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Original Article

Short term effects of laparoscopic ovarian drilling in clomiphene citrate resistant patients with polycystic ovary syndrome

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ABSTRACT

Objective: The study aims to assess the effect of laparoscopic ovarian drilling (LOD) in clomiphene citrate resistant patients with polycystic ovary syndrome (PCO) on the changes occurred in ovarian reserve.
Study design: A prospective cohort study.
Setting: Sohag University Hospital, Sohag, Egypt.
Materials and methods: Thirty-seven patients with PCO were enrolled in the study. We evaluated the effect of LOD on the ovarian reserve using hormonal assay (measuring FSH, LH, AMH, Testosterone, SHBG, E2 and FAI) and sonographic markers (including ovarian volume, antral follicle count (AFC) and ovarian stromal blood flow).
Results: Amongst the 37 patients underwent LOD, regulation of the cycle occurred in 20 patients after 6 months (54.06%) ($p = 0.001$). Occurrence of pregnancy occurred in 4 patients after three months and in 18 patients after 6 months. As regard the hormonal profile, LOD has reducing effect on the serum levels of FSH, LH, AMH, SHBG, Testosterone and free androgen index. This reduction is of statistically significance in case of LH, AMH, testosterone and FAI especially after 6 months ($p = 0.01$, 0.001, 0.05, 0.05 respectively). The deleterious effect of LOD was statistically significant in the AFC which was reduced from 18.1 ± 2.7 to 11.5 ± 1.8 after 6 months ($p = 0.05$). Also, the ovarian blood flow indices were reduced with $p = 0.01$ for all indices.
Conclusions: Using the AMH and AFC as reliable markers of the ovarian reserve and measuring them for women with anovulatory PCO undergoing LOD may provide a useful tool in evaluating the outcome of LOD as the gold standard treatment for CC resistant PCO women.

1. Introduction

Polycystic ovary (PCO) is considered as one of the most common endocrine disorder that occurred in 5–10% of women in reproductive age group. It is the major cause of ovulation – related infertility, accounting for at least 75% of cases with anovulatory infertility [1].

This major disorder is characterized by a marked increase in preantral follicular number arranged peripherally around a dense core of stroma or scattered throughout an increased amount of stroma [2]. The first line of treatment of such disorder was induction of ovulation using clomiphene citrate (CC) and other members of selective estrogen receptor modulators (SERM) [3]. However; 15–40% of patients with CC – resistant PCO patients [4]. Such patients can be managed either by using gonadotropins [5] or by minimal surgical procedure known as laparoscopic ovarian drilling [6].

The mechanism of action of LOD is largely unexplained. In particular, it is not known whether LOD exerts its action through a direct effect on the ovary or through a systemic endocrine mechanism [7]. One of the theories that explain the effect of LOD is the higher ovarian reserve presents in patients with PCO. This proposed mechanism of exaggerated ovarian activity (at supra-physiological state) can be reduced to the physiological level by destruction or removal of some part of the ovary retaining the ovarian activity to physiological state [8].

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Although the available data in the literature is limited, there is no concrete evidence of a diminished ovarian reserve or premature ovarian failure due to LOD in patients with PCOS. Most of the changes in the ovarian reserve markers observed after LOD could be interpreted as normalization of ovarian function rather than reduction in ovarian reserve [8,9].

Anti-mullerian hormone (AMH) or mullerian inhibiting substance (MIS) is a member of transforming growth factor β (TGF – β). It is a dimeric glycoprotein which is produced by the granulosa cells of primary, pre-antral and small antral follicles suggesting an important role of AMH in human folliculogenesis [10]. AMH has been shown to lower the sensitivity of follicles to circulating FSH [11]. Its principle function is the inhibition of primordial follicle growth organization that is important in dominant follicle selection [12]. It has been shown that the serum level of AMH is likely to be 2–3 folds increased in serum from women with PCO than in women with healthy ovaries [13].

The aim of our study is to assess the short term effect of LOD as regard its effect on ovarian reserve (evaluated by assessing the sonographic parameters including AFC, ovarian volume and ovarian stromal blood flow and hormonal parameters including AMH, baseline FSH, LH, E_2 and FSH/LH ratio and finally ovulation monitoring.

2. Materials and methods

This is a prospective cohort study included 37 infertile anovulatory women with CC-PCO who underwent LOD. The study was conducted in Sohag University Hospital, OB/GYN department, on attendants of outpatient clinic complaining from infertility during the period from September 2015 till October 2016.

The patients were selected as infertile patients with PCO who were resistant to CC induction of ovulation. The patient ages range between 19 and 30 years. The age and the body mass index were recorded for all members of study group. CC resistance was defined as failure of ovulation after six successive cycles of ovulation induction using a maximum dose of clomiphene citrate (200 mg/d) for 5 days starting from day 2 to day 6 of the cycle.

PCO women were diagnosed according to the 2003 ESHRE/ASRM (Rotterdam) criteria and their partners had normal semen analysis (according to WHO criteria). The Rotterdam criteria for diagnosis of PCO include presence of at least 2 out of 3 of the following criteria: oligomenorrhea or amenorrhea, clinical and biochemical signs of hyperandrogenism and finally ultrasonographic picture of PCO (≥12 subcortical follicles (2–9 mm in diameter) with dense stroma and/or increased ovarian volume (more than 10 cm^3).

We excluded infertile patients due to causes other than PCO (tubal block, abnormal semenogram, etc.), patients with any organic pelvic disease diagnosed during laparoscopy or diseases potentially affecting the normal ovarian functions as endometriosis and fibroid, hose with previous pelvic surgery (appendectomy, ectopic pregnancy, ovarian cystectomy, myomectomy, those with medical diseases that may affect fertility as diabetes mellitus, liver diseases. Additionally women with hyperprolactinemia or other endocrine disorders that may affect fertility were excluded from the study. Women suffering from other causes of hyperandrogenism as congenital adrenal hyperplasia, androgen secreting tumors and Cushing's syndrome were also excluded.

All participants were subjected to full detailed history including menstrual history, medical history, surgical history, past history, obstetric history or sexual history and any previous investigations done or treatment given. Careful general, abdominal and pelvic examination was done and completing the investigations was carried out. All women gave their written informed consent and agreed to undergo the laparoscopic procedure.

Ultrasonography was performed using transvaginal sonography probe 7.5 mHz (Sonoscape S11, Sonoscape Co Ltd. Beijing, China) to confirm the diagnosis of PCO, to assess the ovarian volume, to exclude ovarian or adnexal pathology and to assess the mean AFC in both ovaries (measuring 2–9 mm). Power Doppler measurements were performed on the early follicular phase before LOD and repeated 3 and 6 months after LOD (also in early follicular phase). The ovarian volume was measured using the following formula (length × width × thickness × 0.523). The procedure was done on the two ovaries and the summation of volumes of both ovaries was calculated giving the total ovarian volume (TOV).

Antral follicles were defined as every hypo echoic rounded structures measuring 2–10 mm seen subcapsular or within the ovarian stroma. AFC defined as the count of all antral follicles measuring 2–10 mm in both ovaries at the baseline examination session (early follicular phase). Serial scans were obtained by slow sweeping of the transvaginal probe from medial to lateral border of the ovary in two perpendicular planes. The procedure was performed on the other ovary to obtain the total antral follicle count.

The ovarian stromal blood flow measurement was achieved using 3D power Doppler ultrasound (Sonoscape S40, Sonoscape Co Ltd. Beijing, China). Flow velocimetry waveforms were obtained from stromal blood vessels away from the ovarian capsule. The gate of Doppler apparatus was positioned when the vessels with good color signals was identified on the screen.

The built in VOCAL (Virtual Organ Computer – aided Analysis) imaging program of the 3 power Doppler histogram analysis was used to determine the ovarian volume as well as the vascularization and blood flow indices. During the analysis and calculation, the manual mode of VOCAL contour editor was used to cover the whole 3D volume and the ovary with a 15 degree rotation step. Hence, 12 contour planes were analyzed for each ovary to cover 180 degree. Vascularization index (VI), Flow index (FI) and Vascularization flow index (VFI) were measured.

Blood samples were collected before LOD and after 3 and 6 months after LOD to measure plasma concentrations of E2, FSH, LH, AMH, SHBG and testosterone. Before surgery, about 5 cc blood sample was taken from each patient and maintained in tubes containing cloth activator material (serum separation, Stago, France). The samples were centrifuged with 3000 rpm and the serum was collected at 2 ml micro tubes and stored at −20 °C freezer until subsequent analysis. Congenital adrenal hyperplasia was excluded with a single measurement of serum 17-hydroxyprogesterone (17-OHP) levels (normal value < 1.98 ug/l). Hyperprolactinemia was excluded with a single assay of serum prolactin (PRL) levels (normal values < 25 ng/ml).

Plasma samples were assayed for the hormones in duplicate using a commercial enzyme-linked immunosorbant assay kit (Pritest ECO, ELISA, ROBOnik (India) Pvt, Ltd) according to the manufacturer's protocol. The sensitivity of the assay was 0.24 ng/ml. The intra- and inter-assay variability were <5% and 8%, respectively. In each woman, the free androgen index (FAI) was calculated using the following formula: FAI = 100 × Total Testosterone/SHBG.

Using the standard precautions used to be followed in laparoscopy, with the patient put in lithotomy position ovarian drilling was done under general anesthesia. After Co2 insufflation of the abdomen using Verres needle the patient was put in moderate Trendelenburg position (30 degrees) then a 10-mm trocar inserted intraperitoneally. The trocar sleeve was left in situ and a 10-mm 0 degree telescope (KARL STORZ co Ltd, Arizona, United States) was inserted and connected to a camera with a video monitor system.

A panoramic view was performed before making incisions for instrumentation. The abdominal cavity especially the pelvic area was carefully inspected. Two further 5-mm trocars were inserted

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