Article

Unilateral ovarian drilling in polycystic ovarian syndrome: a prospective randomized study

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Abstract

Ovarian drilling is a well-accepted intervention for ovulation induction in clomiphene citrate-resistant polycystic ovarian syndrome (PCOS) patients. The aim of this study was to evaluate the effect of unilateral and bilateral ovarian drilling by electrocautery in PCOS women. In this prospective randomized clinical study, 87 patients with ovulation failure as a result of PCOS were randomly allocated to either unilateral (group A; $n = 43$ patients) or bilateral (group B; $n = 44$ patients) laparoscopic ovarian drilling by electrocautery. The average time required for unilateral ovarian drilling was shorter than for bilateral drilling. In patients who ovulated after drilling, there was a significant fall in serum LH concentration (group A, $P < 0.05$, group B, $P < 0.05$). Ovulation, pregnancy and miscarriage rates were similar in both groups. It seems that unilateral ovarian drilling in PCOS is effective, less time-consuming and probably associated with fewer complications.

Keywords: *miscarriage rate, ovarian drilling, ovulation rate, PCOS, pregnancy rate*

Introduction

Anovulation is estimated to cause 40% of female infertility. In most cases, it is related to polycystic ovarian syndrome (PCOS). PCOS is a common endocrinopathy affecting approximately 5–7% of women of reproductive age. The definition of the syndrome has been much debated (Frank, 1995). At a joint consensus meeting of the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE), a refined definition of PCOS was agreed, namely the presence of two out of the following three criteria: oligoovulation and/or anovulation, hyperandrogenism (clinical and/or biochemical), and polycystic ovaries, with the exclusion of other aetiologies (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

When infertility is the main problem affecting a patient suffering from PCOS, ovulation induction is necessary. Weight loss is important to improve the prospects of both spontaneous and drug-induced ovulation. Anovulation can be treated medically in some cases with anti-oestrogens, but a proportion of patients fail to respond, and of those who ovulate, the pregnancy rate is low and the miscarriage rate and the risk of multiple pregnancy are high (Hassan, 2000).

Given the drawbacks of clomiphene and the reported effectiveness of insulin-sensitizing agents such as metformin in the induction of ovulation, its first-line use may potentially reduce the number of clomiphene cycles to which women with PCOS are exposed. The therapeutic options for women who are resistant to anti-estrogens are either parenteral gonadotrophin therapy or laparoscopic ovarian diathermy (Khorram *et al.*, 2005). Gonadotrophin therapy may be more successful, but it is expensive, and there is a significant risk of ovarian hyperstimulation and multiple pregnancy. Therapy with LH-releasing hormone (LHRH) has been used, but the results have been disappointing and the miscarriage rate has also been high (Regan *et al.*, 1990). Laparoscopic ovarian diathermy has taken the place of wedge resection of the ovaries (which resulted in extensive periovarian and tubal adhesions), and carries a reduced

risk of multiple pregnancy compared with gonadotrophin therapy in the treatment of clomiphene-insensitive cases (Amer *et al*., 2003)

Laparoscopic surgery is associated with significantly less pain, earlier discharge from hospital, and more rapid convalescence than equivalent procedures performed by minilaparotomy. However, patients undergoing laparoscopic procedures do experience post-operative pain, especially in the upper and lower abdomen, back and shoulder regions (McMahon *et al*., 1994).

This prospective randomized study was designed to determine the efficacy of unilateral and bilateral laparoscopic ovarian cauterization on FSH, LH, and testosterone concentrations, post-operative analgesia, ovulation, pregnancy, and miscarriage rates in patients with PCOS, with particular attention to unilateral ovarian drilling.

Materials and methods

After obtaining the approval of the Ethical and Scientific Committee of Mansoura University, all the patients were counselled in detail about the procedure, type and duration of anaesthesia, possible complications, chance of success and the possible need for follow-up therapy. Written and verbal consent was obtained from both groups. Eighty-seven patients with ovulatory failure as a result of PCOS were randomly allocated by an independent investigator blinded to the treatment group to either unilateral or bilateral laparoscopic ovarian drilling by electrocautery using the closed envelope method. The study was performed in the Department of Obstetrics and Gynaecology and Fertility Care Unit, Faculty of Medicine, Mansoura University Hospital, from January 2003 to December 2006.

The criteria for inclusion were the following: infertility secondary to anovulation, as indicated by amenorrhoea or oligomenorrhoea, elevated serum LH concentrations and normal-to-low serum FSH concentrations, clinical evidence of androgen excess (acne, hirsutism), and slightly elevated androgen concentrations. The clinical characteristics of the 87 patients are shown in **Table 1**.

Weight reduction and insulin-sensitizing drugs were tried first for 3 months (metformin HCL 500 mg twice daily; Cidophage CID Co., Egypt).

All 87 women had been treated medically with clomiphene citrate and gonadotrophins for anovulation, but the treatments had been unsuccessful. Women with amenorrhoea had hormonal withdrawal treatment to induce menses. They received clomiphene citrate (Clomid; Global Napi Pharmaceuticals, Egypt) 50 mg daily for 5 days, from day 3 to day 7; if there was no response, the dosage was increased up to 150 mg daily for 5 days. Transvaginal folliculometry was performed; if there was still no response, human menopausal gonadotrophin (HMG) (Merional 75 IU; IBSA Institut Biochimique SA, Switzerland) was used to stimulate ovulation. Human chorionic gonadotrophin (HCG) (Choriomon 5000 IU; IBSA Institut Biochimique SA) was used between day 14 and day 18, according to the follicular size. Failure of ovulation was confirmed by a combination of ultrasound scan and low luteal-phase progesterone (day 21). Forty-three women (group A) received unilateral laparoscopic ovarian drilling, and another 44 (group B) had bilateral ovarian drilling.

Technique of drilling

Oral midazolam 0.1 mg (Dormicum Roche; F Hoffmann La Roche Ltd, Basel, Switzerland) was given the previous evening and at 1.5 h before the procedure. Intraoperative monitoring consisted of electrocardiogram, oxygen saturation, end tidal carbon dioxide (ET CO_2), and non-invasive blood pressure. A standardized anaesthetic technique was used for all patients. Anaesthesia was induced with propofol (2–3 mg/kg) (Diprivan 1% w/v; AstraZeneca, UK) and fentanyl 2 μg/kg i.v. (Janssen Pharmaceutica, Belgium), Tracheal intubation was facilitated by atracurium 0.5 mg/kg i.v. (Tracrium; GlaxoSmithKline, Parma, Italy), and the lungs were ventilated with intermittent positive-pressure ventilation by using a mixture of 1.5–2% isoflurane (Flurane; Abbott Laboratories S.A., Geneva, Switzerland) and 66% nitrous oxide in oxygen. Ventilation was adjusted to keep ET CO_2 between 30 and 40 mmHg. All patients received ondansetron 8 mg i.v. (Zofran; Glaxo Welcome, Egypt) and diclofenac 100 mg (Adwiflam; ADWIA Co. S.A.E. 10th of Ramadan City, Egypt) rectally after the induction of anaesthesia.

The operation was performed for all patients using standardized laparoscopic procedures through three puncture technique with a 10 mm videolaparoscope and two lateral punctures. A uterine manipulator was inserted for traction and counter-traction to aid in the exposure and manipulation of the ovary. The pelvic organs were inspected and tubal assessment was confirmed by transcervical injection of methylene blue dye.

The ovary was lifted up and sited away from the bowel and wedged against the pelvic side-wall using the flattened edges of the closed Maryland forceps. The utero-ovarian ligament was not grasped for fixation of the ovary in any case. Overly aggressive manipulation was avoided, since it can cause lacerations in the capsule, follicles and the utero–ovarian ligament, which can result in bleeding. If both ovaries were equal in size, the right ovary was chosen for cauterization, since it is easier. However in cases of unequal ovarian size, the larger one was cauterized. The chosen ovary was cauterized at four points each for 4 s at 40 W at a depth of 4 mm with mixed current, using a disposable monopolar needle (5-mm electrosurgical suction/irrigation device with a wire J hook tip configuration: Reflex ELS; Richard-Allan Medical Industries, USA).

Cooling of the ovary was achieved by irrigation with Ringer's lactate solution, and 250–300 ml of the solution was left in the peritoneal cavity at the end of the operation to minimize the risk of adhesion. All the procedures were performed without complications, and the average surgical time was calculated.

At the end of the operation, anaesthesia was discontinued, and neuromuscular blockade was reversed with neostigmine methylsulphate 0.05 mg/kg (neostigmine; Amriha Pharm. Ind., Alexandria, Egypt) and atropine sulphate 0.02 mg/kg (MISR Co., Egypt).

Post-operative pain was assessed both at rest and on movement (patients being asked to move from the supine to the sitting position) at 30 min and 2, 4, and 6 h post-operatively. The patients were asked to rate the severity of pain via a visual analogue scale (VAS) ranging from no pain (0 cm) to worst imaginable pain (10 cm). The use of these measures was explained to all patients before surgery. An independent investigator blinded to the treatment group obtained the scores. If the VAS score was greater than 5, the patient was prescribed 0.5–1 mg/kg i.v. meperidine (demerol HC1; G. Breon and Co., USA) once every 4 h as required for analgesia. The drugs were administered on demand (within the limits defined above) by an experienced recovery nurse with no knowledge of the perioperative analgesia administered. The time to the first analgesia administration and total analgesic requirements in the first 6 h was recorded.

Post-operative nausea was measured using a VAS score at each of the time intervals outlined, and a record was kept of any vomiting experienced by the patient.

On the day of the operation, blood samples were taken from the patients and then also every 2 weeks for 8 weeks. Pelvic ultrasound scan was performed at each visit to the clinic. The patients were followed up for 1 year for ovulation, pregnancy and miscarriage rates.

Outcome measures

The mean pretreatment and post-treatment FSH, LH, and testosterone concentrations and post-operative nausea, vomiting and pain were the primary outcomes. Ovulation, pregnancy, miscarriage rates during the 1 year follow-up period were the secondary outcomes.

Statistical analysis

Results of the study were reported as arithmetical mean ± SD. Statistical analysis were performed using Student *t*-test and Pearson's correlation test for comparison between different study groups. A probability of ≤0.05 was taken as the limit of statistical significance. Based upon preliminary data (not shown), a prior power analysis indicated that 40 patients in each group would be sufficient to detect a 20% reduction in the duration of the ovarian drilling values, with a type I error of 0.05 and a power of approximately 90%.

Results

The average time for unilateral ovarian drilling (group A) was 18.3 ± 3.5 min and for bilateral ovarian drilling (group B) was 23.5 ± 2.5 min. The mean pretreatment and post-treatment FSH, LH, and testosterone concentrations are shown in **Tables 2** and **3**. Two women were lost to follow-up and excluded from the analysis.

As regards the primary outcomes, there was no significant statistical difference between the hormonal concentration in serum FSH and testosterone when pretreatment and post-treatment concentrations were compared in both responders (**Table 2**) and non-responders (**Table 3**). However, in the responders, there was a significant fall in serum LH concentration after ovarian drilling (group A, $P < 0.05$, group B, $P < 0.05$) (**Table 2**), whereas in the non-responders there was no significant difference in LH concentration before and after treatment (**Table 3**).

As regards the secondary outcomes (ovulation, pregnancy, miscarriage rates), 68 of the 85 patients (80%) ovulated within 6 months of laparoscopic ovarian drilling without additional therapy, but the remaining 17 patients failed to ovulate. Patients who failed to ovulate received clomiphene citrate (50 mg daily) for 5 days, from day 3 to day 7; if there was no response, the dosage was increased up to 100 mg daily for 5 days in addition to insulin sensitizing drug (metformin HCL 500 mg, twice daily).

Thirty-four of the 43 patients (79.1%) who received unilateral ovarian drilling ovulated from both ovaries. Thirty-four of the 44 patients (77.3%) who received bilateral ovarian drilling ovulated from both ovaries. Ovulation was assessed by ultrasound scan and serum progesterone at mid-luteal phase. During the 1 year follow-up period, the pregnancy and the miscarriage rates were 60.5 and 15.4% for group A and 56.8 and 16.0% for group B (**Table 4**). Perhaps surprisingly, most of the pregnancies occurred within the first 6 months (35/51, 68.6%). In group A, 18 patients became pregnant within the first 6 months, while in group B, 17 patients became pregnant within the same period.

The median VAS, first request for analgesia, and the post-operative meperidine consumption (mg) for the first 6 h were similar in both groups. (**Table 5**).

Table 1. Demographic data of the patients and duration of surgery.
Group A = unilateral ovarian drilling; group B = bilateral ovarian drilling.

Variable	*Group A* (n = *43*)	*Group B* (n = *44*)
Age (in years)	31.1 ± 4.2	29.8 ± 3.7
Duration of infertility (years)	9.2 ± 1.1	10.4 ± 1.8
Body mass index	26.1 ± 1.9	25.7 ± 1.8
Duration of surgery (min)	18.3 ± 3.6	23.5 ± 2.5

Values are mean ± SD.

Table 2. Pretreatment and post-treatment serum concentration of hormones in responders.

Hormone	*Unilateral ovarian drilling*		*Bilateral ovarian drilling*	
	Pretreatment	*Post-treatment*	*Pretreatment*	*Post-treatment*
LH (IU/l)	12.9 ± 3.8[a]	7.2 ± 2.1[a]	13.1 ± 2.9[b]	8.9 ± 2.8[b]
FSH (IU/l)	6.3 ±1.3	6.1 ± 1.2	6.8± 1.4	6.2 ± 1.3
Testosterone (nmol/l)	2.4 ± 1.9	2.3 ± 1.2	2.6 ±1.8	2.2 ±1.3

Values are mean ± SD.
[a,b]Values with the same superscript letter are significantly different ($P < 0.05$).

Table 3. Pretreatment and post-treatment serum concentration of hormones in non-responders.

Hormone	*Unilateral ovarian drilling*		*Bilateral ovarian drilling*	
	Pretreatment	*Post-treatment*	*Pretreatment*	*Post-treatment*
LH (IU/l)	14.2 ± 4.8	11.8 ± 4.3	13.9 ± 3.8	11.2 ± 4.1
FSH (IU/l)	8.8 ± 2.3	6.2 ± 3.1	6.1 ± 2.2	5.9 ± 2.9
Testosterone (nmol/l)	3.8 ± 1.4	3.5 ± 2.2	3.7 ± 1.5	3.1 ± 1.2

Values are mean ± SD.

Table 4. Clinical outcomes of 87 patients undergoing laparoscopic ovarian drilling by electrocautery. Group A = unilateral ovarian drilling; group B = bilateral ovarian drilling.

Variable	*Group A (n = 43)*	*Group B (n = 44)*
Ovulation rate (%)	34/43 (79.1)	34/44 (77.3)
Pregnancy rate (%)	26/43 (60.5)	25/44 (56.8)
Miscarriage rate (%)	4/26 (15.4)	4/25 (16.0)

Table 5. Post-operative pain experienced and analgesia required by patients following unilateral (group A) or bilateral (group B) ovarian drilling.

Post-operative parameter	*Group A (n = 43)*	*Group B (n = 44)*
VAS score at :		
0.5 h	5 (3–7)	4 (2–8)
2.0 h	3 (0–6)	4 (1–7)
4.0 h	5 (2–7)	6 (0–8)
6.0 h	4 (1–8)	3 (1–7)
First analgesic request (h)	1.5 ± 0.34	1.2 ± 0.89
Total meperidine consumption (mg) during first 6 h	85 ± 21.34	93 ± 17.89

VAS = visual analogue scale: 0 = no pain, 10 = worst imaginable pain. Values are median (range) or mean ± SD.

Discussion

PCOS is associated with chronic anovulation and infertility. In most cases ovulation can be induced with weight reduction, insulin-sensitizing drugs and clomiphene citrate (CC), but approximately 25% of patients fail to ovulate and require alternative treatment (Franks *et al*., 1988). Human menopausal gonadotrophins have been used, but are associated with the risk of hyperstimulation and multifetal gestation. A variety of surgical options for the treatment of PCOS have been applied during laparoscopy such as biopsy, cauterization and laser surgery (Cohen, 1996).

The reported ovulation rate after laparoscopic ovarian drilling (LOD) varies between 50 and 90% (Daniel and Miller, 1989, Abdel Ghadir *et al*., 1990; Parsanezhad *et al*., 2005).

Since the introduction of LOD by Gjonnaess (1984) in the early 1980s, the technique has become widely accepted as a second line treatment for induction of ovulation in women with PCOS after failure of clomiphene citrate. Not only does LOD produce high ovulation (>80%) and pregnancy (60%) rates, but it also corrects the underlying endocrine abnormalities associated with the disease, such as raised serum concentrations of LH and androgens. In addition, ovarian drilling may render the ovaries more sensitive to clomiphene citrate (Amer *et al*., 2003).

As regards the adverse effects of ovarian cauterization, whether by electrocautery or laser, periovarian adhesion is the main problem. An additional concern is the possibility of ovarian destruction leading to ovarian failure in up to 5.2% after bilateral ovarian wedge resection (BOWR) and laparoscopic surgery (Cohen, 1996).

For these reasons, a strategy of minimizing the number of holes in each ovary has been advocated, with the intention of reducing the peri-ovarian adhesion and ovarian destruction. Cauterization of only one ovary has even been suggested (Khandil and Selim, 2005). It has been reported that ovulation took place from both ovaries in patients who had only one ovary treated with laser beams (Hassan, 2000).

Balen and Jacobs (1994) compared unilateral with bilateral ovarian diathermy in 10 patients with anti-oestrogen-resistant PCOS. They reported a 75% ovulation rate in women who underwent unilateral ovarian diathermy applying four punctures. They also found that unilateral ovarian diathermy resulted in ovulation from the contralateral ovary in the first cycle and then alternatively from each ovary (Balen and Jacobs, 1994). Although the numbers in this study are small, it clearly indicates that the effects of LOD depend on the destruction of a certain amount of ovarian tissue, whether this is inflicted on one ovary or divided between the two ovaries. It is therefore possible that the optimal amount of energy could be delivered to one ovary only without compromising the success rates (Amer *et al*., 2003). Pain after laparoscopy results from stretching of the intra-abdominal cavity, peritoneal inflammation, and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity (Jackson *et al*., 1996). No significant changes were recorded in post-operative analgesia between the studied groups. This may be attributed to the fact that the severity of post-laparoscopic pain may not be affected by the site of the surgical manipulation.

It has been proposed that the degree of ovarian destruction should be determined by the size of the ovary. However, in the present study, there was no relationship between the response to surgery and size of the ovaries (data not shown).

The correct dose of any therapy is the lowest one that works. Furthermore, a combined approach may be suitable for some women where low-dose diathermy is followed by low dose medical ovarian stimulation. In this study, ovulation took place from both ovaries in patients who had only one ovary treated. Ovulation, pregnancy and miscarriage rates were nearly the same in both groups, which is in accordance with the work of Hasan *et al*. (2005) and Al-Mizyen *et al*. (2007).

In conclusion, in patients with PCOS who failed to ovulate after medical therapy, unilateral ovarian laparoscopic drilling was as effective as bilateral drilling, less time-consuming and is probably associated with a lower rate of complications than bilateral drilling. Both techniques were followed by a significant ($P < 0.05$) fall in serum LH concentration. However, the post-operative pain relief, ovulation, pregnancy and miscarriage rates were similar in both groups.

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