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Reproductive outcome in infertile women with clomiphene citrate resistant polycystic ovarian syndrome treated by laparoscopic ovarian drilling

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Running Title: Laparposcopy ovarian drilling in CC-resistant PCOS

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ABSTRACT

Background. In developed countries Laparoscopic ovarian drilling (LOD) has been widely used to induce ovulation in women with polycystic ovarian syndrome (PCOS) who are resistant to clomiphene citrate. But in Nigeria reports of application of this modality of treatment in the management of PCOS patients are very scarce. This is a preliminary report of our experience with LOD in the management of anovulatory infertility due to PCOS.

Objective. To describe the effect of laparoscopic ovarian drilling with diathermy on the reproductive outcome of infertile women with polycystic ovarian syndrome who were resistant to clomiphene citrate (CC).

Subjects and method. This prospective study included 9 women with anovulatory infertility due to PCOS who underwent LOD between January 2007 and July 2008 at Life specialist hospital limited Nnewi, Anambra state, South East Nigeria. Diagnosis of PCOS was based on the Rotterdam's criteria. All the patients had been treated with clomiphene citrate for ovulation induction up to a maximum daily dose of 200mg for at least six months without success.

Result. Ovarian drilling was successfully employed without any surgical complications in all the women with a mean duration of follow-up time of 9.33± 6.46 months (Range: 3-24 months). The patients aged 18-35 years with a mean age of 26.33 ± 5.27 years. Eight out of the 9 patients (88.9%) were nulliparous and belong to social class 1 and II. The number of drills per ovary ranged from 4 to 15 (mean, right ovary=8.55±3.24; left ovary=9.33±3.35). In the follow-up period, all the 9 patients (100%) resumed menstruation and all of them achieved ovulation (ovulation rate= 100%) The mean time to resumption of menstruation and ovulation were 4.25$\pm$3.28 weeks and 5.33$\pm$3.22 weeks respectively. Four pregnancies were recorded from 3 patients giving a cumulative pregnancy rate of 44.5%. One of the patients had successfully delivered, giving a live birth rate of 11.1%. The mean time interval from LOD to pregnancy was 9.33$\pm$6.11 weeks. All the pregnancies were achieved within 4 months of the procedure. The time to ovulation was not significantly affected by age of the woman (x^2=33; p=0.32), duration of infertility (x^2=1.29, p=0.26) and the number of drills per ovary (x^2=26.25; p=0.39).

Conclusion. LOD is very effective in treating anovulation in CC-resistant women with PCOS. It is safe and a onetime treatment and should be made available to our women on a wide scale and at reduced cost.

Key words: Laparoscopic Ovarian Drilling, CC-resistant women, PCOS, Pregnancy.

INTRODUCTION

The surgical treatment of polycystic ovarian syndrome (PCOS) to restore ovulation and regular menstruation was first reported by Stein and Levanthal in 1935[1]. They described seven women with irregular periods (oligomenorrhea), increased body hairs (hirsutism) and obesity that underwent bilateral ovarian wedge resection (BOWR) for histological diagnosis. Surprisingly, all the women resume regular menstruation and two became pregnant subsequently. They followed up this success by reporting in 1964 on a series of 108 women who were treated by BOWR with 95% and 85% success rates in resuming cyclic menstruation and achieving pregnancy respectively[2].

However, due to the pelvic and peri-tubular adhesions that attended BOWR[3,4], clomiphene citrate took over as the treatment modality of choice. But after two decades of preference for medical treatment, the surgical treatment was revisited when Gjonnaess published his account of successful laparoscopic approach to ovulation induction in PCOS patients[5]. Ever since then, laparoscopic ovarian drilling (LOD) has become the major treatment modality for clomiphene resistant PCOS patients with many authors reporting up to 80% and 60% ovulation and pregnancy rates respectively[6-13.] In previous studies quoted above, rates relating to resumption of cyclical menstruation and pregnancy were quoted while now it is ovulation and pregnancy rates. Could you do all three for uniformity and comparison?. In addition to its effect on ovulation and pregnancy, LOD also corrects endocrine abnormalities associated with PCOS including rapid and persistent reduction of serum androgen levels[14-18].

The mechanism of action of LOD is not yet determined[19]. Stein and Levanthal reasoned that the thick capsule of the polycystic ovaries prevented ovulation and postulated that BOWR decreases the mechanical crowding of the cortex by cysts thereby enabling ovulation[1]. The only alternative to LOD for the management of anovulatory infertility due to PCOS is the use of gonadotrophins. But women with PCOS treated with gonadotrophins often have an over production of follicles which may result in ovarian hyper-stimulation syndrome and multiple gestation[18-20]. Moreover, gonadotrophins are very costly and require intense monitoring. Even in patients who do not ovulate after

LOD, there is an increased sensitivity to clomiphene following the procedure[21].a studyus where

In Nigeria, reports on laparoscopic gynaecological procedures are very scarce. Even the very few reports in the literature are mostly diagnostic laparoscopies for evaluation of tubal factor infertility[28-33]. There is therefore a need to encourage operative laparoscopic procedures among the gynaecologists working in this country. In this preliminary report, we profile our clomiphene resistant PCOS patients who had LOD for ovulation induction. We also reported on the reproductive outcome during their short term follow up. The aim is to encourage this modality of treatment for our clomiphene resistant PCOS patients.

SUBJECTS AND METHOD

Setting. Life specialist hospital limited is a private health facility with interest in gynaecological laparoscopic operations. It has been a centre for diagnostic laparoscopy since 2000 and upgraded its facilities in 2006 for operative laparoscopic surgeries following further training of the lead laparoscopy surgeon (Dr. J. Ikechebelu) in laparoscopic hospital India.

Patient recruitment (Inclusion criteria). Only patients who were diagnosed with PCOS using the Rotterdam criteria (2003) were scheduled for LOD. They had been treated with clomiphene citrate up to a daily dose of 200mg for at least six menstrual cycles. Failure of ovulation after this period qualifies them for the procedure.

Method. The socio-demographic and other general information of the patients were documented at presentation. The number of drills made at surgery was noted and patients were followed up during subsequent visits and also using telephone with respect to resumption of regular menstruation. Ovulation was documented with day 12-14 follicle tracking via transvaginal ultrasound study and any pregnancy after the procedure. Data analysis was done with Epi info version 2006 using chi square and Fischer's exact tests for comparisons. P-value of less than 0.05 at a confidence interval of 95% was taken as statistical significan.

Procedure. The laparoscopies were performed in the immediate post menstrual phase of the cycle. All cases were done under general anaesthesia with intubation and positive pressure ventilation in the steep tredelenburg position. In all cases the three port approach was used - 10mm infra umbilical and two 5mm lateral ports in the lower

abdomen, lateral to the inferior epigastric vessels. We had no need to use Palmer's point (left upper quadrant laparoscopy). Very simple instruments i.e. a 5mm suction irrigation cannula and a monopolar (OM surgical, India) insulated needle electrode were used. Pneumoperitoneum was achieved with CO_2 and the intra abdominal pressure was set at 14mmHg. Immediately after inserting the scope, a general inspection of the pelvis is made in order to look for other infertility factors. The tubes are examined and dye test for tubal patency is done.

Our first step in drilling is to lift the ovaries out of the ovarian fossa. Rather than grasping the ovary at the ovarian ligament, we used the Nutan Jain's technique[34] of lifting the ovaries by an irrigation cannula inserted through an ipsi-lateral lower abdominal 5mm port. The cannula is wedged against the cervico uterine junction, giving a strong platform for drilling. A good uterine manipulator is used to manipulate the uterus. The monopolar needle is inserted from the contra-lateral 5mm port and approaches the ovary at right angles. 4-15 drills were made on each ovary depending on the size of the ovary utilizing 40 watts pure cutting current for 4 seconds. Usually we drill both ovaries avoiding the areas close to the ovarian ligament as much as possible to avoid encountering blood vessels.

Thorough suction irrigation and lavage is usually carried out to cool the ovaries and clear the pelvis of any blood, clots, char or debris. See pictures 1–6. At the end of the surgery, patient is placed on antibiotics and analgesics and discharged the next day with monthly followed up visits.

Cost. The procedure is offered to the patients at $100. This treatment is not covered by the present National Health Insurance Scheme (NHIS) of the country and prospective patients have to pay from their pockets to have the LOD performed.

RESULTS

Ovarian drilling was successfully employed without any surgical complications in all the patients and the mean duration of follow-up was 9.33 $\pm$ 6.46 months (Range: 3-24 months) The patients were aged 18-35 years and majority of them were within the age group of 20-29 years (Table 1) with a mean age of 26.33 $\pm$ 5.27 years. Eight out of

the 9 patients (88.9%) were nulliparous and belong to social class 1 and II. Majority of the patients were students (n=5, 55.6%) and had acquired tertiary education (n=8, 88.9%). The number of drills per ovary range from 4 to 15 (mean; right ovary = 8.55 ± 3.24; left ovary = 9.33 ± 3.35).

In the follow-up period, all the 9 patients (100%) resumed menstruation and all of them achieved ovulation (ovulation rate = 100%). The mean time to resumption of menstruation and ovulation were 4.25 ± 3.28 weeks and 5.33 ± 3.22 weeks respectively. Four pregnancies were recorded from 3 patients giving a cumulative pregnancy rate of 44.5%. One of the patients had successfully delivered, giving a live birth rate of 11.1%. The mean time interval from LOD to pregnancy was 9.33 ± 6.11 weeks. All the pregnancies were achieved within 4 months of the procedure. Additional treatment in form of clomiphene citrate was used in 7 of the 9 patients.

Table 2 shows that the time interval from LOD to ovulation was not significantly affected by age (x^2=0.9, p=0.4), duration of infertility (x^2=0.2, p=0.58), the number of drills per ovary (x^2=0.06; p=0.0.4) and the post operative dose of clomiphene used(x^2=1.22, p=0.4).

DISCUSSION

The bio-social characteristics of our patients show high profile women. This may be related to the fact that our hospital offers specialist services. In our area, access to specialist care is often limited to the rich leaving the less privileged to the general practioners and the public hospitals. There is no doubt that numerous poor people with infertility due to PCOS will not be able to access LOD on account of financial constraints. Infertility in sub-Saharan Africa is associated with so much psychosocial stress that there is a great need to subsidize the treatment modalities that have been found to be beneficial to enhance access to care. Besides infertility is not a priority area for many donor agencies supporting reproductive health projects in Africa. Yet almost on daily basis, African women are subjected to various forms of physical and psychological abuses on account of childlessness leading to failed marriages[35]. It is therefore suggested that both national and international agencies genuinely interested in improving the reproductive health of African women should also commit themselves to the provision of modern treatment modalities for infertility to these women. These modalities include Laparoscopic procedures and the various assisted reproductive techniques.

Our 100% ovulation rate how confident are you of this. Is transvaginal ultrasound 1005 predictive of ovulation; any supporting literature?achieved within 6 months of follow up is very encouraging and strongly supports this treatment modality for our clomiphene resistant PCOS patients and must be seen as a saving grace. There is no doubt that only few wealthy patients in our environment can afford the alternative, what is place of aromatase inhibitors? which is the use of gonadotrophins with its associated ovarian hyper-stimulation syndrome, multiple gestation and need for intensive monitoring. Our ovulation rate was more than that reported by Kato et al[6] in Japan (84.2%), Marionwoski et al[16] in Poland (77.7%) and Omu et al[30] in Benin Nigeria (82%). Postoperative use of clomiphene citrate in most of our patients may be partly responsible for this.

We recorded a cumulative pregnancy rate of 44.5% from 3 patients during the follow up period. All the 3 patients got pregnant within 4 months of the procedure.

This is a further incentive for support for LOD as a treatment modality for our CC resistant PCOS patients. Our pregnancy rate is similar to 39.3% reported by Omu et al[30] in Benin Nigeria. But it is lower than that reported by kato et al[6] in Japan (76.9%), Api et al[14] (64.4%), Cleeman et al[37] in Denmark (61%), Su Hy et al[11] in Taiwan (83.3%) and Fernandez et al[38] in France (73%). This difference in the pregnancy rates may be related to other factors involved in the aetio-pathogenesis of infertility in our environment.

The time to ovulation in this study was not significantly affected by the age of the patient, the duration of infertility, number of drills pre ovary and the postoperative dose of clomiphene used. In other studies, increased body mass index, duration of infertility more than 3 years and levels of luteinizing hormone more than 10iu/l were reported as poor predictors of success[12,39,40]. We did not assess the influence of luteinizing hormone and body mass index on the ovulation rate. However, increased number of drills especially close to the ovarian ligament has been associated with increased risk of ovarian failure and post operative adhesion. We did not encounter any ovarian failure in our series.

Conclusion. LOD is very effective in treating anovulation in clomiphene citrate resistant women with PCOS. There is the need to provide this treatment modality on a wide scale to our infertile women with PCOS at an early age when it will impact positively on their reproductive life.

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Table 1: Bio-social characteristics of patients

Characteristics	*n= 9*	*%*
Age		
15-19	1	11.1
20-24	3	33.3
25-29	2	22.2
30-34	2	22.2
≥34	1	11.1
Parity		
0	8	88.9
≥1	1	11.1
Occupation		
Student	5	55.6
Trading	3	33.3
Civil servant	1	11.1
Education		
Primary	0	0.0
Secondary	1	11.1
Tertiary	8	88.9
Social class		
1	4	44.4
2	4	44.4
3	1	11.1

Table 2. Factors affecting ovulation within 4 weeks of procedure

Factors	*No (%)*	X^2	*P-value*
Duration of infertility			
≤ 3 years	1 (11.1)		
> 3 years	5 (55.6)	0.08	0.58
Age			
≤ 30 years	1(11.1)		
> 30 years	4(44.4)	0.9	0.4
No of punctures per ovary			
≤ 10	4(44.4)		
> 10	1(11.1)	0.06	0.4
Dose of clomiphene			
100mg	2(22.2)		
200mg	1(11.1)	1.22	0.37

Can Table 1 fit into one page of being bisected within two pages?