



Comparative Study between Metformin and Laparoscopic Ovarian Drilling for Ovulation Induction, Achievement of Pregnancy and Live Birth in Asian Women with Polycystic Ovarian Syndrome: A Prospective Trial

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Abstract

Objective: To compare the efficacy of metformin and laparoscopic ovarian drilling to be used in anovulatory patients with polycystic ovarian syndrome (PCOS) for ovulation induction and pregnancy achievement. **Materials and Methods:** Setting and Design: A prospective clinical trial conducted in the outpatient department of Gynaecology and Obstetrics of BIRDEM hospital from August 2008 to August 2013. **Patient(s):** Three hundred and eight newly diagnosed patients with PCOS based on ESHRE/ASRM criteria. These patients were assigned to two groups: Group 1 (152 patients) received 500 mg of metformin three times a day; Group 2 (156 patients) received laparoscopic ovarian drilling. **Main Outcome Measure(s):** Rate of ovulation, pregnancy rate (PR), and live birth. Ovulation was monitored by serum progesterone, transvaginal sonography up to six cycles or till pregnancy occurred upto six months. **Result(s):** The ovulation rate was 68.4% in the metformin group, 59% in the laparoscopy treatment group. The pregnancy rate was (20.1% and 16.6%) and live birth rate was (18.4% and 15.4%) in metformin and laparoscopy treatment groups, respectively. The rate of spontaneous first trimester loss was three and two in metformin and laparoscopy group respectively. There were no ectopic pregnancies in metformin group and two in laparoscopy group. There was no second trimester pregnancy loss in metformin group, three in laparoscopy group. There were no multiple pregnancies in metformin group, two in lapa-

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roscopy group.

Keywords

Polycystic Ovarian Syndrome, Metformin, Laparoscopy

Subject Areas: Global Health, Gynecology & Obstetrics

1. Introduction

Infertility has been attributed to various factors, amongst which anovulation is the cause of about 40% of all female infertility. Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting 5% - 10% of reproductive age women [1]. It was originally described as a triad consisting of obesity, hirsutism and oligomenorrhoea, infertility [2]. This condition is a potential health hazard with long-term sequelae, notably type 2 diabetes, cardiovascular disease and hyperlipidemia [3]. An internationally accepted definition has been adopted in 2003 by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine, known as the ESHRE/ASRM Rotterdam consensus [4]. It required the presence of two of the following three diagnostic criteria: 1) oligomenorrhea or anovulation; 2) clinical or biochemical evidence of hyperandrogenism and 3) the presence of polycystic ovarian morphology. Women suffering from PCOS have low fecundity with anovulation [5] and to an extent, early pregnancy loss [6] and pregnancy complications [7]. Induction of ovulation would restore ovulation and pregnancy. For many years clomiphene citrate (CC) has been the standard treatment for ovulation induction for these patients. Women who fail to ovulate or get pregnant with CC usually were recommended for ovarian diathermy surgery, gonadotropin treatment or even IVF. However, these treatments are expensive and associated with side effects [8]. Because hyperinsulinemia may contribute to hyperandrogenism and infertility in women with PCOS, agents that can ameliorate insulin resistance and reduce circulating insulin level can be used [9] [10]. The most extensively studied insulin-lowering agent in the treatment of PCOS was metformin.

Metformin is a biguanide oral antihyperglycemic agent, which has been extensively used in the treatment of type 2 diabetes mellitus. It lowers blood glucose levels mainly by inhibiting hepatic glucose production and increases in the peripheral glucose uptake [11]. Several other actions may contribute, such as increased intestinal use of glucose and decreased fatty acid oxidation [10]. Therefore, metformin can reduce peripheral insulin concentrations and improve glucose tolerance and metabolism. There are also preliminary *in vitro* data indicating that metformin may directly decrease ovarian androgen production [12]. Most studies have demonstrated the efficacy of metformin in inducing ovulation [13]-[15], whereas other reports disagree with these findings [16] [17]. Although metformin can be successful for unexplained infertility, women who are suffering for polycystic ovarian syndrome tend to have a positive response to metformin's ability to help the body respond better to insulin. Metformin can help make cycles more regular and increase fertility.

Gjonnaess reported an ovulation rate of 92% and a pregnancy rate of 70% after laparoscopic ovarian electrocoagulation in patients with PCOS [18]. This was the spark that reignited interest in surgical management of the disease and heralded the era of minimally invasive surgery in the treatment of these patients. Following this report, several studies described the success and utility of this procedure, with ovulation rates ranging from 64% to 92% and pregnancy rates from 41% to 80%, [17] [19]-[24].

A meta-analysis of 13 randomized trials [25]-[27], comparing metformin with placebo, metformin plus CC, or CC alone in women with PCOS, concluded that metformin increased the ovulation rate by a factor of approximately four. The aim of the study was to compare the efficacy of metformin and laparoscopic ovarian drilling to be used in anovulatory patients with polycystic ovarian syndrome (PCOS) for ovulation induction and pregnancy achievement.

2. Materials and Methods

The male factor was normal in these two groups. All women in the study group were suffering from primary subfertility. An informed consent was taken from all the patients and the study was approved by the Scientific

Counsel and Ethical committee of the institute. The patients who were newly diagnosed as PCOS and age less than 35 years old were included in the study group. Patients were excluded from the study if they were known to be diabetic or had underlying liver, renal, or heart disease, thyroid disorders or other hormone disorders, history of menstrual regulation (MR), induced abortion or dilation and curettage (D & C), pelvic inflammatory disease (PID) and also those whose partner's sperm quality indicated male factor infertility on at least two occasions (sperm count < 10 millions/mL, motility < 30%, morphology < 30%). Tubal patency was not tested before treatment. Pregnant patients were followed up until an ultrasound could document the viability of pregnancy. Patients randomized to the metformin arm were given the tablets at the initial dose of 500 mg and increased in a stepwise fashion during the first 3 weeks to accommodate the side effects until patients were taking a total dose of 1500 mg/day. With ovulation, the dose of drugs were unaltered in the group. Ovulation was detected either with a follicle diameter >16 mm on transvaginal ultrasonography, or serum progesterone level. Serum progesterone (P) was done to assess the status of ovulation at day 0 and at day 120. If a woman ovulated, she continued taking the same dose of metformin until pregnancy was achieved. In females who became pregnant, metformin was continued for up to 12 weeks of pregnancy. In all groups urine pregnancy test was done 3 weeks after missed period. Pregnancy was confirmed by a gestational sac with fetal pole detection on ultrasonography. Laparoscopic Procedures: The patients included in this study were all operated upon by the author. Ovarian drilling was performed under general anaesthesia. The patient was put in Trendelenburg position. A subumbilical incision was made and a 10-mm trocar inserted intraperitoneally and pneumoperitoneum was created. The trocar sleeve was left in situ and a 10-mm 0 degree telescope was inserted and connected to a camera with a video monitor system. The abdominal cavity especially the pelvic area was carefully inspected. Two further 5-mm trocars were inserted through small incisions in each of the iliac fossae, one for a grasping forceps and the other for a unipolar diathermy electrode. The ovary was stabilized by grasping the ovarian ligament with a grasping forceps then 4 to 6 ovarian punctures was made to a depth of 6 mm using a unipolar electrode in both ovaries. Adequate care was taken to avoid aggressive drilling, which may lead to excessive tissue destruction, adhesion formation, and even ovarian failure. Diagnostic laparoscopy was performed in all patients. After a thorough assessment of the tubes, uterus, pelvis and liver in the upper abdomen, methylene blue hydrotubation was done to assess tubal patency.

3. Statistical Analysis

Data is expressed as mean \pm SD and evaluated statistically by using Student's paired t-test. For comparison of ovulation between Group I, Group II. Chi-square test is used & P-value is calculated. SPSS version 14 was used for analysis.

4. Results

There were no significant differences in baseline variables in the study groups (**Table 1**) with regard to age, BMI and waist-to-hip ratio among the three groups. The mean age was 28.9 years and the mean BMI and waist-to-hip ratio were 33.3 and 0.77 respectively. All the patients studied had morphological features of PCOs on TVS. The patients also had abnormal menstruation presenting as amenorrhea, which is defined as absent menstruation for more than 6 months, or oligomenorrhea, which is defined as intermenstrual intervals of more than 35 days. In this study it was noted that hirsutism was not a main feature of patients diagnosed with PCOS.

Both groups had comparable proportions of primary subfertility and also duration of infertility was not significantly different among the study populations. There was also no significant difference regarding biochemical parameters, like FSH and LH, within the study groups (**Table 2**).

Baseline serum progesterone in two groups was very low indicating anovulation in these women but following administration of metformin and laparoscopic drilling serum progesterone was increased significantly from Day 1 to Day 120 with P-value of <0.001 in each group (**Table 3**) confirming ovulation in these patients.

The ovulation rate in metformin group and laparoscopy group was 68.4% and 59% respectively. The pregnancy rate (PR) was 20.1% in metformin group compared to 16.6% in laparoscopy group. The rate of spontaneous first trimester loss was three and two in metformin and laparoscopy group respectively. There were no ectopic pregnancies in metformin group and two in laparoscopy group. There were no second trimester pregnancy loss in metformin group, three in laparoscopy group. There were no multiple pregnancies in metformin group, two in laparoscopy group. The live birth per cycle in which ovulation occurred was higher in the metformin

Table 1. Baseline characteristic of women with polycystic ovary syndrome.

Characteristics	Metformin group	Laparoscopy group
	n (152)	n (156)
Age, mean (SD)	29.6 (4.35)	29.3 (4.95)
WHR, mean (SD)	0.76 (0.45)	0.77 (0.14)
BMI, mean (SD)	32.9 (4.2)	33.0 (4.1)
Primary infertility, n (%)	112 (71.8)	136 (89.5)
Length of infertility (y), mean (SD)	2.9 (0.15)	3.3 (0.14)
Morphology feature of PCO on U/S, n (%)	152 (100)	156 (100)
Oligomenorrhea, n (%)	118 (76.9)	124 (78.9)
Amenorrhea, n (%)	34 (23.1)	32 (21.1)

Note: BMI: body mass index; WHR: waist-to-hip ratio.

Table 2. Baseline biochemical characteristics.

	Metformin group	Laparoscopy group	P value
	n (152)	n (156)	
FSH (IU/L)	4.5 (1.95)	4.9 (1.75)	NS mean (SD)
LH (IU/L)	11.3 (5.41)	12.2 (2.95)	NS mean (SD)

Note: NS: not significant.

Table 3. Serum progesterone in metformin and laparoscopy groups at Day 0 and at Day 120.

Serum progesterone (ng/ml)	Day 0	Day 120	P-value
Metformin Group	1.6 ± 0.9	11.3 ± 6.8	0.001**
Laparoscopy Group	1.5 ± 0.6	10.3 ± 4.7	0.001**

**Statistically highly significant.

group (18.4%) than (15.4%) in the laparoscopy groups, although the difference was not significant (**Table 4**).

Metformin at incremental doses was well tolerated and there were no drop outs in this study group. Three patients complained of nausea, dizziness and headache, but despite these side effects they continued through the study period. Metformin treatment also did not have any significant effect on biochemical parameters, particularly FSH, LH after 3 months of treatment and laparoscopy had the same effect as metformin (**Table 5**).

5. Discussion

One of the key aspects of achieving fertility is the process of ovulation by which an egg grows, matures and is ejected from the ovary on a regular (usually monthly) basis. Several medications like metformin, clomiphene citrate, letrozole are used by infertility specialists to enhance fertility and frequently they work by affecting ovulation. Surgical treatment in the form of wedge resection was the accepted treatment in polycystic ovarian syndrome. In the reported series the ovarian drilling resulted in ovulation in 90% of cases and conception in 70% of cases. Significant number of subsequent studies have produced similarly encouraging results. Laparoscopic ovarian drilling subsequently replaced the wedge resection as surgical treatment for women with PCO. Oral medications are often preferred as initial therapy due to their minimal expense, need for infrequent monitoring, and few side effects.

Our results demonstrated that ovulation was likely to occur after treatment with metformin and laparoscopy alone. In our study, the PR and live birth rate were slightly higher in the metformin group than laparoscopy group.

All of our patients had morphological features of PCO on ultrasound. Hsu *et al.* [28] noted a prevalence of PCO in 91% of the patients with PCOS. We tried to reduce the intra observer bias by assigning only two doctors

Table 4. Rates of ovulation, pregnancy, pregnancy loss, and live birth.

	Metformin	Laparoscopy
	n (152)	n (156)
Ovulation	104/152 (68.4%)	92/156 (59%)
Pregnancy	32/152 (20.1%)	24/156 (16.6%)
First trimester loss	3	2
Ectopic	0	2
Second trimester loss	0	3
Multiple gestation	0	2
Live birth	28/152 (18.4%)	24/156 (15.4%)

Table 5. Biochemical parameters at entry and after 3 months.

	LH (IU/L)		FSH (IU/L)	
	Initial	3 months	Initial	3 months
Metformin	11.3 (5.41)	11.7 (5.10)	4.5 (1.95)	4.3 (2.0)
Laparoscopy	12.2 (2.95)	11.2 (3.45)	4.9 (1.75)	5.0 (1.9)

to do the TVS for the diagnosis of PCO. Metformin does not have an effect on the biochemical parameters of FSH, LH. This differs from some studies showing that metformin reduces the effect of LH and causes an elevation in serum FSH [29] [30] and agreed with studies showing that metformin has no effect on hormonal parameters [20] [31] [32].

Historically, the overall successful pregnancy rates after ovulation induction range from as low as 9% to as high as 25% [33]. In our study, consistent with the number of successful ovulatory cycles, pregnancy rate was notably higher in the metformin group compare to the laparoscopy group. Our results in this study are encouraging both in terms of the initiation and persistence of regular ovulatory cycles and in terms of pregnancies. It was reported that the beneficial effects of the surgical treatments are of limited duration, in most studies up to one year [26] [24].

6. Conclusion

For proper ovulation and conception not only an increase in serum progesterone is helpful but improvement in insulin resistance is required which is the key factor in the pathogenesis of PCOS. Our study showed that treatment with metformin, laparoscopy may be used as the first-line medications in anovulatory patients with polycystic ovarian syndrome (PCOS) for ovulation induction and pregnancy achievements. The study also demonstrated that metformin is superior to laparoscopy in inducing ovulation, pregnancy rate and live birth rate with polycystic ovarian syndrome. We could assert that laparoscopic ovarian drilling is an efficient treatment method for infertile anovulatory patients. The results obtained are as favourable as the biochemical profile of patients before surgery is less deteriorated. The costs incurred by the procedure can also recommend it as second-line therapy in compare to metformin therapy, more over laparoscopy is an invasive procedure.

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