<3	37	85	80
	3-6	28	67	75
	>6	14	36***	45***

[a]*Menstrual pattern definition: regular cycles= cycle length between 25 and 35 days; *p<0.05; **p<0.01; ***p<0.001.*

patients ovulate occasionally and some may resume regular menstrual cycles for variable periods of time. This explains why some anovulatory PCOS patients conceive spontaneously while being investigated for infertility or waiting for treatment. Women with BMI ≥35 kg/m^2, serum testosterone concentration ≥5 nmol/l and/or duration of infertility longer than 3 years seem to be resistant to LOD. With regards to LH levels, there was no impact on the ovulation rate but, once ovulation was achieved, LH levels had a significant impact on the pregnancy rates. Age, menstrual pattern and LH/FSH ratio did not seem to influence the outcome of LOD.

PCOS women with BMI ≥35 kg/m^2 achieved significantly lower ovulation and pregnancy rates after LOD compared with moderately overweight and normal weight women. However, although BMI had a significant impact on the overall ovulation rate, it did not seem to influence the overall pregnancy rates. Important to be noted, we found that once ovulation was achieved, the BMI had no impact on the pregnancy rate. These findings are consistent with other report[15] which showed that BMI had no impact on the overall conception rates after LOD. The findings from the present study are in agreement with a previous study reported by Gjonnaess[16] which reviewed 252 patients who underwent LOD and found that women with marked obesity (BMI ≥35 kg/m^2) achieved significantly lower ovulation rates compared with women with normal and moderately elevated BMI.

Our data showed that increasing serum levels of testosterone is associated with a statistically significant reduction of the chances of success of LOD. Furthermore, a subgroup of PCOS women with hyperandrogenism (testosterone ≥5 nmol/l) appeared to be resistant to LOD. This is in disagreement with Abdel-Gadir and contributors[10] which showed that androgen levels had no impact on the success of LOD. This disagreement could be due to the relatively smaller sizes of the groups studied in our group (n=40).

Surprisingly, there was an inverse relationship between the duration of infertility and the chances of success of LOD. Indeed the duration of infertility has been found to be one of the most important independent predictor of success of LOD. A further significant drop in both the ovulation and pregnancy rates was observed in patients with >3 years of infertility, with only a 45% chance of conception compared with 80% in women with infertility of <3 years. A possible explanation for this is that women with longer duration of infertility are more likely to have other subtle subfertility factors.

It is worth keeping this analogy in mind, that LOD responders with higher LH levels (≥10 IU/l) have a significantly higher chance of conception than those with lower LH levels. Interestingly, some recent 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 elevated[17-19]. Taken together, the mechanism of action of LOD remains to be fully elucidated.

Conclusion

Women who conceived following the surgery had a shorter duration of infertility, were treated with diathermy (rather than laser), were younger and were more likely to have evidence of polycystic ovarian disease. Our data showed that obesity, hyperandrogenism and long duration of infertility in women with PCOS were the main determinants of the outcome. The ovulation and pregnancy rates in women with infertility duration of less than three years, treated with diathermy, reached 85 and 80%, respectively. ■

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