Research Article

Unilateral versus Bilateral Laparoscopic Ovarian Drilling in Clomiphene Citrate Resistant Polycystic Ovarian Syndrome in Minia Governate: Randomized Clinical Trial

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Abstract

Background: The study explores unilateral versus bilateral laparoscopic ovarian drilling in patients with clomiphene citrate resistant polycystic ovarian syndrome in terms of improving the reproductive hormonal profiles, ovarian reserve and ovulation outcome in El-Minia Governate. **Methods:**The effectiveness of unilateral (N: 55 women) versus bilateral (N: 55 women) LOD were done in terms of improving infertility outcomes in clomiphene resistant PCOD patients. **Results:** There is no significant difference in both studied groups regarding serum FSH level before and six months after LOD in both groups ($p > 0.05$), however there is a significant difference in both studied groups regarding serum LH level before and six months after LOD ($p < 0.001$). However, no significant difference in serum LH levels either before or after LOD when compared both groups ($p > 0.05$). There is a significant difference in both studied groups regarding the serum AMH level before and six months after LOD in both groups ($p < 0.001$) , also there is a significant differences when compared the two groups after six months from LOD ($p < 0.01$).**Conclusions:** Unilateral laparoscopic ovarian drilling had similar efficacy as bilateral laparoscopic ovarian drilling in terms of restoration of normal menstrual cycles, ovulation and pregnancy rates with improving both ovarian reserve and AFC.

Keywords: Unilateral laparoscopic ovarian drilling/ polycystic ovarian syndrome/ clomiphene resistance

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders among women in reproductive age. It is the leading cause of anovulatory cycles in infertile women (Castello et al., 2012). Induction of ovulation with clomiphene citrate (CC) is the standard first line of treatment in PCOS patients (Legro et al., 2007). Clomiphene resistant is defined as failure to ovulate after receiving a maximum dosage of 150 mg per day for the five days beginning on the third day of menstrual cycle (Ott et al., 2011). Laparoscopic ovarian drilling (LOD) is a method to induce ovulation in polycystic ovarian patients instead of administration of gonadotrophins (Hameed and Ali, 2012). Despite minimal morbidity associated with this method, LOD has some advantages and benefits in the form of elimination of the cycle monitoring, decreasing the risk of ovarian hyperstimulation syndrome (OHSS), multiple pregnancies that associated with gonadotrophins (Salah, 2013).

As well as occurring spontaneous ovulation in some patients without further treatment (Fernandez et al., 2011). Two disadvantages of Laparoscopic ovarian drilling are the possibility of tubo-ovarian adhesions and premature ovarian failure (Wang et al., 2015). A few studies have compared unilateral laparoscopic ovarian drilling (ULOD) and bilateral laparoscopic ovarian drilling (BLOD) and concluded that unilateral ovarian drilling is equally effective as bilateral ovarian drilling n inducing ovulation and achieving pregnancy, besides minimizing the risk of adhesions and premature ovarian failure (Al-Mizyen and Grudzinsku, 2007). Moreover, flushing of the ovaries with normal saline prevents over-heating and many use an anti-adhesion preparation (Arya et al., 2017). The aim of this study was to compare unilateral versus bilateral laparoscopic ovarian drilling in patients with clomiphene citrate resistant polycystic ovarian syndrome in terms of improving the reproductive hormonal

profiles, ovarian reserve and ovulation outcome in El-Minia Governate.

Materials and Methods

All patients were informed about the study and the possible complications of the operation by a specialist. A written, dated and signed informed consent was obtained from all participants after explaining the nature, purpose, and duration of the study. The study with approved by the department ethical committee. The study group was drawn from infertile women whose initial attendance at Outpatient infertility Clinics of Gynecology and Operation rooms based at Tertiary University Hospital (Minia Maternity and Children University Hospital, Minia, Egypt), from July, 2019 to April, 2020. Participants' attending the outpatient Clinic of Gynecology Operation and LOD was done for free for all patients at Minia Maternity and Children University Hospital.

Laboratory procedures

Laboratory hormonal profile assay pre and six months post-operative was done by participants except AMH assay which was done by the investigators pre and post-operative in the department of clinical pathology at Minia University Hospital. Radiological: Abdominal and vaginal ultrasound for free Examinations: Full clinical examination and ultrasonography examination for free to all participants.

Study Design

It is an interventional prospective study, all women were examined clinically, so their weight, height and body mass index (BMI) were recorded before and after the study.

Participants

This study included 110 women with a diagnosis of PCOS who were resistant to clomiphene citrate. Clomiphene citrate resistance was defined as three cycles with CC (150 mg) daily without ovulation. Diagnosis of PCOS done according to the European Society for Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) sponsored PCOS Consensus Workshop criteria (the Rotterdam criteria). The diagnosis of PCOS was made according to modified Rotterdam criteria (The Rotterdam ESHRE / ASRM-sponsored PCOS consensus workshop group, 2004).

Plan of the Study

One hundred ten infertile women with the diagnosis of PCOS (sample size was calculated through G3 power refers to 110 patients in power of 80% with clinical significance of 0.5%) were divided randomly into two groups according to the method of laparoscopic ovarian drilling:

Group I: included 55 patients with PCOS underwent laparoscopic right unilateral ovarian drilling

Group II: included 55 patients with PCOS underwent laparoscopic bilateral ovarian drilling

* Clinical evaluation including determi-nations of weight, height, BMI, was done before LOD and after three months.
* Biochemical evaluation including serum levels of prolactin, total testosterone, LH, FSH, progesterone and AMH was done before LOD and six months after operation. FSH, LH, prolactin, AMH was done on day three of the menses, while progesterone assay was done on day 21 of the cycle.
* Ovulation was detected before LOD and through three and six months follow- up (ovulation was defined by one leading follicle of 18 – 20 mm or measurement of midluteal serum progesterone)
* Achievement of pregnancy was detected using serum β- HCG or intrauterine gestational sac by ultrasound.

Blood Sample Collection

Five ml of venous blood was collected from all subjects after 12 hours of fasting, before and after three months of LOD The samples were left at room temperature for 15 minutes clotting, centrifuged and then serum was separated and stored in deep freezing at – 80 o C until analysis.

Ultrasound Studies

Transvaginal ultrasound examination (TVS) was done using a 7.5MHz transducer (Voluson, p8 machine) for all women of the two groups. Transvaginal ultrasound examination was done before drilling to confirm the presence of ultrasound criteria of PCOS, to evaluate endometrial thickness, detection of ovulation (at day 12-14 of the menstrual cycle) and to exclude

other pelvic pathology. Ovarian volume and antral follicle count were measured in the early follicular phase of the menstrual cycle (cycle day 2-5) before LOD and after three months.

Surgical Procedure of Laparoscopic Electro-Cautery

General anesthesia with endotracheal intubation, the patient was put in the dorsal lithotomy position with her buttocks extending beyond the edge of the table to allow free mobilization of the uterus by the vacuum intrauterine canula. This was done to perform pelvic laparoscopy and vaginal manipulations. Then the footplate of the electrosurgical unit was applied to the patient's thigh. Sterilization, toweling, evacuation of the urinary bladder with Foley's catheter insertion. Immediately before surgery, an antibiotic therapy was given by IV route. The Veress needle was inserted at the lower margin of the umbilical scar.

Pneumoperitoneum was achieved by insertion of the Veress needle usually at a small incision 2 mm made at the inferior rim of the umbilicus with the patient being put in Trendelenburg position with the head lowered to approximately 15 degree, to allow the patient's bowel to slide into the upper abdomen as the insufflation progresses. After pneumoperitoneum has reached intra- abdominal static pressure of 12 – 15 mmHg (the automatic CO insufflator gauge is set at pre- selected pressure 12 -15 mmHg which is suitable for pelvic surgery, the CO flow will stop automatically).

The 2 mm incision is extended to 1 cm by a point scalpel was stabbed into the lower margin of the umbilicus in the direction almost parallel to the abdominal wall. The Trendelenburg position was increased and then a 10 mm trocar and its sleeve were introduced through the abdominal wall in a direction 45 degree to the horizontal towards the pelvis. The laparoscope trocar and sleeve were inserted through the umbilical incision in a twisting corkscrew technique that involves pushing the trocar down to the fascia, with a short twisting corkscrew motion; the trocar is pushed through the rectus fascia. This technique is to avoid a sudden thrust that might abruptly slip and contact the intra-abdominal or retro-peritoneal organs.

The trocar was removed from the sleeve, the gas hose was connected to the gas port on the sleeve, and the laparoscope telescope, was connected to the cable of the light source (switch on), then was advanced down to the trocar sleeve into the pelvis. The color monitor was connected to the video recorder to record the operation. The second and third punctures were done. The first step in the insertion of a second instruments was to trans illuminate the lower abdominal wall and select on a vascular site for the incision of the second incision trocar in the public area (for cosmetic reasons); A small transverse skin incision 4 – 5 mm is made with a small pointed scalpel. The trocar and sleeve for 5 mm operating instruments were inserted through the second incision down to the fascia. At this point, the surgeon looks to the attached video monitor and slowly advances the trocar and sleeve until it has perforated the peritoneum under vision to avoid incidental injury of viscera or pelvic blood vessels or inferior epigastric vessels. The routine tubal patency testing with methylene blue was followed for all patients. The ovarian ligament was grasped with a traumatic grasping forceps introduced through second puncture; the ovary was moved in the front of the body of the uterus or towards the anterior abdominal wall to prevent injury of the pelvic organs. The drilling needle was used to penetrate the ovarian capsule at right angle to a standard depth of 4 mm at points with 40W cutting current and coagulated with 40W current if bleeding occurred, the number of punctures was calculated according to this equation: NP = 60J / cm3 / 30 W x 5 second. The ovary was cooled by lactated Ringer's solution. At the end of the procedure, repeated suction irrigation of the pelvis with lactated Ringer's solution was done and 500 cc was left intra- peritoneally. Then second instruments were removed under vision, the abdomen was deflated and the 10 mm umbilical sleeve was removed under vision, skin incisions were closed.

Hormonal Profile Assay

On the third day of a spontaneous or progesterone withdrawal menstrual cycle, after an over night fast, 5 ml of blood samples were drawn, serum was separated by the centrifugation, then stored at – 80 0 until assayed using

ELISA technique. FSH, LH, prolactin, TSH, progesterone, total testosterone, and AMH were assayed before and three months after laparoscopic ovarian drilling to all participating patients.

Outcome Measures:

1. Resumption of menstrual regularity, i.e. initiation of menses or significant shorting of cycles. Women with resumption of normal menstrual cycle, defined as being between 21- 35 days.
2. Resumption of spontaneous ovulation documented by one leading follicle of 18 – 20 mm or midluteal progesterone >5ng/ ml.
3. Improvement in androgen levels by measuring testosterone level (nmol / L).
4. Improvement of hirsutism and acne clinically.
5. Effect on ovarian reserve by measuring AMH level (ng / ml).
6. Achievement of pregnancy at the first six months after laparoscopic ovarian drilling.

Hirsutism Measures

The degree of hirsutism was assessed using the modified Ferriman and Gallwey scoring system. This system grades terminal hair growth on a scale from 0 (no terminal hair) to 4 (extensive terminal hair growth) at nine anatomical sites (upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, and thigh) and uses the sum of nine areas to generate an overall hirsutism score. A patient's score may therefore range from a minimum score of 0 to a maximum score of 36. Score ≥ 8 was indicated hirsutism. The modified Ferriman and Gallwey scoring system (Ferriman et al., 1961).

Health and Safety Regulation

The biological specimens, materials and reagents were handled according to health and safety regulations, settled by Minia University and Minia University Hospitals. A form of assessment of risk associated with procedures in the Obstetrics and Gynecology.

Statistical Analysis

Data were analyzed using descriptive and analytic statics. For numeric variables, data will be described as mean±SD, while for categorical variables, data will be shown as number and percentage. For statistical analysis, independent t- test was used to compare mean values of FSH, LH, total testosterone, prolactin, progesterone and AMH levels before and six months after laparoscopic ovarian drilling. Fisher's exact test was used to compare relative proportions of variables between two groups. Differences will be considered significant at $p < 0.05$.

Results

This study was conducted on 110 patients who had laparoscopic ovarian drilling and are divided into two groups (group I with ULOD and group II (BLOD) with the following results**.**

Table (1): Demographic characteristics of the two groups before laparoscopic ovarian drilling.

Variable	Group 1(ULOD) N = 55	Group II (BLOD) N = 55	P- value
Age (years)			
Range	18 – 37	18 – 38	
Mean ± SD	27.7 ± 4.6	28.3 ± 4.2	0.643
Weight (kg)			
Range	59 – 88	61 – 90	
Mean ± SD	72 ± 6.8	73 ± 6.7	0.184
Height (m2)			
Range	1.54 – 168	1.51 – 171	0.321
Mean ± SD	1.6 ± 0.05	1.6 ± 0.06	
BMI (kg l m2)			
Range	23.2 – 33.57	24.3 – 34.1	
Mean ± SD	28.9 ± 3.6	29.4 ± 3.9	0.34
Type of infertility			
Primary: Freq (%)	30 (54.5 %)	28 (50.9)	
Secondary: Freq (%)	25 (45.5 %)	27 (49.1)	0.92
Duration of infertility			
Range	2 – 7	2 – 8	
Mean ± SD	4.9 ± 0.6	5.5 ± 0.8	0.64
Duration of surgery (min)	16.7± 3.4	23.8± 3.1	< 0.05

*** Significant difference at p < 0.05**

Table (2): Comparison between serum FSH level in both groups before and six months after laparoscopic ovarian drilling.

Variable	Group I (ULOD) N = 55	Group II (BLOD) N = 55	P1 value
FSH (IU/L) (Before LOD)			
Range	5 – 8.4	4.2 – 9.3	
Mean ± SD	4.5 ± 2.3	4.6 ± 2.8	0.69
FSH (IU/L) (After LOD)			
Range	4.7 – 7.9	4.3 - 8.1	
Mean ± SD	4.3 ± 2.2	4.1 ± 2.9	0.58
P2 value	0.76	0.059	

There is no significant difference in both studied groups regarding serum FSH level before and six months after LOD in both groups ($p > 0.05$)

Table (3): Comparison between serum LH level in both groups before and six months after laparoscopic ovarian drilling.

Variable	Group I (ULOD) N = 55	Group II (BLOD) N = 55	P1 value
LH (IU/L) (Before LOD)			
Range	5.7 – 12.4	5.2 – 11.3	
Mean ± SD	7.5 ± 2.8	6.8 ± 2.9	0.69
LH (IU/L) (After LOD)			
Range	4.1 – 7.9	4.9 - 6.9	
Mean ± SD	4.4 ± 2.2	4.1 ± 2.9	0.58
P2 value	< 0.001	< 0.001	

There is a significant difference in both studied groups regarding serum LH level before and six months after LOD ($p < 0.001$). However, no significant difference in serum LH levels either before or after LOD when compared both groups ($p > 0.05$).

Table (4): Comparison between serum AMH level in both groups before and six months after laparoscopic ovarian drilling.

Variables	Group I (ULOD) N = 55	Group II (BLOD) N = 55	P1 value
AMH (ng/ml) (Before drilling)			
Range	3.7 – 14.1	4.3 – 13.8	
Mean ± SD	8.3 ± 2.1	9.1 ± 2.6	0.54
AMH (ng/ml) (After LOD)			
Range	3.1 – 12.3	3.6 – 10.3	
Mean ± SD	7.9 ± 2.7	6.8 ± 3.6	< 0.01
P2 value	< 0.001	< 0.001	

There is a significant difference in both studied groups regarding the serum AMH level before and six months after LOD in both groups ($p < 0.001$), also there is a significant differences when compared the two groups after six months from LOD ($p < 0.01$).

Table (5): Comparison of antral follicular count among the both groups before and six months after laparoscopic ovarian drilling.

Variables	Group I (ULOD) N = 55	Group II (BLOD) N = 55	P1 value
AFC (Before LOD)			
Mean ± SD	12.8 ± 5.2	13.3 ± 4.6	0.69
AFC (After LOD)			
Mean ± SD	11.9 ± 3.7	10.8 ± 3.6	< 0.01
P2 value	< 0.01	< 0.001	

Table (6): Detection of ovulation by transvaginal ultrasound three and six months after laparoscopic ovarian drilling in both groups.

Variables	Group I (ULOD) N = 55	Group II (BLOD) N = 55	P1 value
TVS (3 months after LOD)			
Non- ovulating (%)	35 (63.6%)	33 (60 %)	
Ovulating (%)	20 (36.4%)	22 (40 %)	0.42
TVS (6 months after LOD)			
Non-ovulating (%)	19 (34.5 %)	18 (32.7 %)	0.34
Ovulating (%)	36 (65.5 %)	37 (67.3 %)	0.58
P2 value	< 0.001	< 0.001	

There is statistically significant difference in ovulation rate before and three and six months of LOD in both groups ($p<0.001$). However, no significant difference in pregnancy rate when compared three and six month s of LOD of both groups ($p > 0.05$).

Table (7): Comparison between pregnancy rate three and six months after laparoscopic ovarian drilling in both groups.

Variables	Group I (ULOD) N = 55	Group II (BLOD) N = 55	P1 value
Pregnancy rate			
(3 months after drilling)			
Negative pregnancy test (%)	43 (78.2 %)	42 (76.4 %)	
Positive pregnancy test (%)	12 (21.8%)	13 (23.6 %)	0.59
(6 months after drilling)			
Negative pregnancy test (%)	30 (54.5 %)	28 (50.9 %)	
Positive pregnancy test (%)	25 (45.5 %)	27 (49.1 %)	0.23
P2 value	< 0.01	< 0.01	

There is statistically significant difference in pregnancy rate before and three and six months of LOD in both groups ($p<0.01$). However, no significant difference in pregnancy rate when compared three and six month s of LOD of both groups ($p > 0.05$).

Discussion

Polycystic ovarian syndrome (PCOA) is one of the most common endocrine disorders among females of reproductive age. It is the leading cause of infertility due to anovulation. Women who are resistant to clomiphene citrate can be treated with gonadotrophins. However, these are high- priced option and require intensive monitoring which can be demanding both for the patient and the clinicians.

Ovarian hyper- stimulation, multiple pregnancy, and high miscarriage rate remains the significant risk (Laul et al., 2018). Laparoscopic ovarian drilling (LOD) and gonadotrophins are recommended to induce ovulation in those women. The main shortcoming s of LOD are the risk of post- operative adhesions and the concern about a negative impact of the procedure on the ovarian reserve secondary to excessive ovarian damage. (Abu Hashim et. Al., 2018). One study (Amer et al., 2009), suggested that LOD could be recommended as a first line if laparoscopy is indicated for other reasons in these women and as an adjunct to CC treatment.

Benefits of LOD include minimal morbidity associated with a laparoscopic procedure, the eliminated need for cycle monitoring, the low risk of multiple pregnancies (Farquhar et al., 2005). Furthermore, some CC- resistant women respond once again to CC after laparoscopic electrocautery (Bayram et al., 2004).

The surgical approach is not associated with ovarian hyperstimulation and can lead to consecutive ovulation without need for further treatment. However, tubo- ovarian adhesions and theoretical risk of premature ovarian failure (POF) following LOD are of concern. Therefore, the role treating only one ovary in reducing further tubo-ovarian adhesions need further assessment (Roy et al., 2009).

In the present study, all of the patients in the two groups had menstrual irregularities that have been improved after drilling with high significant difference between both groups before and after LOD (p value < 0.001), but no significant difference between both groups (BLOD versus ULOD with p value = 0.65).

In group I; 19 patients (34.5%) had amenorrhea and 36 patients (65.5%) had oligohypomenorrhea before drilling, after drilling; 6 patients (10.9%), have amenorrhea and 12 patients (21.8%) have oligohypomenorrhea and 37 patients (67.3 %) have regular menstruation.
In **group II**; 20 patients (36.4%) had amenorrhea and 35 patients (63.6%) had oligohypomenorrhea before drilling, after drilling; 5 patients (9.1%), have amenorrhea and 12 patients (21.8%) have oligo-hypomenorrhea and 38 patients (69.1%) have regular menstruation. Moreover, most common sin in our patients was acne which was seen in (50.9% in **group I**) versus (49.1% in **group II**) with no significant difference between both groups (p = 0.71). However, the acne improved in both groups after laparoscopic ovarian drilling with highly significant difference before and after the laparoscopic ovarian drilling in both groups (18.2% in group I versus 16.4% in group II; p < 0.001).

This is in agreement with other studies demonstrated that a large series of patients diagnosed with PCOS (65%-100%) have clinically evident menstrual dysfunction that had regain their regular menstruation (65%) six months after LOD (Carmina et al., 2006). This study was conducted 110 patients underwent laparoscopic ovarian drilling.

They were divided into two main groups (group I included 55 patients with unilateral ovarian drilling, and group II included 55 patients, with bilateral ovarian drilling). The two groups were matched as regard age, height, BMI, duration and type of infertility. In consistent with our results Rupa et al., (2018) enrolled sixty women between 30 and 40 years old presented with a diagnosis of anovulatory infertility due to polycystic ovarian syndrome and found that there was no enrolled significant difference in all groups in the mean age or body mass index of women participated in the study. The mean age at enrollment was 33.6 ± 4.1, and 32.4 ± 5.3 years for groups I, and II respectively (p < 0.47).

The body mass index was 27.5 ± 2.4 for group I, and 28.7 ± 2.1 for group II (p < 0.23) (Kandil and Selim, 2005). Another study by Laul et al., (2018) found that the average age of patients in both the groups was found to be 27 years. The duration of marriage in both groups was same with a mean duration of infertility of 4 years. Majority of the patients had only elementary education. Irregular menstrual cycle represents 65% of the patients in group I and 55% of the patients in group II, and oligomenorrhea represents 35% in group I and 45% in group II. Both groups were comparable. 50% of patients in group I and 65% in group II had their BMI > 30 (Laul et al., 2018).

In the current study we found that the post-operative three and six months, number of antral follicles were higher in group I (ULOD) than group II (BLOD) with significant differrences between both groups (p < 0.01). In consistent with our results Abu Hashim et al., (2018), found that a significantly higher AFC at 6 months follow-up period was reported with ULOD as compared to BLOD.

This finding may denote the insufficient follicle destruction in the dose-adjusted ULOD, therapy explaining the reported lower ovulation and pregnancy rates at 6 months follow- up in this trial (Rezk et al., 2016). Kandil and Selim, (2005), results are in accordance with ours as they found that a highly significant decrease in number of antral follicles (16.5 ± 1.3 versus 14.0 ± 2.1; p < 0.007) were noted after bilateral ovarian drilling but not after unilateral ovarian drilling. In the current study we found that the pre-operative total ovarian volume was insignificant between two groups (p < 0.001) but as regard post- operative, group I shows higher total ovarian volume with significant differences between two groups (p < 0.001).

Kandil and Selim, (2005) observed that the mean post-treatment summed ovarian volume was less than the mean pre-treatment volume in the three groups and this was always associated with a decrease in the number of antral follicles, and this in consistent with our results. In the current study we found that the post-operative three, and six months level of AMH, **group I** (ULOD) shows higher level of AMH than the group II (BLOD) with significant differences between two groups ($p < 0.01$). A plausible explanation for the reduction in serum AMH after BLOD could be the effect of the thermal damage decreasing its production from the granulosa cells of primary, primordial, and small antral follicles. However, does this reflect a real decline in ovarian reserve or just a normalization of AMH overproduction of ovaries of PCOS remain uncertain (Abu Hashim et al., 2018).

On the other hand meta-analysis by Abu Hashim et al., (2018) revealed no significant difference in serum AMH concentration six months after ULOD or BLOD.

This result should be interpreted with caution due to the associated heterogeneity. Notably, a high significant difference was found in one RCT between the dose- adjusted ULOD and BLOD groups with regard to the AMH level at three and six months follow- up period with lower levels achieved in the BLOD group. Nasr, (2013) found that after unilateral LOD, serum AMH levels showed a significant reduction, compared to pre- operative values and controls (6.24 ± 1.13 ng/ml; $p < o.05$). Similarly, BLOD resulted in a significant reduction in serum AMH levels, compared to pre- operative values and control (5.98 ± 1.21ng/ml; $p < 0.5$).

However, there was no statistically significant difference in serum AMH levels six months after unilateral versus bilateral laparoscopic ovarian drilling, and this not like our results, this may be due to different number of study population. In the current study we found that there were no significant differences between two groups as regard pregnancy rate. In consistent with our results in a Meta-analysis by Abu Hashim et al., (2018), demonstrated no evidence of a significant difference in rates of ovulation, pregnancy rate, live birth, or miscarriage when ULOD was compared with BLOD. Thereby, a suggested recommendation to apply a ULOD rather than a BLOD is generally in agreement with these data (Abu Hashim et al., 2018). Another agreement with our result by Laul et al., (2018) found that there was no statistically significant difference after unilateral and bilateral ovarian drilling in overall clinical response, ovulation rate, change in biochemical parameters, pregnancy rate and miscarriage rate. Youssef and Atallah, (2007) evaluated 87 patients with ovulation failure as a result of PCOS who were randomly allocated to unilateral ovarian drilling (N = 43) and bilateral ovarian drilling (N = 44). They found that ovulation; pregnancy and miscarriage rates were similar in both groups as well as the fall in serum LH levels.

Summary

Polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory infertility and responsible for 70% of infertility due to anovulation, which characterized by presence of small follicles in the periphery of the ovary, menstrual disturbance, excess androgen secretion, weak or anovulation. Rotterdam team (2003) were put diagnostic criteria for diagnosis of polycystic ovarian syndrome include two of the three of the followings; oligo or anovulation, presence of the small follicles in the periphery of the ovary and clinical and biological clinical signs of hyperandrogenism. The line of treatment is usually clomiphene citrate and it induces ovulation in approximately 80% of patients although the pregnancy rate is only about 34% - 40%.

If patients fail to respond in terms of ovulation to a dose of 150 mg/day, they are considered as clomiphene resistant. Laparoscopic ovarian drilling has been widely established as an elective second line method of ovulation induction in CC-resistant PCOS patients with high ovulation (70%-80%) and pregnancy rate (60%-80%). Advantages of LOD over gonadotropin stimulation include less complication rate, less time need for cycle monitoring and the low risk of multiple pregnancies.

The surgical approach is not associated with ovarian hyperstimulation and can lead to consecutive ovulation without the need for further treatment. The aim of this study was to compare unilateral versus bilateral ovarian

drilling in clomiphene citrate resistant polycystic ovarian syndrome regarding ovulation and pregnancy rate, ovarian reserve, degree of improvement in hirsuitism and reproductive hormonal profiles after 3 and 6 months after surgery in El-Minia Governate. In this study 120 PCOS patients according to Rotterdam (2003) criteria that resistant to clomiphene citrate, were recruited from outpatient Infertility Clinic of Maternity Hospital of Minia University from July, 2019 to April, 2020.

Complete history was taken as well as physical examination, trans-vaginal ultrasound and hormonal profile (serum FSH, LH, testosterone, progesterone, prolactin, and AMH) were done for all patients before drilling and after six months follow- up. Patients were randomly allocated into two **groups: 1. Group I:** Included 55 patients underwent unilateral laparoscopic ovarian drilling with fixed thermal dose. II. **Group II:** Included 55 patients underwent bilateral laparoscopic ovarian drilling with fixed thermal dose. There was no statistically significant difference between the two groups as regard age, BMI, duration of infertility, menstrual pattern, hirsutism and hormonal profile. In this study, all of the patients in the two groups had menstrual irregularities that have been improved after drilling with high significant difference between before and after drilling in two groups ($p < 0.001$), but no significant difference between the two groups after drilling. Regarding hirsutism, there was significant decrease in the two groups after 6 months of LOD ($p < 0.034$ in ULOD vs $p < 0.026$ in BLOD) respectively but no significant differrence in between the both groups. The mean serum FSH level in the two groups before and after LOD (ULOD; 4.5 ± 2.3 vs 4.3 ± 2.2 with $p > 0.5$; BLOD; 4.6 ± 2.8 vs 4.1 ± 2.9 with $p < 0.001$) respectively, with no significant differrence between both groups $p > 0.5$. The mean serum of LH level in the two groups before LOD drilling was (ULOD; 7.5 ± 2.8 vs 4.4 ± 2.2 with $p < 0.001$; BLOD; 6.8 ± 2 vs 4.1 ± 2.9 with $p < 0.001$) respectively with no significant difference between both groups ($p > 0.5$).

The mean serum of total testosterone level in the two groups before LOD drilling was (ULOD; 2.7 ± 1.1 vs 1.3 ± 0.7 with $p < 0.001$; BLOD; 2.3 ± 0.9 vs 1.1 ± 0.6 with $p < 0.001$) respectively with no significant difference between both groups ($p > 0.5$). The mean serum prolactin level in the two groups before LOD drilling was (ULOD; 4.5 ± 2.3 vs 4.3 ± 2.1 with $p > 0.5$; BLOD; 4.8 ± 2.8 vs 4.1 ± 2.6 with $p > 0.5$) respectively with also no significant difference between both groups ($p > 0.5$). As regard the mean serum of progesterone level in the two groups before LOD drilling was (ULOD; 2.0 ± 0.8 vs 7.9 ± 3.7 with $p < 0.001$; BLOD; 2.3 ± 0.6 vs 8.6 ± 4.6 with $p < 0.001$) respectively with no significant difference between both groups ($p>0.5$). The ovulation rate after three and six months of ULOD diagnosed by TVS was (36.4% vs 67.3%; $p<0.001$) respectively; while after three and six months of BLOD diagnosed by TVS was (40% vs 65,5% ; $p < 0.001$) respectively, but with no significant difference in between the both groups.

The cumulative pregnancy rate after six months follow-up was in group I (2 – 5 months), and in group II (2 – 6 months) with ($p = 97$). There was no statistically significant difference between the two groups as regard pregnancy rate and time needed to achieve pregnancy ($p > 0.5$). Regarding ovarian reserve markers, the mean serum level of AMH in the group I before and after ULOD was (8.3 ± 2.1 vs 7.9 ± 2.7; $p < 0.01$) and in group II before and after BLOD was s (9.3 ± 2.6 vs 6.6 ± 3.6; $p < 0.001$) with significant difference between both groups in favor of ULOD (7.9 ± 2.7 vs 6.6 ± 3.6; $p < 0.01$). As regard the mean AFC of in the two groups before LOD drilling was (ULOD; 12.8 ± 5.2 vs 11.9 ± 3.7 with $p < 0.01$; BLOD; 13.3 ± 4.6 vs 10.8 ± 3.6 with $p < 0.001$) respectively with statistical significant difference between both groups after LOD in favor of ULOD (11.9 ± 3.7 in ULOD vs 10.8 ± 3.6 ; $p < 0.01$).

Conclusion and Recommendations

1. In conclusion, laparoscopic ovarian drilling is an alternative modality of treatment in clomiphene citrate resistant polycystic ovarian syndrome.
2. Unilateral laparoscopic ovarian drilling had similar efficacy as bilateral laparoscopic ovarian drilling in terms of restoration of normal menstrual cycles, ovulation and pregnancy rates with improving both ovarian reserve and AFC.

3. Unilateral laparoscopic ovarian drilling is effective alternative minimally invasive procedure for patients with resistant PCOD.
4. Further research, including adequately powered and blinded randomized controlled trials (RCTs) is needed to evaluate the long –term effects of the fixed- dose ULOD, especially ovarian reserve and AFC.
5. Larger RCTs are awaited to investigate whether the dose adjusted or fixed-dose ULOD should be used. Certainly, it would add important data of evidence.

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