Laparoscopic Ovarian Drilling for Polycystic Ovarian Syndrome in Clomiphene Citrate-Resistant Women with Anovulatory Infertility

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Objectives: To evaluate the efficacy of laparoscopic ovarian drilling in clomiphene citrate-resistant women with polycystic ovarian syndrome (PCOS), and to determine the factors affecting the pregnancy rate.

Design: Prospective study (Canadian Task Force classification II-2).

Setting: Tertiary referral teaching hospital.

Patients: One hundred ninety-eight women with clomiphene citrate- resistant PCOS.

Intervention: Laparoscopic ovarian drilling, all procedures were performed by the author over a four year period between June 1996 and June 2000, with follow-up for 2 years.

Main outcome measures: Ovulation and pregnancy rate.

Results: Follow-up data, which were available for 181 patients, showed a spontaneous ovulation rate of 70.1%, cumulative ovulation rate of 98.3%, and pregnancy rate of 84.5%. Women who conceived following surgery were obese, had higher pre-operative luteinizing hormone (LH) levels, were younger and were more likely to have typical ultrasonographic features of polycystic ovarian disease. Logistic multiple regression analysis showed that the pre-operative LH levels, body mass index (BMI) and the age of the patient were the main determinants of the outcome.

Conclusion: Our results demonstrate that laparoscopic ovarian drilling is an effective procedure in clomiphene-resistant anovulatory women with PCOS. The pregnancy rate in women with pre-operative LH levels of more than 10 IU/L, a BMI of $\geq$30 kg/m^2, with age $\leq$30 years reached 97.3%.

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Polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory infertility in women of reproductive age[1,2]. It is a heterogenous group of conditions characterized by the combination of hyperandrogenism and ovulatory dysfunction, in the absence of overt pituitary, thyroid, or adrenal disease[3]. Patients may have hirsutism, acne, obesity, hyperinsulinism or increased insulin resistance, typical ultrasonographic appearances of bilateral polycystic ovaries,

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and an elevated luteinizing hormone (LH): follicle-stimulating hormone (FSH) ratio.

There are several treatment options. Clomiphene citrate (CC) remains the first line of treatment for infertile women with PCOS[4-6]. Women who are clomiphene resistant can be treated either surgically or medically with human menopausal gonadotrophin (HMG), purified FSH, or combinations of gonadotrophins with gonadotrophin releasing hormone (GnRH) agonist. However, medical treatment is associated with an increased risk of ovarian hyperstimulation syndrome (OHSS), multiple pregnancies and miscarriages[7-9]. Furthermore, it is costly, stressful and time-consuming form of treatment requiring regular and careful hormonal and ultrasound monitoring.

Bilateral ovarian wedge resection was the first established surgical procedure for anovulatory PCOS women[10]. However, it came into disrepute because of the risk of postoperative adhesion formation with subsequent mechanical subfertility[11,12]. Introduction of laparoscopic ovarian drilling together with the rapidly expanding field of operative laparoscopy, surgical management has received renewed interest[13]. In recent years, a number of studies reported the success and utility of this form of treatment that resulted in good ovulatory and pregnancy rates[14,15]. The aim of the current study was to analyze the efficacy of laparoscopic ovarian drilling in our PCOS women with CC-resistant anovulatory infertility, and to determine the various factors influencing the outcome of this laparoscopic procedure.

METHODS

Patients

One hundred ninety-eight women were diagnosed with PCOS based on criteria laid down by the 1990 National Institute of Health-National Institute of Child Health and Development consensus conference[16]. They had anovulatory infertility that did not respond to CC (i.e. failed to ovulate). One hundred eighty-four women had received over six cycles of CC 50-200 mg, including seventy-two who received additional gonadotrophin therapy for four to six cycles, and eighteen had additional an in-vitro fertilization (IVF) treatment. Five patients had previously experienced moderate to severe ovarian hyperstimulation syndrome, which required hospitalization and three patients had bilateral ovarian wedge resection. Although some women received long-cycle clomiphene, dexamethasone, bromocriptine, metformin, or gonadotrophin, these were not strict entry criteria and patients were enrolled for drilling after six cycles of CC. Pre-operative transabdominal or transvaginal ultrasound examination was performed on all patients. Hormonal profiles for LH, FSH, testosterone, Prolactin, and thyroid function tests were done in the fasting state between day 3 and 5 of the spontaneous or progestin-induced cycle. All women and their partners were investigated for other common causes of infertility and male factor was excluded by semen analysis.

Operative Procedure

The patients included in this study were all operated upon by the author between June 1996 and June 2000. Ovarian drilling was performed under general anaesthesia. The patient was put in moderate (30 degrees) Trendelenburg position.

A subumbilical incision was made and the Verres needle introduced through it. A pneumoperitoneum was created, the needle then removed and a 10-mm trocar inserted intraperitoneally. The trocar sleeve was left in situ and a 10-mm 0 degree telescope was inserted and connected to a camera with a video monitor system. A preliminary laparoscopic evaluation was performed before making incisions for instrumentation. The abdominal cavity especially the pelvic area was carefully inspected. Two further 5-mm trocars were inserted through small incisions in each of the iliac fossae, one for a grasping forceps and the other for a unipolar diathermy electrode. The ovary was stabilized by grasping the ovarian ligament with a grasping forceps, then the ovarian cortex was pierced to a depth of 6 mm using a unipolar electrode set to a power of 30-50 watts and cauterized for 2-4 seconds. The number of punctures made depended on the size of the ovary and number of subcapsular cysts visible at laparoscopy. All punctures were done away from the hilum and mesovarium to protect against damage to the ovarian blood supply. Adequate care was taken to avoid overly aggressive drilling, which may lead to excessive tissue destruction, adhesion formation, and even ovarian failure. At the completion of the procedure, 200ml of normal saline was then introduced into the pouch of Douglas in order to enhance ovarian cooling after diathermy.

Diagnostic hysteroscopy and laparoscopy were performed on all patients. After a thorough assessment of the tubes, uterus, pelvis, and liver in the upper abdomen, methylene blue hydrotubation was done to assess tubal patency. Additional pathology such as endometriosis, pelvic adhesions and blocked tubes was also treated, and women who had bilaterally or unilaterally successful trials of tubo-ovarian adhesiolysis and tubal patency were enrolled in the study. On the other hand, women who had an intrauterine pathology such as intrauterine adhesion, pedunculated intrauterine myomata and large endometrial polyp underwent concomitant hysteroscopic adhesiolysis, myomectomy and polypectomy respectively.

After the drilling, all patients were followed regularly for up to 2 years. Their menstrual cycles patterns were recorded and ovulation was monitored by plasma progesterone levels at the mid luteal phase (day 21). Those who had a progesterone level of ≥30 nmol/L were considered to be ovulating. Women who did not ovulate spontaneously after surgery were induced to do so with CC, and those who were CC resistant received gonadotrophins. However, patients with endometriosis were given additional danazol or GnRH agonist for the first 3 months.

Data were analyzed using Statistical Package for Social Sciences (SPSS) computer program. Independent samples T-test was used to compare continuous variables, Chi-Square tests were used to compare discrete variables, and logistic multiple regression analysis was used to examine the impact of various factors on the outcome of treatment. Significance was taken as $P < 0.05$.

RESULTS

We observed that one hundred and thirteen of our women (57.1%) were hirsute with a Ferriman and Gallwey score of ≥8. Obesity was noted in one hundred and two women (51.5%) with a body mass index of ≥30 kg/m^2. Pre-operative ultrasound examination showed typical appearances of bilateral polycystic ovaries in 60.6% of patients and normal finding in 39.4%. The LH: FSH ratio was found to be elevated (≥2) in 94 (47.5%) women; however, LH levels (>10 IU/L) were elevated in 125 (63.1 %). The testosterone levels were raised (≥ 2.9 nmol/L) in 53 (26.8%) patients and 42 women (21.2 %) had hyperprolactinemia (range 28-91.5 ng/ml). Computerized tomography or magnetic resonance imaging of the pituitary did not reveal either a microadenoma or macroadenoma in any patient. Four patients had hypothyroidism. The other characteristics of these women are presented in Table 1.

Table 1. **Characteristics of women who underwent laparoscopic ovarian drilling. Values are given as n (%) and mean [SD] {range}.**

Characteristics	Results		
Age (years)	30.5	[5.7]	{18.0-39.0}
Body mass index (kg/m^2)	29.8	[6.5]	{16.4-44.1}
Duration of infertility (years)	4.6	[3.5]	{1.0-25.0}
Plasma LH level (IU/L)	13.3	[5.6]	{1.9-47.8}
Plasma FSH level (IU/L)	6.1	[3.0]	{0.7-41.5}
Plasma LH: FSH ratio	2.3	[1.1]	{0.5-10.4}
Plasma testosterone level (nmol/L)	2.4	[1.3]	{0.4-9.7}
Plasma prolactin level (ng/ml)			
Hirsutism	21.2	[13.9]	{4.7-91.5}
Yes			
No	113	(57.1)	
Ultrasonography	85	(42.9)	
Typical of PCOS			
Atypical of PCOS	120	(60.6)	
Infertility	78	(39.4)	
Primary			
Secondary	92	(46.5)	
	106	(53.5)	
Menstrual cycle pattern			
Regular	25	(12.6)	
Oligomenorrhea	132	(66.7)	
Amenorrhoea	41	(20.7)	
Other infertility factors*			
Absent	93	(47.0)	
Tubal adhesions	47	(23.7)	
Endometriosis ± tubal adhesions	58	(29.3)	
Previous treatment			
Clomiphene	126	(63.6)	
Clomiphene + HMG	54	(27.3)	
Clomiphene + HMG + IVF	18	(9.1)	

* Laparoscopic findings.

The number of punctures drilled on each ovary varied from 5 to 15 (mean 9.1). Positive findings on laparoscopy are presented in Table 1. Based on these findings, three main patients groups were identified: (a) ninety- three women (47.0%) had PCOS with no other infertility factors; (b) forty-seven women

(23.7%) had additional pelvic adhesions between the tube, ovary, uterus, and pelvic wall or bowel, of these, six women (3.0%) had associated fimbrial phimosis, 11 patients (5.6%) had a small fimbrial cyst, two patients (1.0%) had tubercles on both tubes, and five women (2.5%) had an intrauterine adhesion (including one who also had a bilateral cornual block); and (c) fifty-eight women (29.3%) had additional endometriosis, of these, 33 women (16.7%) had endometriosis without pelvic adhesions and 25 women (12.6%) had both endometriosis and adhesions (including fourteen women who also had a chocolate cyst, three who had a pedunculated intrauterine myomata and two who had a large endometrial polyp).

Concomitant laparoscopic procedures were adhesiolysis in 72 patients (36.4%), fulguration of endometriotic areas in 58 (29.3%), drainage of ovarian endometrioma with the removal of chocolate cyst in 14 (7.1%), and fimbrioplasty in six (3.0%). On the other hand, ten patients (5.0%) had a concomitant hysteroscopic surgery. A hysteroscopic myomectomy was performed in three (1.5%), polypectomy in two (1.0%), and adhesiolysis in five (including one who also had a hysteroscopic bilateral tubal cannulation). Seven patients who had a previously diagnosed bilateral tubal block, in six of them bilateral or unilateral tubal patency was achieved after laparoscopic fimbrioplasty, and the remaining one in whom a bilateral cornual block was diagnosed had a concomitant hysteroscopic bilateral tubal cannulation. There was no intra-operative or post-operative complication. After surgery, 172 women (86.9%) were discharged home within 6 hours and the remaining 26 (13.1%) after 24 hours.

Table 2. **Outcomes of laparoscopic ovarian drilling**

Outcome measure	Number of patients	%
Menstrual cycle pattern		
Regular	160	88.4
Irregular	21	11.6
Ovulation		
Spontaneous	127	70.1
With help of clomiphene citrate	51	28.2
No	3	1.7
Pregnancy		
Spontaneous	59	32.5
With help of clomiphene citrate	83	45.9
With help of HMG	11	6.1
No	28	15.5
Pregnancy outcomes		
Ongoing / delivery	120*	66.3
Miscarriage	31†	17.1
Ectopic	2	1.1
No pregnancy	28	15.5

* *Eight women in this group had a further delivery later.*

† *Nine women in this group subsequently conceived again. Of these, five had six deliveries later (one delivered twice), but four had another five miscarriages (including one who had another 2 miscarriages).*

Seventeen women were lost to follow-up. Data from the remaining 181 patients were analyzed and the outcome measures in terms of restoration of a regular menstrual pattern, ovulation and conception, are presented in Table 2. We achieved a cumulative ovulation rate of 98.3%. Of these, 70.1% ovulated spontaneously and 28.2 % ovulated with CC, but three (1.7%) remained persistently anovulatory even after treatment with HMG.

One hundred fifty-three patients eventually conceived, resulting in a pregnancy rate of 84.5%. Of these, 32.5% conceived spontaneously after drilling, 45.9% with the help of CC and 6.1 % with HMG. Thirty-one of the women who conceived, had miscarriages in the first trimester, resulting in an abortion rate of 17.1%. Of these, nine subsequently conceived again and five of them had a term delivery later. Therefore, the overall "take home baby" rate is 125 out of 181= 69%. However, the total number of miscarriages was 36 (including three who had 2 miscarriages and one who had three miscarriages), leading to acumulative abortion rate of 19.9%.

There were two cases (1.1%) of ectopic pregnancy and two cases of multiple gestations (one had twin pregnancy and another had triplets). Both multiple pregnancies occurred in HMG stimulated cycles after drilling. However, there were no cases of OHSS reported after surgery in this study group and no patient had suffered a premature ovarian failure.

Following the drilling, seventeen of our patients had a second-look surgery. Of these, 13 women who underwent subsequent caesarean section, two women with ectopic pregnancy who underwent laparoscopic salpingectomy, and one who had subsequent laparoscopic appendicectomy. At the time of the second-look surgery, intraoperative adhesions were found in two of them (2/17, 11.8%).

Table 3. **Cumulative conception rate with time.**

Time in months	Total number of conceptions	Cumulative conception rate (%)
2	49	27.1
4	77	42.5
6	103	56.9
8	118	65.2
10	130	71.8
12	145	80.1
18	165	91.1
24	172	95.0

The pregnancy rate as a function of time after drilling is presented in Table 3. The total number of conceptions was 172, leading to a cumulative conception rate of 95%. Most conceptions (145, 80.1%) occurred in the first year after surgery. Twenty (11%) patients conceived in the first 6 months of the next year and the remaining seven (3.9%) conceived in the second half of the next year after drilling.

The influence of various factors on the outcomes was analyzed and the findings are presented in Table 4. Multivariable logistic regression analysis showed that the three most important factors affecting the outcomes are (in decreasing order of importance) the pre-operative LH levels, body mass index and the age of the patient. The ultrasonographic findings, although significantly different between the pregnant and non-pregnant group, were not significantly helpful in predicting the clinical outcome over and above that achieved by the three factors already selected. In women with a pre-operative LH level of more than 10 IU/L, had a BMI of ≥30 kg/m^2, the pregnancy rate was 96.8% (61/63) and 97.3 % (36/37) if their age was ≤30 years.

Table 4. **Influence of different factors on the outcomes. Values are given as n or mean [SE].**

Factors	Conceived	Did not conceive	P-values
Age (years)	29.9 [0.5]	32.6 [1.0]	0.02
Body mass index (kg/ m^2)	30.6 [0.6]	26.4 [0.9]	0.002
Duration of infertility (years)	4.2 [0.3]	5.5 [0.9]	0.08
Plasma LH Level (IU/L)	13.8 [0.5]	9.9 [0.8]	0.001
Plasma FSH level (IU/L)	6.1 [0.1]	5.9 [1.4]	0.70
Plasma LH: FSH ratio	2.3 [0.1]	2.5 [0.4]	0.34
Plasma testosterone level (nmol/L)	2.4 [0.1]	1.9 [0.1]	0.09
Plasma Prolactin level (ng/ml)	20.9 [1.1]	23.0 [3.9]	0.47
Hirsutism			
Yes	86	13	
No	67	15	0.34
Ultrasonography			
Typical of PCOS	94	11	
Atypical of PCOS	59	17	0.03
Infertility			
Primary	78	9	
Secondary	75	19	0.07
Menstrual cycle pattern			
Regular	14	5	
Oligomenorrhea	108	16	0.27
Amenorrhoea	31	7	
Associated infertility factors			
No	75	10	
Tubal adhesions	37	9	0.42
Endometriosis ± tubal adhesion	41	9	

DISCUSSION

Polycystic ovarian syndrome is a spectrum of disorders that ranges from individuals with normal body weight, regular menstrual cycles with ultrasonic features of polycystic ovaries to those with the full clinical picture of oligomenorrhea, obesity, hirsutism and hyperandrogenemia[17]. Approximately 2% of women in the general population have this syndrome and about 30% of women presenting with infertility[18]. The characteristics ultrasound picture of bilateral, symmetrically enlarged, polycystic ovaries was reported in 70-100% of the cases[19-22], which is consistent with 60.6% in this study. A high proportion (70-90%) of women with PCOS had irregular menstruation[1,23], and this was the case in 87.4% of our patients.

Women with PCOS exhibit disproportionately high mean concentrations of LH with relatively constant low or normal levels of FSH[24-27]. Furthermore, an increased LH bioactivity and a largely accelerated frequency and amplitude of LH pulsations have been described in such cases[28]. However, up to 20-40% of women with PCOS did not have elevated LH levels or reversed LH: FSH ratio[29-32]. In our study, although most patients (63.1%) had raised LH levels, most (52.5%) did not have reversal of the LH: FSH ratio. Hyperprolactinemia has been demonstrated in 10-27% of PCOS women[33-35], and this was comparable with 21.2% of our patients.

Gjonnaess[13] reported an ovulation rate of 92% and a pregnancy rate of 70% after laparoscopic ovarian electrocoagulation in patients with PCOS. This was the spark that reignited interest in surgical management of the disease and heralded the era of minimally invasive surgery in the treatment of these patients. Following this report, several studies described the success and utility of this procedure, with ovulation rates ranging from 64% to 92% and pregnancy rates from 41% to 80%[21,36-43]. Our results in this study are encouraging both in terms of the initiation and persistence of regular ovulatory cycles and in terms of pregnancies. We achieved a spontaneous ovulation rate of 70.1%, cumulative ovulation rate of 98.3%, and pregnancy rate of 84.5% in our series. It was reported that the beneficial effects of the surgical treatments are of limited duration, in most studies up to one year[12,44]. However, pregnancies have been known to occur after 12 months and in our study there were twenty-seven additional pregnancies between 12 and 24 months.

Our results are very similar to those reported by others showing a good outcome in patients with higher pre-operative LH levels[21,45,46]. It also affirms evidence demonstrating better pregnancy rates in younger women and those with typical ultrasonographic features of PCOS[21,47]. Although others described a positive correlation between the outcomes and short duration of infertility[21,48], this was not the case in our study. On the other hand, it has been reported that the co-existence of mild to moderate endometriosis and adhesions (non-obstructive tuboperitoneal disease) do not appear to have substantial influence on the outcomes of surgery[21,49], but patient with tubal disease had poorer outcomes[46]. However, in this series, we found that the co-existence of other infertility factors (including endometriosis, pelvic adhesions and tubal diseases) did not adversely influence the pregnancy rates (P=0.42).

The impact of obesity or high BMI on the outcome of laparoscopic ovarian electrocautery is disputable. Both reduced ovulation rates[39] and normal ovulation or pregnancy rates compared with those in non-obese women were reported[21,45,46]. In our study, we found a strong positive correlation between the outcomes of surgery and obesity. The obese women (BMI $\geq$30 kg/m^2) had a pregnancy rate of 93.5%, compared with 75% for non-obese (P=0.002). With this encouraging result, we suggest that obesity should not be considered a contraindication to laparoscopic ovarian drilling, although the risk of anaesthia-related effects are increased in obese women, and there may be also more difficulties in creating a pneumoperitoneum during laparoscopic procedures.

All our patients had previously been treated unsuccessfully with CC and several had had HMG and other treatments. The spontaneous ovulation rate in our study was 70.1% and another 28.2% of patients ovulated with the help of CC. Fifty-nine women (32.5%) conceived spontaneously after surgery, and another 45.9% of patients conceived with the help of CC or HMG (6.1%). Our results validate those of similar earlier reports and confirmed the notion that laparoscopic ovarian drilling increases the sensitivity of the ovaries to CC[39,41,42,47,49] and gonadotrophins[47,50,51]. It is also associated with higher ovulation and pregnancy rates, while reducing the dosage and duration of HMG treatment[51] together with the reduction in the incidence of OHSS in such patients[52]. Furthermore, it was found that the pregnancy rate after IVF in those who were previously treated with ovarian drilling was higher[53] and OHSS rates were lower than in other women with PCOS[54]. Taken together, these findings suggest that, if the ovaries could be reached, the co-existence of bilateral tubal block or severe tuboperitoneal disease should not be considered a contraindication to laparoscopic ovarian drilling even if the women decided to go through with an in-vitro fertilization (IVF) treatment, especially those who have previously had an IVF cancelled owing to the risk of OHSS or who have experienced OHSS in a previous treatment cycle.

A part from general complications that may occur during any laparoscopic surgery, periadnexal adhesion formation and premature ovarian failure are the two main potential complications of laparoscopic ovarian drilling. In previously published studies, the mean frequency of post-operative adhesions has been reported to be 29.1% (range 0-100%)[14,37,49,55,56], which is comparable with 11.8% (2/17) of our patients. Adhesiolysis during second-look surgery does not necessarily improve pregnancy rates[57]. Although adhesion may occur after laparoscopic ovarian drilling, it is usually mild, unilateral[37,56] and less frequent than after conventional bilateral ovarian wedge resection[14]. The fact that 84.5% of our patients have conceived indicates that significant adhesion formation did not occur in them, at least.

CONCLUSION

On the basis of our results, we conclude that laparoscopic ovarian drilling is an effective procedure for PCOS women with CC-resistant anovulatory infertility. The procedure can be done on an outpatient basis with less trauma and fewer post-operative adhesions. Multiple pregnancy and OHSS rates are considerably reduce in those women who conceived after drilling, but if CC or HMG has to be given after surgery, the frequency of multiple gestations may rise. The co-existence of other infertility factors is not a contraindication for the treatment. The outcome is more likely to be successful if the pre- operative LH level is more than 10 IU/L, BMI is ≥30 kg/m^2, and the age is ≤30 years.

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