LAPAROSCOPIC OVARIAN DRILLING TREATMENT OPTION FOR POLYCYSTIC OVARY AND INFERTILITY

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ABSTRACT

To find out the effectiveness of laparoscopic ovarian drilling (LOD) in patients clinically and radiologically diagnosed as Polycystic Ovarian Syndrome (PCOS) suffering from infertility and to find out factors that may predict the outcome of LOD. This prospective study included 186 patients with anovulatory infertility due to PCOS who underwent LOD during the period from January 1st 2007 to December 31st 2008. Diagnosis was made according to the European Society of Human Reproduction and Embryology (ESHRE) criteria for PCOS. Body Mass Index (BMI), serum Testosterone level and serum LH was taken from the patients. All patients were followed up till they got pregnant or for a period of 12 months after the procedure. Out of 186 patients, 102 (55%) conceived after long term infertility ranged from 3-15 years, Antenatal complications were not significant as there was 1 twins pregnancy, 3 miscarriages and 1 ectopic pregnancy, Patients with Body Mass Index $\geq$ 35 kg/m^2 and serum testosterone level $\geq$ 4.5 nmol/l seems to be poor responders for LOD, meanwhile those with Serum LH level > 10 IU/L appears to be associated with higher pregnancy rate after LOD. LOD gave good fertility rates in patients with PCOS in which medical ovulation induction failed, marked obesity and hyperandrogenism are a marked predictor for resistance to LOD, while high level of LH predicts to a higher probability of pregnancy.

KEY WORDS: Laparoscopic Ovarian Drilling, Polycystic Ovarian Syndrome, anovulation, infertility.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most common female endocrine disorders affecting approximately 5 -10 % of women of reproductive age (12–45 years old) and is thought to be one of the leading causes of female sub-fertility.

It comprises a heterogeneous mixture of clinical and diagnostical findings. Polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory infertility, being found in 75% of cases[1,2,3,4].

The pathology of polycystic ovarian disease (PCOD) was described by Stein and Leventhal in 1935. It is characterized by infertility, oligomenorrhoea or amenorrhea, hirsutism, acne, and bilaterally enlarged cystic ovaries sonographic appearance of polycystic ovary (figures 1& 2).

The principal features are obesity, anovulation (resulting an irregular menstruation or amenorrhea), acne, and excessive amounts of androgenic (masculinizing) hormones[5].

The aetiology of the PCOS is based on two major concepts, hyperandrogenism and insulin resistance. The classical hypothesis as proposed by Yen postulates an initial androgen excess. Androgens are aromatized in peripheral tissue to estrogens, resulting in an imbalance of luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion on the pituitary level with endogenous hyper secretion of LH. The LH strongly stimulates the intra ovarian androgen production. This classical concept has been extended by the role of hyperinsulinaemia in PCOS patients. Insulin resistance can be found in up to 50% of women with PCOS. Insulin like LH stimulates directly the ovarian biosynthesis of steroid hormones, in particular, of ovarian androgens. Furthermore, insulin decreases the sex-hormone-binding globulin (SHBG) production in the liver, thus, further elevating free androgen levels. Therefore, both pathways end in the stimulation of ovarian theca cells with elevated ovarian androgen production, resulting in disturbed folliculogenesis, cycle disorders and chronic anovulation. This pivotal role of the ovary for the aetiology of the PCOS has favored therapeutical concepts, which might directly correct the intra ovarian pathology[6].

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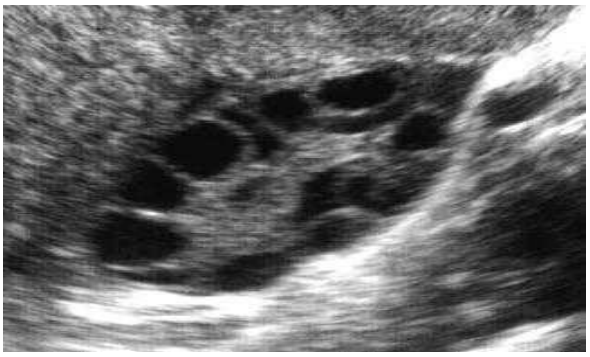
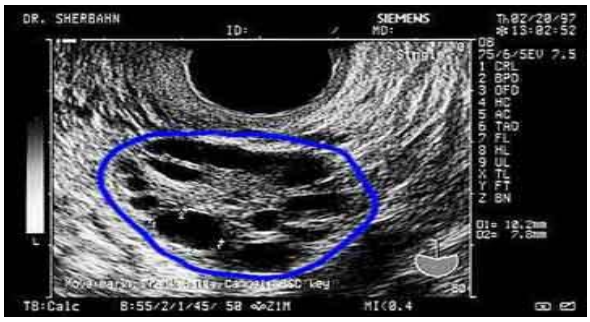


(Figure 1) Sonographic appearance of polycystic ovary



(Figure 2) Sonographic appearance of polycystic ovary

Laparoscopic ovarian drilling (LOD) has been widely used to induce ovulation in PCOS women after failure of treatment with Clomiphene Citrate (CC) and Human menopausal Gonadotropin (HmG)**.** Laparoscopic drilling of the ovaries is an alternative treatment for patients with clomiphene citrate resistant polycystic ovary syndrome. This involves a single procedure, which has minimal morbidity, which can lead to consecutive ovulations with minimal risks of multiple pregnancy. Patients may also respond to clomiphene citrate after this treatment **.** The mechanism of action of LOD is not fully understood and therefore it is not exactly clear why some PCOS patients fail to 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. Hence another possible explanation of failure to respond is an inherent resistance of the ovary to the effects of drilling[7,8,9,10].

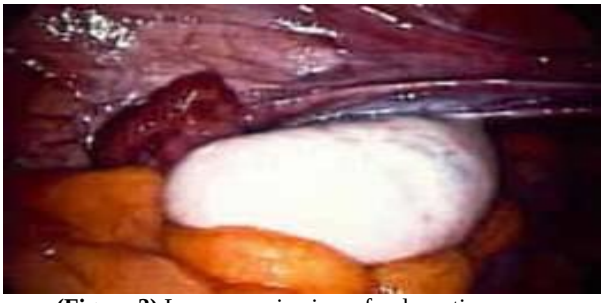
If it were possible to identify the factors that determine the sensitivity of PCOS patients to LOD, then fruitless treatment could be avoided and success rates improved[11,12].

MATERIALS AND METHODS

Between January 1st 2007 to December 31st 2008 186 patients with primary or secondary infertility due to PCOS underwent LOD at the Infertility Unit, department of Gynecology, Misurata Oncology Center. All patients were evaluated clinically, radiologically and biochemically and BMI was calculated. All patients had infertility of > 1 year duration, 154 had been treated with Clomiphene Citrate (CC) up to 200 mg / day for 5 days from D2 – D6 and for a period of 6-12 months, while 32 patients were induced with Human menopausal Gonadotropin and failed to conceive.

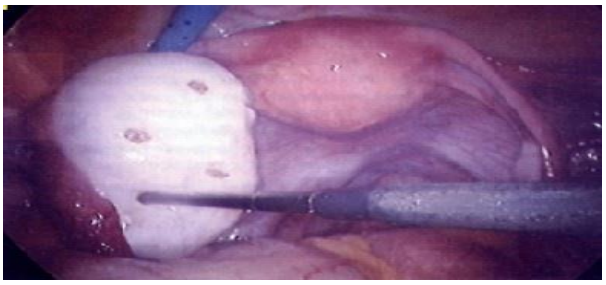
Diagnosis of PCOS was made according to the ESHRE criteria for diagnosis of PCOS: The main criteria are chronic anovulation, clinical and / or biochemical signs of hyperandrogenism and polycystic ovaries by ultrasound. At least two out of these three criteria must present. Furthermore, other etiological factors like cushing syndrome, androgen-producing tumors or congenital adrenal hyperplasia are excluded. Serum hormonal concentrations (FSH, LH and Testosterone) were all measured prior to the procedure using well established assays. All patients underwent transvaginal scanning prior to LOD using Aloka 1500 with a convex 6.5 MHz transvaginal probe.

Laparoscopic view of polycystic ovary as shown in (figure 3).



(Figure 3) Laparoscopic view of polycystic ovary

LOD was done bilaterally using monopolar electrosurgical unit**.** Coagulation current at 35 W power setting was used, 4-5 punctures made for each ovary in different areas with a 5 seconds puncture duration**.** Laparoscopic ovarian drilling as shown in (figure 4).



(Figure 4) Laparoscopic ovarian drilling

Postoperative monitoring; patients were asked to keep a record of their menstrual cycle, then they were followed up by ultrasound and by investigations to find out if spontaneous ovulation happed or not, if not then ovulation induction medication was added and patients were followed up till they conceived or for a period of 12 months.

Analysis of Data

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

Data were tabulated using frequency distribution tables and analyzed using proportions and chi square

test. A p-value of less than 0.05 was taken as the level of statistical significance.

RESULTS

The influence of patients preoperative characteristics including age, BMI duration of infertility, presence or absence of acne or hirsutism, menstrual pattern, serum FSH, serum concentrations of LH and testosterone were studied. As shown in (table 1) and (table 2).

(Table 1) Blood LH and testosterone levels were divided into three categories: normal , moderately elevated and markedly elevated

	Normal	Moderately elevated	Markedly elevated
LH (IU/L)	< 10	10 – 19.9	≥ 20
Testosterone (nmol/L)	< 2.6	2.6 – 4.4	≥ 4.5

(Table 2) The characteristics of all 186 patients whom underwent LOD for infertility were as follows

(Table 2-A)

Characteristic	Patient No.	Mean	S.D.
Age (years)	186	32.1 yrs	(4.1)
BMI (kg/m^2)	186	33.4	(5.2)
Duration of infertility (years)	186	3.3 yrs	(2.1)
S. LH (IU/L)	162	13.1	(6.3)
S. FSH (IU/L)	162	5.2	(1.3)
S. Testosterone (nmol/L)	112	2.9	(1.4)

(Table 2-B)

	Patient No.	%
Menstrual Pattern	186	
- Regular	35	19
- Oligomenorrhoea	151	81
Hirsutism	186	
- Yes	121	65
- No	65	35
Acne	186	
- Yes	113	61
- No	73	39
Infertility	186	
- Primary	132	71
- Secondary	64	29
evidence of PCO	186	
- U/S evidence	153	82
- Biochemical Criteria for PCO.	33	18

Menstrual pattern definition: regular cycles: cycle length between 25 and 35 days; oligomenorrhoea: cycle length > 35 days

A total of 186 patients with anovulatory infertility associated with PCOS who underwent LOD were included in this study. The characteristics of this group of women are shown in (table 2).

Among the 186 patients included in the study, 108 (58%) ovulated after LOD with the addition of Clomiphene Citrate and 17 (9%) ovulated spontaneously giving an overall ovulation rate of 125 (67%) patients, 102 (55%) conceived. One patient conceived with twins, giving a multiple pregnancy rate of (1%). Of the 102 pregnancies, three (3%) ended in miscarriages and one (1%) was ectopic pregnancy.

The results in (table 3) shows that women with over weight (BMI ≥ 35 kg/m2) achieved significantly less pregnancy rates (13%, respectively) compared with obese (BMI 29.1-34.4 kg/m2) women (49%) and with women with normal/ underweight (BMI < 29 kg/m2) (52%).

(Table 3) Factors affecting the success rates of LOD

	Category	N	Pregnancy Rate %	Chi square with p value
Age	≤ 35	174	46	X^2_{df-1} 0.073, p-value >0.05
	> 35	12	49	
BMI (kg/m^2)	< 29	107	52	X^2_{df-2} 8.922, p-value <0.05
	29.1 – 34.4	63	49	
	≥ 35	16	13	
LH (IU/L)	< 10	48	36	X^2_{df-2} 1.208, p-value >0.05
	10.1 – 19.9	83	44	
	≥ 20	31	45	
Testosterone (nmol/L)	< 2.6	56	54	X^2_{df-2} 4.732, p-value >0.05
	2.6–4.4	48	47	
	≥ 4.5	8	10	

As far as the androgens are concerned, ovulation and pregnancy rates showed significant reduction with increasing androgen levels: in women with testosterone levels ≥4.5 nmol/l, the rate was 10%, which were significantly lower than those (47%) of women with moderately elevated testosterone (2.6–4.4 nmol/l). Patients with normal serum testosterone levels (< 2.6 nmol/l) showed higher pregnancy rate (54%) than the other groups.

There was a trend towards higher conception rates with increasing levels of LH. 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 higher pregnancy rate than that of responders with serum LH concentrations <10 IU/l.

DISCUSSION

Common symptoms of PCOS includes Oligomenorrhoea, amenorrhea irregular or absent menstrual periods, infertility generally resulting from chronic an ovulation (lack of ovulation).

Hirsutism, excessive mild symptoms of hyperandrogenism such as acne. In most instances, these symptoms are transient and only reflect the immaturity of the hypothalamic-pituitary-ovarian axis during the first years following menarche. Approximately three-fourths of patients with PCOS (by the diagnostic criteria of NIH/NICHD 1990) have evidence of hyperandrogenemia**.** PCOS can present in any age during the reproductive years. Due to its often vague presentation it can take years to reach a diagnosis, Serum insulin, insulin resistance and homocysteine levels are significantly higher in subjects having PCOS but have no significant effect on fertility[13].

Not all women with PCOS have polycystic ovaries (PCO), nor do all women with ovarian cysts have PCOS. Although a pelvic ultrasound is a major diagnostic tool, it is not the only one. The diagnosis is straightforward using the Rotterdam criteria, even when the syndrome is associated with a wide range of symptoms.

Standard diagnostic assessments

History-taking, specifically for menstrual pattern, obesity, hirsutism, and the absence of breast development. A clinical prediction rule found that these four questions can diagnose PCOS with a sensitivity of 77.1% (95% confidence interval [CI] 62.7%–88.0%) and a specificity of 93.8% (95% [CI] 82.8%–98.7%)[14]. Gynecologic ultrasonography, specifically looking for small ovarian follicles. These are believed to be the result of disturbed ovarian function with failed ovulation, reflected by the infrequent or absent menstruation that is typical of the condition. In normal menstrual cycle, one egg is released from a dominant follicle essentially a cyst that bursts to release the egg. After ovulation the follicle remnant is transformed into a progesterone producing corpus luteum, which shrinks and disappears after approximately 12–14 days. In PCOS, there is a so called "follicular arrest", i.e., several follicles develop to a size of 5–7 mm, but not further. No single follicle reach the pre ovulatory size (16 mm or more). According to the Rotterdam criteria, 12 or more small follicles should be seen in an ovary on ultrasound examination. The follicles may be oriented in the periphery, giving the appearance of a 'string of pearls Laparoscopic examination may reveal a thickened, smooth, pearl-white outer surface of the ovary. (This would usually be an incidental finding if laparoscopy were performed for some other reason, as it would not be routine to examine the ovaries in this way to confirm a diagnosis of PCOS). Blood level of androgens including androstenedione and testosterone may be elevated[15]. The free testosterone level is thought to be the best measure with ~ 60% of PCOS patients demonstrating supra normal levels. The Free androgen index of the ratio of testosterone to sex hormone-binding globulin (SHBG) is high, is meant to be a predictor of free testosterone, but is a poor parameter for this and is no better than testosterone alone as a marker for PCOS, possibly because FAI is correlated with the degree of obesity. Some other blood tests are suggestive but not diagnostic[16].

The ratio of LH (Luteinizing hormone) to FSH (Follicle stimulating hormone) is greater than 1:1, as tested on Day 3 of the menstrual cycle. The pattern is not very specific and was present in less than 50% in one study. There are often low levels of sex hormone binding globulin, particularly among obese women[17].

Pathogenesis

Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of male hormones (androgens), particularly testosterone, either through the release of excessive luteinizing hormone (LH) by the anterior pituitary gland or through high levels of insulin in the blood (hyperinsulinaemia)[18]. In women whose ovaries are sensitive to this stimulus. The syndrome acquired its most widely used name due to the common sign on ultrasound examination of multiple (poly) ovarian cysts. These "cysts" are actually immature follicles, not cysts ("polyfollicular ovary syndrome" would have been a more accurate name), the follicles have developed from primordial follicles, but the development has stopped ("arrested") at an early antral stage due to the disturbed ovarian function. The follicles may be oriented along the ovarian periphery, appearing as a 'string of pearls' on ultrasound examination. The condition was first described in 1935 by Dr. Stein and Dr. Leventhal, hence its original name of Stein-Leventhal syndrome[5]. PCOS is characterized by a complex set of symptoms, and the cause cannot be determined for all patients. However, research to date suggests that insulin resistance could be a leading cause. PCOS may also have a genetic predisposition, and further research into this possibility is taking place. No specific gene has been identified, and it is thought that many genes could contribute to the development of PCOS. A majority of patients with PCOS have insulin resistance and/or are obese. Their elevated insulin levels contribute to or cause the abnormalities seen in the hypothalamic-pituitary-ovarian axis that lead to PCOS[18]. Adipose tissue possesses aromatase, an enzyme that converts androstenedione to estrone and testosterone to estradiol. The excess of adipose tissue in obese patients creates the paradox of having both excess androgens (which are responsible for hirsutism and virilization) and estrogens (which inhibits FSH via negative feedback)[19].

Also, hyperinsulinaemia increases GnRH pulse frequency, LH over FSH dominance, increased ovarian androgen production, decreased follicular maturation, and decreased SHBG binding; all these steps lead to the development of PCOS. Insulin resistance is a common finding among patients of normal weight as well as those overweight patients. PCOS may be associated with chronic inflammation, with several investigators correlating inflammatory mediators with an ovulation and other PCOS symptoms[20]. 20 to 30% of ovulatory PCOS women fail to respond to LOD. It may be due to the amount of LOD is not sufficient to produce an effect in patients. But studies revealed that LOD increases the endogenous FSH and only a minimal amount of thermal energy is required. Another possible explanation may be failure to respond is an inherent resistance ovary to the effects of drilling[21]. Another cause may be hyperprolactaenaemia observed in some patients after LOD. It is important to monitor the patients for prolactin levels after LOD. The drawback with LOD is to quantify the dose of diathermy to a particular patient. It is difficult to decide the dose for a particular patient without knowing the dose re-

sponse. There is a need to optimize the dose of LOD in response to ovarian size. However the predictors of success of LOD depends on the body mass index, serum testosterone concentration and duration of infertility. These predictors will help in selection patients for LOD with infertility more than 3 years, high testosterone levels are advised to take gonadotrophin therapy and IVF. In this study, we have evaluated the impact of various clinical, biochemical and Ultrasonographic features of PCOS on the clinical outcome of LOD in 186 PCOS women. In addition, we have also reported on the factors affecting the duration of the beneficial effects of LOD. Eighteen percent of PCOS women in this study had apparently regular menstrual cycles prior to LOD. Although chronic anovulation in women with PCOS is usually associated with menstrual irregularities, several authors have reported that 16–24% of these women do have apparently regular menstrual cycles. Furthermore, many anovulatory PCOS 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[22]. Our data showed three main factors to have a significant impact on the efficacy of LOD, namely BMI, hyperandrogenism and serum LH levels. Women with marked obesity (BMI $\geq$ 35 kg/m2), marked hyperandrogenism (testosterone $\geq$ 4.5 nmol/l) and low serum LH seem to be resistant to LOD. With regards to LH levels, once ovulation was achieved, LH levels had a significant impact on the pregnancy rates. Not all women with PCOS have difficulty becoming pregnant. For those who do, anovulation is a common cause. Ovulation may be predicted by the use of urine tests that detect the preovulatory LH surge, called ovulation predictor kits (OPKs). However, OPKs are not always accurate when testing on women with PCOS[23]. Charting of cervical mucus may also be used to predict ovulation, or certain fertility monitors (those that track urinary hormones or changes in saliva) may be used. Methods that predict ovulation may be used to time intercourse or insemination appropriately. While not useful for predicting ovulation[24]. basal body temperatures may be used to confirm ovulation. Ovulation may also be confirmed by testing for serum progesterone in mid-luteal phase, approximately seven days after ovulation (if ovulation occurred on the average cycle day of fourteen, seven days later would be cycle day 21). A mid-luteal phase progesterone test may also be used to diagnose luteal phase defect. Methods that confirm ovulation may be used to evaluate the effectiveness of treatments to stimulate ovulation[25]. For overweight women with PCOS, who are anovulatory, diet adjustments and weight loss are associated with resumption of spontaneous ovulation. For those who after weight loss still are anovulatory or for anovulatory lean women, CC and FSH are the principal treatments used to help infertility. Previously, even metformin was recommended treatment for anovulation. But in the largest trial to date, comparing clomiphene with metformin, clomiphene alone was the most effective[26]. The most drastic increase in ovulation rate occurs with a combination of diet modification, weight loss, and treatment with metformin and clomiphene citrate[27]. It is currently unknown if diet change and weight loss alone have an effect on live birth rates comparable to those reported with clomiphene and metformin. For patients who do not respond to clomiphene, diet and lifestyle modification, there are options available including assisted reproductive technology procedures such as controlled ovarian hyperstimulation with FSH injections and in vitro fertilization (IVF)[28]. Ovarian stimulation with FSH followed by hCG has an associated risk in women with PCOS of ovarian hyperstimulation syndrome — an uncomfortable and potentially dangerous condition with morbidity and rare mortality[29]. Thus recent developments have allowed the oocytes present in the multiple follicles to be extracted in natural, unstimulated cycles and then matured in vitro, prior to IVF. This technique is known as In vitro maturation (IVM). The RCOG (The Royal College of Obstetricians and Gynecologists) published an opinion paper on "Metformin therapy for the management of women with polycystic ovary syndrome", The paper concluded that while initial studies appeared to be promising, more recent large randomized controlled trials have not observed beneficial effects of metformin either as first-line therapy or combined with clomiphene citrate for the treatment of the anovulatory woman with PCOS. Most work has been undertaken in the management of anovulatory infertility and there are no good data from randomized controlled trials on the use of metformin in the management of other manifestations of PCOS. It is clear that the first aim for women with PCOS who are overweight is to make lifestyle changes with a combination of diet and exercise in order to lose weight and improve ovarian function.

The European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine consensus on infertility treatment for PCOS concluded that there is no clear role for insulin sensitizing and insulin lowering drugs in the management of PCOS, and should be restricted to those patients with glucose intolerance or type 2 diabetes rather than those with just insulin resistance. Therefore, on current evidence that metformin is not a first line treatment of choice in PCOS(RCOG Dec. 2008)

CONCLUSION

LOD gives good fertility rates in patients with PCOS in which medical treatment failed,

Obesity and hyperandrogenism seems to predict resistance to LOD, while high level of LH appears to predict higher probability of pregnancy.

LOD is a safe and cost effective procedure. A single treatment results in uni- follicular ovulation.

No need of continuous monitoring as seen with hormonal treatment and no fear from ovarian hyperstimulation. Correction of hormonal levels prevents miscarriages. LOD increase the sensitivity to Gonadotropin and it is effectiveness in PCO.

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