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ORIGINAL ARTICLE

Clomiphene resistant polycystic ovarian syndrome: Analysis of outcomes following laparoscopic ovarian drilling in infertile women in Ilorin, North-central, Nigeria

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ABSTRACT

Background: Laparoscopic ovarian drilling (LOD) is one-off treatment modality for clomiphene citrate (CC)-resistant polycystic ovarian syndrome (PCOS) avoiding the need of medical therapy and its attendant complications. **Aims and Objectives:** This study aimed at determining the efficacy of LOD in women with anovulatory infertility secondary to CC-resistant PCOS and factors influencing reproductive outcomes. **Materials and Methods:** A cross-sectional study of infertile women who underwent LOD on account of CC-resistant PCOS between January 2012 and December 2015 at a tertiary institution. **Results:** Patients aged 24–38 years (29.7 ± 3.6 years) and their body mass index (BMI) ranges from 20 to 35 (26.3 ± 4.3). The majority (90.5%) were nulliparous. Most (61.3%) had primary infertility. Their duration of infertility ranges from 1 to 13 years (4.3 ± 2.7) and ovarian volume ranges from 10 to 24 cm^3 (mean, right ovary = 15.2 ± 3.2; left ovary = 16.3 ± 3.2). The number of drills per ovary ranged from 4 to 14 (mean, right ovary = 7.4 ± 2.1; left ovary = 7.3 ± 2.1) and the luteinizing hormone/follicle stimulating hormone (LH)/FSH ratio ranges from 2 to 6 (3.2 ± 1.4). All achieved spontaneous resumption of menses and ovulation with mean durations of 4.0 ± 1.8 days and 5.3 ± 3.2 weeks, respectively. Eighty-three (60.6%) clinical pregnancies were recorded, of which 68 (49.6%) resulted to live births (61 singletons and 7 twin births) and 14 (10.2%) early first trimester miscarriages. The mean time interval from LOD to pregnancy was 4.4 ± 1.1 months. There was a significant association between BMI, duration of infertility, FSH/LH ratio, and pregnancy outcomes ($P < 0.05$). **Conclusion:** LOD is the most preferred treatment modality for CC-resistant PCOS as it resulted in higher pregnancy rate.

Key words: Clomiphene citrate-resistant, Ilorin, Nigeria, outcomes

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of reproductive age.[1] It is associated with chronic anovulation and infertility. The diagnosis is made by clinical and ancillary investigations revealing the presence of irregular menstrual cycles, an ovulation, elevated total, and free testosterone levels (hyperandrgenemia), and the presence of polycystic ovaries (ovarian morphology as the presence of 12 or more follicles measuring 2–9 mm in diameter and an increased ovarian volume >10 cm^3).[2]

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In most cases, ovulation can be induced with clomiphene citrate (CC), a selective estrogen receptor modulator; however, 25% of patients fail to ovulate/conceive after 3–6 cycles of treatment with CC (CC-resistant/failure) and require alternative treatments.[3] The reason may be a high intraovarian androgen environment affecting the oocyte quality as well as ovulation, tenacious cervical mucus and unfavorable endometrium.[4] Other treatment modalities for clomiphene resistant PCOS included gonadotrophins and/or metformin as well as surgical interventions.[2]

Surgical wedge resection was the first established treatment offered to infertile women with anovulatory PCOS but was largely abandoned due to a significant risk of postoperative pelvic adhesions which could account for low pregnancy rate.[2] Laparoscopic ovarian drilling (LOD) was introduced by Gjonnaess in 1984 as an alternative surgical method with the aim of minimizing postsurgical adhesions and improved pregnancy rate.[5] Many uncontrolled observational studies have claimed that ovarian drilling is followed, at least temporarily, by a high rate of spontaneous ovulation and conception or that subsequent medical ovulation induction becomes easier.[2] The most plausible mechanisms of action are the destruction of ovarian follicles and a part of the ovarian stroma, inducing a reduction of serum androgens and inhibin levels, which results in an increase of follicle stimulating hormone (FSH) and restore the ovulation function.[5] Laparoscopic ovarian drilling may also increase ovarian blood flow, allowing a high delivery of gonadotrophins and postsurgical local growth factors.[5]

Currently, LOD is a second-line treatment in PCOS patients, especially those with CC resistance.[1,5] The potential benefits of LOD include spontaneous mono-follicular ovulation thereby minimizing the need for intensive monitoring and eliminating the risk of ovarian hyper stimulation and lower cost.[2,5] These have made LOD an attractive option of ovulation induction for CC-resistant in resource-limited countries as the cost of gonadotrophins is beyond the reach of majority of infertile couples. Hence, the study aimed at a determining the efficacy of laparoscopic ovarian drilling (LOD) in women with anovulatory infertility secondary to CC-resistant PCOS and factors influencing reproductive outcomes.

Materials and Methods

This is a cross-sectional prospective study of infertile women with CC-resistant PCOS (diagnosed using Rotterdam criteria) who underwent LOD at the Assisted Reproductive Technology Unit of University of Ilorin Teaching Hospital, Ilorin between January 1, 2012 and December 31, 2015. Infertile women who were found to have inadequate coital exposure in the past 1 year, with the bilateral tubal blockade, grade III-IV endometriosis and whose spouse has male factor infertility were excluded from the study. All patients with abnormal hormone profiles, prolactin, hypo- and hyper-thyroidism were treated before enrolled into the study. Patients' information obtained included sociodemographic variables, intra-operative findings, and reproductive outcomes.

Informed consent was obtained from 137 eligible patients for the study. All patients were evaluated and confirmed fit for surgery. A complete blood counts, urinalysis, electrolyte, urea, and creatinine estimation were requested preoperatively. Patients also had bowel preparation with Dulcolax and enema saponis. All procedures were performed under general anesthesia. Pneumoperitoneum was created with Veress needles using the inferior crease of the umbilicus in the midline. The 10 mm infra- umbilical port was placed on the infra umbilical crease through a transverse incision and two 5 mm lateral ports were placed in the lower abdomen just above the anterior superior illac spine lateral to inferior epigastric vessels using baseball diamond concept.

The laparoscope was then introduced through the infra-umbilical port. A general inspection of the pelvis was performed looking for other infertility factors. The tubes are examined, and chromotubation for tubal patency was carried out.

A monopolar hook was introduced at right angle to the ovary avoiding injury to the hilum. Forty (40) watts of cutting current was used making 4 to 15 holes each lasting 4 s at a depth of 3–4 mm to the ovaries. A thorough suction irrigation of the ovaries and peritoneal lavage with normal saline was done after the drill to cool the ovaries and clear the pelvis of any blood clots and debris. The port wound was closed by subcuticular suturing using Vicryl 2/0.

Patients were followed up during subsequent visits and also with the aid of mobile telephone to obtain information as regards resumption of menstruation and ovulation. Ovulation was confirmed using ovulation test kit (predict®), day 12-14 follicular transvaginal ultrasound study and any pregnancy after the procedure. However, if natural conception fails after 3 months of the procedure, they were subjected to ovulation induction with an incremental dose of 50 mg of CC on days 2–6 to a maximum of 150 mg daily per cycle and timed intercourse for three consecutive cycles.

Statistical analysis

Data were collected using a pro forma designed for that purpose, and descriptive statistical analysis was performed using a commercial statistical package (SPSS/PC version 16.0, SPSS Inc., Chicago, III, USA). The value of $P < 0.05$ was considered to be statistically significant.

Results

One hundred and thirty-seven infertile women underwent successful LOD during the study period with a mean duration of follow-up time of 9.3 ± 6.5 months (range: 3–24 months). The patients aged 24–38 years with a mean age of 29.7 ± 3.6 years and their body mass index (BMI) ranges from 20 to 35 (26.3 ± 4.3). Majority (90.5%) were nulliparous. One hundred and ten (80.3%) belong to the middle social class. Most (61.3%) had primary infertility. The mean age of their husband was 35.7 ± 5.3 years (range 26–50 years). Their duration of infertility ranges from 1 to 13 years (4.3 ± 2.7) and the ovarian volume ranges from 10 to 24 cm^3 (mean, right ovary = 15.2 ± 3.2; left ovary = 16.3 ± 3.2). The number of drills per ovary ranged from 4 to 14 (mean, right ovary = 7.4 ± 2.1; left ovary = 7.3 ± 2.1) and the luteinizing hormone (LH)/FSH ratio ranges from 2 to 6 (3.2 ± 1.4). Most 65 (47.4%) CC following failure of achieving natural conception after 3 months of LOD [Table 1].

All achieved spontaneous resumption of menses and ovulation following ovarian drilling with mean durations of 4.0 ± 1.8 days and 5.3 ± 3.2 weeks, respectively. Eighty-three (60.6%) clinical pregnancies were recorded, of which 68 (49.6%) resulted to live birth (61 singletons and 7 twin births) and 14 (10.2%) early first trimester miscarriages. The mean time interval from LOD to pregnancy was 4.4 ± 1.1 months [Table 2].

There was a significant association between BMI, duration of infertility, FSH/LH ratio and pregnancy outcomes ($P < 0.05$). However, patients' age, parity, husband's age, social class, types of infertility, ovarian volume, the number of drills per ovary did not significantly affect the outcome [Table 3].

Discussion

The LOD procedure has been widely used to induce ovulation in PCOS women after failure of CC treatment and the spontaneous ovulation and pregnancy rates achieved in the current study was comparable to those reported in the literature.[4-10] The study analyzed the

Table 1: Sociodemographic characteristics of patients (*n*=137)

Variable	Frequency (%)
Age wife (years)	
24-29	65 (47.4)
30-35	70 (51.1)
>35	2 (1.5)
Mean±age	29.7±3.6
Range	24-38
Parity	
0	124 (90.5)
1	13 (9.5)
Mean±age	0.1±0.3
Range	0-1
Age husband (years)	
<30	9 (6.6)
30-34	55 (40.1)
35-39	48 (35.0)
40-44	12 (8.8)
≥45	13 (9.5)
Mean±SD	35.7±5.3
Range	26-50
Social class	
Low	27 (19.7)
Middle	110 (80.3)
Type of infertility	
Primary	84 (61.3)
Secondary	53 (38.7)
Duration of infertility (months)	
1-5	99 (72.3)
6-10	35 (25.5)
>10	3 (2.2)
Mean±SD	4.3±2.7
Range	1-13
BMI (kg/m^2)	
Normal (19-24)	45 (32.8)
Overweight (25-29)	62 (45.3)
Obese class 1 (30-34)	23 (16.8)
Obese class 2 (35-39)	7 (5.1)
Mean±SD	26.3±4.3
Range	20-35
LH/FSH	
2	69 (50.4)
3	15 (10.9)
4	24 (17.5)
5	20 (14.6)
6	9 (6.6)
Mean±SD	3.2±1.4
Range	2-6
Number of drills (right)	
4-6	51 (37.2)
7-9	64 (46.7)
10-12	22 (16.1)
Mean±SD	7.4±2.1
Range	4-12

Contd...

Table 1: Contd...

Variable	Frequency (%)
Number of drills (left)	
4-6	57 (41.6)
7-9	65 (47.4)
10-12	13 (9.5)
13-15	2 (1.5)
Mean±SD	7.3±2.1
Range	4-14
Ovarian volume (right)	
10-14	62 (45.3)
15-19	65 (47.4)
20-25	10 (7.3)
Mean±SD	15.2±3.2
Range	10-24
Ovarian volume (left)	
10-14	30 (21.9)
15-19	90 (65.7)
20-25	17 (12.4)
Mean±SD	16.3±3.2
Range	10-24

SD=Standard deviation, BMI=Body mass index, LH=Luteinizing hormone, FSH=Follicle-stimulating hormone

Table 2: Outcomes following laparoscopic ovarian drilling (*n*=137)

Variable	Frequency (%)
Resumption of menses (days)	
1-3	57 (41.6)
4-6	76 (55.5)
>7-9	4 (2.9)
Mean±SD	4.0±1.8
Range	1-9
Clinical pregnancy	
Yes	83 (60.6)
No	54 (39.4)
Time to conception after drilling (months)	
Nil	54 (39.4)
1-3	14 (10.2)
4-6	69 (50.4)
Mean±SD (*n*=83)	4.4±1.1
Range	
Miscarriage	
Yes	14 (10.2)
No	123 (89.8)
Multiple pregnancy	
Yes	7 (5.1)
No	130 (94.9)
Live birth	
Yes	68 (49.6)
No	69 (50.4)

SD=Standard deviation

efficacy of LOD in women with anovulatory Infertility due to CC-resistant PCOS as well as factors influencing the reproductive outcome.

All the patients that had LOD in the study resumed normal menses and ovulation with the mean duration of 4.0 ± 1.8 days and 5.3 ± 3.2 weeks, respectively. This is higher than previous studies that recorded 67.3% and 58.8%, respectively[6] and also 73.3% and 82%[7] perhaps the difference may be attributed to the fact that in the current study the number of drills, i.e., thermal energy on the ovaries was adjusted based on the size of the ovary. Adjusting the dose of thermal energy depending on the ovarian volume was found to give better outcomes.[4] However there was no significant difference between ovarian volume, the number of drills per ovary and reproductive outcome.

The cumulative conception rate of the study was 60% with a live birth rate of 49.6%. A similar study recorded a pregnancy rate of 61%.[8] This is higher than 46.9% conception rate recorded in another study[6] but lower than 84.5% pregnancy rate recorded in a similar study.[9] It was reported that the beneficial effect of LOD is of limited duration. In most studies, the effect last up to 1 year,[8] but pregnancies have been known to occur after 12 months in some studies.[8] However in the current study, most of the patients conceived in the first 4–6 month after LOD. The mean interval of conception and LOD was 4.4 ± 1.1 month. This result is comparable to 3.95 ± 4.1 recorded in another study.[8]

In this study, 10.2% of pregnancies recorded ended as spontaneous abortions within the first trimester and 7 twin pregnancies were recorded. In a previous study in India, 6% of pregnancies ended in spontaneous abortions.[10] However, in most previous studies multiple pregnancy was not recorded following LOD[6,7,10] probably it was recorded in this study because the study was conducted in an area where there is high rate of twining[11,12] and could have been as a result of CC[13] that was administered to some patients 3 months after LOD because multiple pregnancy rarely occurred in infertile women who conceive following LOD.[7]

All our patients had anovulatory infertility ranging from 1 to more than 10 years duration and had been unsuccessfully treated with CC to a maximum of 150 mg/day before LOD. Patients with CC-resistant PCOS have the choice of gonadotropins therapy or LOD. However, LOD is more cost effective than gonadotropins as single treatment result in several mono ovulatory cycle thus allowing multiple attempts at conception, whereas one course of gonadotropin therapy yields a single ovulatory cycle with the inherent need for intensive monitoring.[1] The gonadotropins are also very costly and may not be readily affordable by most patients', they are also temperature regulated and

Table 3: Relationships between the sociodemographic characteristics of patients and their pregnancy outcomes

Variable	Pregnancy outcome		χ^2	*P*	OR	95% CI
	Yes (*n*=83), *n* (%)	No (*n*=54), *n* (%)				
Age wife (years)						
24-29	37 (56.9)	28 (38.5)	0.860	0.650	1.00	
30-35	45 (64.3)	25 (35.7)			1.36	0.64-2.89
>35	1 (50.0)	1 (50.0)			0.76	0.02-29.20
Mean±age	29.8±3.7	29.7±3.4	0.138 (*t*)	0.891		
Parity						
0	72 (58.1)	52 (41.9)	2.451 (Yates)	0.117	1.00	0.78-27.16
1	11 (84.6)	2 (15.4)			3.97	
Mean±age	0.1±0.3	0.0±0.2	1.874 (*t*)	0.063		
Age husband (years)						
<30	8 (88.9)	1 (11.1)	5.791	0.215	1.00	
30-34	33 (60.0)	22 (40.0)			0.19	0.01-1.68
35-39	30 (62.5)	18 (37.5)			0.21	0.01-1.92
40-44	7 (58.3)	5 (41.7)			0.17	0.01-2.39
≥45	5 (38.5)	8 (61.5)			0.08	0.00-1.03
Mean±age	35.2±5.0	36.4±5.6	1.211 (*t*)	0.228		
Social class						
Low	17 (63.0)	10 (37.0)	0.080	0.778	1.00	0.34-2.28
Middle	66 (60.0)	44 (40.0)			0.88	
Type of infertility						
Primary	46 (54.8)	38 (45.2)	3.082	0.079	1.00	0.87-4.22
Secondary	37 (69.8)	16 (30.2)			1.91	
Duration of infertility (months)						
1-5	59 (59.6)	40 (40.4)	5.587 (LR)	0.037	1.00	
6-10	24 (68.6)	11 (31.4)			1.48	0.61-3.64
>10	0	3 (100.0)			0.00	0.00-2.90
Mean±age	4.0±2.4	4.7±3.1	1.442 (*t*)	0.152		
BMI (kg/m^2)						
Normal (19-24)	38 (84.4)	7 (15.6)	72.001 (LR)	<0.001	1.00	
Overweight (25-29)	45 (72.6)	17 (27.4)			0.49	0.16-1.42
Obese class 1 (30-34)	0	23 (100.0)			0.00	0.00-0.05
Obese class 2 (35-39)	0	7 (100.0)			0.00	0.00-0.19
Mean±age	25.0±3.5	29.6±3.8	7.118	<0.001		
LH/FSH						
2	69 (100.0)	0	159.302 (LR)	<0.001	1.00	
3	0	15 (100.0)			0.00	0.00-0.01
4	0	24 (100.0)			0.00	0.00-0.01
5	14 (70.0)	6 (30.0)			0.00	0.00-0.02
6	0	9 (100.0)			0.00	0.00-0.01
Mean±age	2.5±1.1	4.2±1.0	8.718 (*t*)	<0.001		
Number of drills (right)						
4-6	30 (58.8)	21 (41.2)	0.726	0.695	1.00	
7-9	41 (64.1)	23 (35.9)			1.25	0.55-2.85
10-12	12 (54.4)	10 (45.5)			0.84	0.27-2.59
Mean±age	7.3±1.9	7.5±2.4	0.484 (*t*)	0.629		
Number of drills (left)						
4-6	36 (63.2)	21 (36.6)	3.898 (LR)	0.355	1.00	
7-9	39 (60.0)	26 (40.0)			0.88	0.39-1.94
10-12	8 (61.5)	5 (38.5)			0.93	0.23-3.83
13-15	0	2 (100.0)			0.00	0.00-0.61
Mean±age	7.2±2.0	7.3±2.1	0.357 (*t*)	0.721		

Contd...

Table 3: Contd...

Variable	Pregnancy outcome		χ^2	*P*	OR	95% CI
	Yes (*n*=83), *n* (%)	No (*n*=54), *n* (%)				
Ovarian volume (right)						
10-14	41 (66.1)	21 (33.9)	2.405	0.300	1.00	
15-19	35 (53.8)	30 (46.2)			0.60	0.27-1.30
20-25	7 (70.0)	3 (30.0)			1.20	0.24-1.65
Mean±age	15.1±3.2	15.2±3.1	0.162	0.872		
Ovarian volume (left)						
10-14	16 (53.3)	14 (46.7)	4.736 (*t*)	0.094	1.00	
15-19	60 (66.7)	30 (33.3)			1.25	0.70-4.40
20-25	7 (41.2)	10 (58.8)			0.612	0.15-2.39
Mean±age	16.2±2.8	16.3±3.7	0.144 (*t*)	0.886		

LR=Likelihood ratio, *t*=Independent *t*-test, Yates=Yates' continuity correction, OR=Odds ratio, CI=Confidence interval, LH=Luteinizing hormone, FSH=Follicle-stimulating hormone, BMI=Body mass index

issues of potency is at risk because some pharmaceutical stores in our environment cannot stock it properly because of infrequent electricity supply.

In this study, the evaluation of influence on reproductive outcome of LOD was also done. Three main factors were shown to have significant impact on efficacy of LOD, i.e., the duration of infertility, BMI and LH/FSH ratio. LOD had a successful pregnancy outcome in patients with normal BMI (84.4%) and in those whose BMI is <30 kg/m^2 (72.6%) but not successful in those with BMI of >30 kg/m^2, this finding is similar to that observed in previous studies;[7-10] hence, alternative methods of treatment may need to be employed for this group of patients such as weight reduction, metformin treatment, gonadotropin therapy or IVF to achieve conception.[10]

The duration of infertility of 5 years and below had the strongest impact as a predictor of success. This result is in agreement with previous study.[6] A possible explanation for the role of the duration of infertility may be the emergence of other subfertility factors as duration of infertility increases.[6]

In this study, all patients who had LH/FSH ratio of 2 got pregnant following LOD. In few studies it was observed that LOD responders who had lower pretreatment LH level or a lower LH/FSH ratio were more likely to continue to benefit from treatment for a longer period compared with those who had higher pretreatment LH or LH/FSH ratio are more likely to experience a recurrence of their anovulatory status after several month of treatment.[10] In a similar study LOD responder with pretreatment serum LH concentration of 12 IU/L achieved higher pregnancy rate.[6] LOD reduces serum concentration of LH or LH/FSH ratio to follow up period, as LH levels fall spontaneous ovulation and conception rate increases.[7]

Conclusion

LOD is an effective treatment modality in CC-resistant PCOS. It results in high rate of regularization of menses, ovulation, and conception rate without major complications. It is more effective in infertility duration of 5 years and below, pretreatment LH/FHS ratio of 2 and in those patients with normal BMI and BMI <30 kg/m^2. LOD is therefore recommended in our environment for the treatment of CC-resistant PCOS.

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Conflicts of interest
There are no conflicts of interest.

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