

# MANAGEMENT OF ANOVULATORY INFERTILITY (POLYCYSTIC OVARY SYNDROME) WITH CLOMIPHENE ALONE AND IN COMBINATION WITH METFORMIN

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## ABSTRACT

**Objective** To compare the efficacy of clomiphene alone and in combination with metformin in patients presenting with polycystic ovarian syndrome (PCOS).

**Study design** A clinical trial.

**Place & Duration of study** Department of obstetrics and Gynaecology, Unit II, Bahawal Victoria Hospital Bahawalpur, from October 2006 to December 2007.

**Methodology** A total of sixty patients were included in the study and divided into two groups of thirty each fulfilling the inclusion criteria. Group A patients were given metformin 500mg thrice daily with gradually increasing dose over a period of 3 weeks to achieve actual dose and clomiphene citrate 50mg once daily for 5 days starting on 2<sup>nd</sup> day of menstrual cycle. Group B patients were given clomiphene citrate only, 50mg once daily, for 5 days starting on 2<sup>nd</sup> day of menstrual cycle.

**Results** Menstrual regularity was found in 22 (73%) patients in Group A compared with 13 (43%) patients in Group B. Ovulation detected by follicular tracking on ultrasonography was found in 19 (63%) patients in Group A compared with 11 (36.6%) patients in Group B. Conception confirmed on urine pregnancy test in 16 (53%) patients in Group A compared with 8 (26.6%) patients in Group B, and conception confirmed on sonographic detection of gestation sac was found in 14 (46.6%) patients in Group A compared with 8 (26.6%) patients in Group B.

**Conclusions** A combination of metformin and clomiphene citrate significantly regulated the menstrual cycle and increased the ovulation and conception rates in the management of anovulatory infertility.

**Key words** Polycystic ovaries, Metformin, Clomiphene citrate, Ovulation induction.

## INTRODUCTION:

Polycystic ovarian syndrome is a common endocrine disorder affecting 5 -10% of women of reproductive age and the most common cause of anovulatory infertility.<sup>1,2</sup> The polycystic ovarian syndrome is a heterogeneous condition the pathophysiology of which appears to be multifactorial and polygenic.

The definition of the syndrome has been much debated. Key features include menstrual cycle disturbance and hyperandrogenism and obesity. There are many extra ovarian aspects to the pathophysiology of PCOS, yet ovarian dysfunction is central.<sup>3</sup> It is characterized by anovulation, infertility and hyperandrogenism with clinical manifestation of irregular menstrual cycles, hirsutism and acne.<sup>4</sup> By the age of 40 years up to 40% will have type 2 diabetes or impaired glucose tolerance. PCOS is, therefore an important health concern and represents a major health issue affecting young women today.

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After puberty the periods are normal for sometimes then they becomes irregular.<sup>5</sup> In 1980, Burghen et al proved that an association exists between PCOS and hyperinsulinemia.<sup>6</sup> Dunaif et al in 1987 determined that insulin resistance was present in both lean and obese women with PCOS, but they noted that resistance was greater in obese PCOS subjects.<sup>7</sup> Insulin resistance occurs in 30% of lean and 75% of obese PCOS patients.<sup>8</sup> The discovery that insulin resistance has a key role in the pathophysiology of PCOS has led to a promising form of therapy in the form of insulin sensitizing drugs. The presence of obesity adds to the insulin resistance and hyperinsulinemia associated with obesity which is specifically unique to the anovulatory polycystic ovary state.<sup>9</sup>

A number of pharmacological agents have been used to amplify the physiological effect of weight loss, notably metformin. This biguanide inhibits the production of hepatic glucose and enhances the sensitivity of peripheral tissue to insulin, thereby decreasing insulin secretion.<sup>10</sup> It has been shown that metformin ameliorates hyperandrogenism and abnormalities of gonadotrophin secretion in women with PCOS and can restore menstrual cycle and fertility.<sup>4,11</sup> The objective of this study was to compare the effects of clomiphene alone and in combination with metformin in the patients presenting with PCOS.

#### **METHODOLOGY:**

This was a comparative study conducted at Department of Obstetrics and Gynaecology, Bahawal Victoria Hospital Bahawalpur. The first sixty patients of polycystic ovarian syndrome fulfilling the inclusion criteria were enrolled. The patients were randomly allocated to one of the two groups of 30 each namely group A and B. The diagnosis of PCOS was based on the presence of polycystic ovaries on ultrasonography with two or more of the following criteria.

Oligomenorrhoea (<6 cycles in preceding year)  
hirsutism  
hyperandrogenism  
Elevated LH or LH: FSH >2.

Hormonal investigations performed included. Serum FSH and LH level along with LH/FSH ratio, serum prolactin and testosterone, fasting serum insulin levels. Semen analysis of the male partner to rule out male factor infertility was also carried out. All other endocrine causes of female infertility including congenital adrenal hyperplasia, Cushing syndrome, hyperprolactinemia and thyroid disease were excluded by relevant investigations.

Group A patients were given metformin 500 mg three times daily along with clomiphene citrate 50 mg daily for five days starting from 2nd day of menstrual cycle. Group B patients were started on clomiphene citrate 50 mg daily for five days from 2nd day of menstrual cycle. All patients were followed for six cycles for evidence of regulation of menstrual cycles; ovulation as detected by follicle tracking (ovarian volume, size in mm and number of follicles) on ultrasonography by experts who were blind to the therapy being given to the patients. Dominant follicles on 12th day with absent follicles on day 16th indicated occurrence of ovulation. Conception was confirmed in those women who did not menstruate within one week of a serum progesterone test by positive urine pregnancy test. Metformin was continued up to 08 weeks of pregnancy. Clinical pregnancy was confirmed, when a gestational sac was detected on ultrasonography. With ovulation the dose of clomiphene citrate was unaltered. Metformin was continued in same dosage for cycles till ovulation/ conception occurred. The statistical analysis was performed using Chi square test.

#### **RESULTS:**

In Group A (metformin plus clomiphene group) 22 (73%) patients achieved regular menstrual cycles, compared with 13 (43%) patients in clomiphene only group B. In Group A 19 (63%) patients ovulated as compared with 11 (36.6%) in Group B. Conception confirmed on urine pregnancy test was found in 16 (53%) patients in Group A compared with 8 (26.6%) patients in Group B. Conception confirmed on the presence of gestation sac on ultrasound was found in 14 (46.6%) patients in Group A compared with 8 (26.6%) patients in Group B (Table I – IV).

Out of 30 patients who received metformin 3 had mild nausea and gastrointestinal upset in the initial three weeks of treatment. None of the patients had severe side effects of lactic acidosis. No teratogenic effects were observed in patients who conceived after treatment with metformin for ovulation induction.

#### **DISCUSSION:**

Clomiphene citrate and gonadotrophins were most commonly used drugs for ovulation induction in PCOS, but realization of this pathogenetic mechanism has given a new direction to the treatment of PCOS with insulin sensitizing drugs, giving promising results and significantly higher success rates of ovulation and pregnancy as compared with clomiphene citrate.<sup>12,13</sup> Among these drugs metformin is most widely used being safe without any teratogenic effects. After this new development many studies have been carried out

<b>Table I: Type of Menstrual Cycle</b>			
Outcome	Group A	Group B	Total
Regular	22 (73%)	13 (43%)	35 (58%)
Amenorrhea	8 (26%)	17 (56%)	25 (41.6)
Total	30	30	60
Chi Sq = 5.554 - P. Value = 0.018			

<b>Table II: Ovulatory Responses on Follicular Tracking in Patients with PCOS</b>			
Outcome	Group A	Group B	Total
Women ovulated	19 (63%)	11 (36.6%)	30 (50%)
Women not ovulated	11 (63%)	19 (36.6%)	30 (50%)
TOTAL	30	30	60
Chi Sq = 4.267 - P. Value = 0.039			

<b>Table III: Conception Confirmed on Urine Pregnancy Test in Patients with of PCOS</b>			
Outcome	Group A	Group B	Total
Conceived	16 (53%)	8 (26.6%)	24 (40%)
Not conceived	14 (46.6%)	22 (73%)	36 (60%)
Total	30	30	60
Chi Sq = 4.444 - P. Value = 0.035			

<b>Table IV: Ultrasound Demonstration of Gestation Sac in Patients of PCOS</b>			
Outcome	Group A	Group B	Total
Conceived	14 (46.6%)	08 (26.6%)	22 (73%)
Not conceived	16 (63%)	22 (73%)	38 (63%)
Total	30	30	60
Chi Sq = 2.584 - P. Value = 0.108			

world wide to establish the role of metformin in patients of PCOS,<sup>14</sup> but only few studies on Pakistani population are available.<sup>15</sup>

In one placebo controlled study by Nestler and Cowkers, 89% treated with metformin ovulated spontaneously or in response to clomiphene citrate as compared with 12% treated with placebo.<sup>10</sup> In a study carried out by Vandermolen et al,<sup>13</sup> 75% of patients taking metformin and clomiphene citrate ovulated whereas only 27% of the patients taking clomiphene citrate only ovulated. Conception rate in those who ovulated in metformin group was 75% whereas in only clomiphene group it was 33%. In another study carried out by Malikawi and Qublan

ovulation rate (68.8%) in patients who took clomiphene citrate plus metformin was significantly higher than the patients who received only clomiphene (25%).<sup>14</sup> Pregnancy rates in metformin plus clomiphene and only clomiphene group were 56.3% and 16.6% respectively. Imtiaz et al studied the role of metformin in ovulation induction and subsequent conception in Pakistani patients with PCOS having hyperinsulinemia; 72% of their patients ovulated within 3-9 months of treatment of metformin, and 32.5% of those who ovulated conceived.<sup>15</sup>

Rate of ovulation increased in metformin group after 2-3 treatment cycles. The prolonged administration of insulin sensitizing drugs ameliorates the insulin

resistance. This supports the view that mechanism of action of this drug in PCOS is directly related to improvement of insulin sensitivity or reduction of circulating insulin levels. In present study it has been shown that the addition of metformin along with clomiphene citrate in patients of PCOS significantly increased the ovulation rate and pregnancy rate. During 6 months treatment 63% patients ovulated in metformin plus clomiphene group and 36.6% in the clomiphene only group. Conception rate was 40% versus 20% between the groups. These findings are consistent with those of previous studies. Our findings on the role of metformin in increasing the ovulation rate and subsequent conception are in agreement with the results of above quoted studies.

**CONCLUSIONS:**

A combination of metformin and clomiphene citrate significantly regulated the menstrual cycle and increased the ovulation and conception rates in study patients.

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