



POLYCYSTIC OVARIAN SYNDROME (PCOS); PREGNANCY RATE FOLLOWING OVULATION INDUCTION BY CLOMIPHENE ALONE AND WITH COMBINATION OF METFORMIN

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ABSTRACT... Objective: To compare effectiveness of clomiphene alone and in combination with metformin in terms of conception rate in patients presenting with polycystic ovary syndrome. **Study Design:** Randomized clinical trial. **Place and duration of study:** Department Obstetrics and Gynecology Unit I, Nishtar Hospital Multan, 6 months from 12th September 2009 to 11th March 2010. **Methodology:** Primary subfertile women visiting outpatient department of Nishtar Hospital Multan with significant irregular menstrual cycle, oligo menorrhoea and ultrasonographic features of polycystic ovaries were enrolled in the study. Semen samples from male partners were analyzed according to the WHO criteria. Women whose partner's semen analysis was abnormal were excluded from study. Group 'A' was given clomiphene citrate alone and second group (i.e. group B) was given clomiphene citrate and metformin. All patients were followed till six cycles for regularity of menstrual cycle (determined by history) ovulation by follicular tracking on ultrasonography, if patient (conceived), conception was confirmed by urine pregnancy test and gestational sac on ultrasonography pelvis. Final outcome was measured at six month. Information was entered in specifically designed proforma. **Results:** Frequency of PCOS was 14.05%. Mean age of the patients was 31.03 ± 0.58 vs. 29.89 ± 0.53 years in group A and B respectively. Oligomenorrhoea was present in 18(50%) vs. 18 (50%) women, amenorrhoea in 7(19.4%) vs. 8(22.2%) patients and weight gain in 14(38.9%) vs. 15(41.7%) cases in group A and B respectively. Conception was achieved in 26(72.2%) vs. 18(50.0%) patients in group A and B respectively. **Conclusions:** Metformin does not seem to help in achieving higher rates of pregnancy when combined with CC as compared to CC alone.

Key words: Polycystic ovary syndrome (PCOS), Metformin, Clomiphene citrate (CC), Conception.

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INTRODUCTION

The polycystic ovary syndrome is the most prevalent endocrine disorder of women of reproductive age group affecting 5 to 10% of women¹ and may be the most common cause of female infertility². Anovulation², early pregnancy loss³, and later pregnancy complications⁴. Obesity is also common in such ladies. The cause of polycystic ovary syndrome is not known.

Polycystic ovarian syndrome is characterized by two of the following three criteria.

1. Oligo-and/Oranovulation
2. Polycystic ovaries on ultrasound.

3. Clinical and/or biochemical hyperandrogenism.

The problem of polycystic ovarian syndrome has been subject of extensive research over the past six decades as it is the most common cause (75%) of anovulatory infertility². Infertility is a big social dilemma especially in our setup causing divorce and 2nd marriage trends. Treating metabolic abnormalities of PCOS has been noted to improve ovulation and fertility in such women⁵.

In PCOS ovulation can be induced with antiestrogen like clomiphene citrate⁶. It is

successful in ovulation induction in 80% of cases⁷.

Because of the link between insulin resistance and PCOS metformin has been put forward as a drug to induce ovulation in women with PCOS⁸. As insulin resistance seems to be a key feature in PCOS increase in serum concentration of insulin is common in both lean and obese women with PCOS. Insulin stimulates androgen secretions by ovarian stroma and affects normal development of ovarian follicles. Insulin also leads to suppression of liver production of sex hormone binding globulin and increases free androgens⁹.

Metformin inhibits production of hepatic glucose and thereby decreases insulin secretion so can be used to treat hyperinsulinemia in PCOS¹⁰.

Surgical methods include wedge resection used previously. It is to be condemned as it is the operation that is associated with destruction of already diseased ovaries and might transfer the patient from ovulatory problem to ovulatory and tubal problem because of post operation adhesions¹¹.

Laparoscopic ovarian drilling is being frequently performed for ovulation induction but requires Laparoscopic surgical instruments, not available in most hospitals therefore most doctors lack experience and skill in performing Laparoscopic surgery. This surgical procedure is associated with its own risks. On the other hand, females of low income group are unable to afford this procedure in private hospital.

METHODOLOGY

This randomized clinical trial was carried out in Department of Obstetrics and Gynaecology Unit I, Nishtar Hospital Multan. Over a period of 6 months from 12th September 2009 11th March 2010 Non probability purposive sampling technique was used to select 72 patients.

Inclusion criteria included

1. Age less than 35 years
2. Infertility: Primary
3. Oligo or amenorrhoea.

4. Polycystic ovaries on pelvic or transvaginal ultrasound.
5. Normal semen analysis according to WHO 1999 criteria.

Exclusion Criteria included

- All other endocrinological causes of female infertility including congenital adrenal hyperplasia, Cushing's Syndrome, hyperprolactinemia and thyroid disease.

Information about age, weight, duration of infertility, former pregnancies, and menstrual cycle patterns were obtained and previous infection. Contraception and consumption of medicine for infertility treatment were recorded.

Informed consent was taken by explaining risks/benefits of the medicines to the patient as well as her husband. Approval of Hospital Ethical Committee was sought.

Required number of chits (i.e 72) were made 50% were marked as 'A' and the rest with 'B'. Patients were asked to pick one slip when consenting for treatment. In this way two groups were made.

Group 'A' was given clomiphene citrate alone and second group (i.e group B) was given clomiphene citrate and metformin according to following regimens.

The patients were given clomiphene 50 mg once daily for 5 days started from second day of menstrual cycle upto three cycles.

Metformin 500 mg three times a day was given. The dose was gradually increased over a period of 3 weeks to achieve required dose. All patients were followed till six cycles for regularity of menstrual cycle (determined by history) and ovulation by follicular tracking on ultrasonography (dominant follicle on day 12 and absent follicle on day 16. If patient missed the cycle (conceived), conception was confirmed by urine pregnancy test and gestational sac on ultrasonography pelvis. Final outcome was measured at six month.

This information was entered in proforma specifically designed for the study (attached as annexure).

Data were entered and analyzed using computer programme SPSS-10 to find out frequencies and percentages of outcome variables like conception rate. P-value equal or less than 0.05 was considered as significant.

RESULTS

Total number of patients during study period was 2135, out of which 300 had PCOS, so frequency of PCOS was 14.05%. For age wise distribution of patients with PCOS, 3(8.3%) in group A and 4(11.1%) patients in group B were between 21-25 years, 14(38.9%) vs. 14(38.9%) patients were between 26-30 years in group A and B respectively, while 19(52.8%) vs. 18(50.0%) patient were between 31-35 years in group A and B respectively. The means age of the patients was 31.03 ± 058 vs. 29.89 ± 0.53 years in group A and B respectively. Age of the patients ranged from 21-35 years (Table No. I & II).

Regular menstrual cycle was observed in 11(30.6%) vs. 10 (27.8%) in group A and B respectively. Menstrual irregularities were most common clinical presentation. Oligomenorrhea was present in 18(50%) vs. 18(50%) women in group A and B respectively, amenorrhea in 7(19.4%) vs. 8(22.2%) patients in group A and B respectively, and weight gain in 14(38.9%) vs. 15(41.7%) cases in group A and B respectively. Hirsutism was less common present among 4 (11.1%) vs. 3(8.3%) cases respectively in group A and B.

Raised serum LH, FSH, prolactin and testosterone were evident in 26(72.2%) vs. 27(75%), 13(36.1%) vs. 21(58.3%), 4(11.1%) vs. 5(13.9%) and 7(19.4%) vs. 9(25%) cases in group A and B respectively.

Conception was achieved in 26(72.2%) vs. 18(50.0%) patients in group A and B respectively as show in Table No. III.

Age (in years)	No. of patients	
	Group A (n=36)	Group B (n=36)
21-25	3 (8.3%)	4 (11.1%)
26-30	14 (38.9%)	14 (38.9%)
31-35	19 (52.8%)	18 (50.0%)

Table-I. Age-Wise Distribution of Patients with PCOS

Key: PCOS = polycystic ovary syndrome.
Group A = Patients given clomiphene citrate alone.
Group B = Patients given clomiphene citrate and metformin.

Variable (Mean \pm S.E.M)	No. of patients	
	Group A (n=36)	Group B (n=36)
Age (in years)	31.03 ± 0.58	29.89 ± 0.53
Serum FSH J (IU/L)	9.61 ± 0.40	10.58 ± 0.34
Serum LH J (IU/L)	12.53 ± 0.51	12.58 ± 0.40
Serum Prolactin (mIU/L)	350.11 ± 7.94	322.89 ± 10.31
Serum testosterone (nmol/L)	2.56 ± 0.16	2.67 ± 0.16

Table-II. Descriptive Statistics

Conception	No. of patients	
	Group A (n=36)	Group B (n=36)
Yes	26 (72.2%)	18 (50.0%)
No	10 (27.8%)	18 (50.0%)

Table-III. Outcome

DISCUSSION

Polycystic ovary syndrome is a common reproductive disorder associated with many characteristic features, including hyperandrogensim, insulin resistance and obesity which may have significant implications for pregnancy outcomes and long-term health of the woman.

Clomiphene citrate was the first agent used in experiments for ovulation induction in

oligomenorrhic women¹². For many years it was and may still be the first therapeutic option managing anovulatory infertility. The treatment with clomiphene citrate in anovulatory PCOS women is associated with an ovulation rate of 60 – 85% & pregnancy rate of 30-40%¹³. The effect of metformin in combination to clomiphene citrate has been evaluated in a number of studies. Some studies has found a significant benefit while the others did not. However the addition of metformin to clomiphene citrate in clomiphene citrate-resistant women significantly improves the ovulation rate. A meta analysis in a Cochrane review reported a significant benefit for metformin compared to placebo for ovulation in anovulatory women with PCOS¹⁴. Another meta analysis showed a significant positive effect of metformin when added to clomiphene citrate in the clomiphene citrate-resistant PCOS patient¹⁵.

Present study was carried out to compare effectiveness of clomiphene alone and in combination with metformin in terms of conception rate in PCOS patients. In our study, oligomenorrhea was present in 50% of the patients in each group followed by amenorrhea in 19.4% vs. 22.2% patients in the two groups and weight gain in 38.9% vs. 41.7% patients in Group A and B respectively.

Ayisha Raja and colleagues¹⁶ have reported oligomenorrhea in 52% vs. 64% patients, dysmenorrhea in 52% vs. 56% cases and hirsutism in 64% vs. 66% patients in metformin + CC and CC only groups respectively.

In a study carried out by Fauiza et al¹⁷ in Pakistani patients oligomenorrhea was found in 75% of their cases. In the same study, hirsutism was found in 84.6% of cases which is quite high.

Fouzia Kashif et al¹⁸ have mentioned in their study 81% cases had history or menstrual irregularity and in 72% women hirsutism was seen, while history of weight gain was present in 62% of the patients.

In present study, in group B patient (given clomiphene citrate in combination with metformin)

pregnancy could be achieved in 18(50.0%) cases while in group A (give clomiphene citrate alone) conception was achieved in 26(72.2%) cases. A number of studies have similar findings negating the role of metformin when combine with clomiphene citrate in achieving conception.

In the study by Neveu et al¹⁹ they prospectively randomized 154 patients with PCOS. Pregnancy rates were equivalent in the three groups (clomiphene citrate, metformin, or the combination of both). They also observed a better ovulatory response in the women with a lower BMI in the clomiphene citrate group and patients with a BMI of 27-35 responded better to metformin for ovulation induction. The mean BMI of the study was 31. This study had a better ovulation rate in the metformin group and the combination group (CC + Metformin) (P=0.005), but no difference in pregnancy rates between the three groups (P=0.332). This study concluded that it is not beneficial to add metformin to clomiphene citrate in primary ovulation induction protocols.

In a study by Legro et al,²⁰ 626 PCOS patients were randomized. The primary outcome of their study was live birth rates. They concluded that clomiphene citrate (22.5%) is superior to metformin (7.2%) but similar to the combination group (26.8%) in achieving live birth rates. The conception rate among subjects who ovulated was significantly lower in the metformin group (21.7%) than in either the clomiphene group (39.5%, P = 0.002) or the combination-therapy group (46.0%, P<0.001). They did not observe any difference in the abortion rates between the three groups and observed a significantly better live birth rate if the BMI is less than 30 regardless of the treatment options used. Conception, pregnancy, and live birth were significantly more likely to occur after treatment with clomiphene alone than after metformin alone. They supported the use of clomiphene citrate alone as first-line therapy for infertility in women with the polycystic ovary syndrome.

Palomba S et al²¹ in a recent systematic review of head-to-head randomized controlled studies

observed no difference in fertility improvement comparing CC with metformin (OR = 1.22, 95% CI 0.23-6.55 P = 0.815). Homogeneous data showed no difference in fertility improvement between the combination treatment and CC monotherapy (OR = 0.99, 95% CI 0.70-1.40, P = 0.982). They concluded that in PCOS patients with anovulatory infertility and not previously treated, the administration of metformin plus CC is not better than monotherapy (metformin alone or CC alone).

Safdar Ali Malik et al²² have ovulation rates as high as 75% patients while pregnancy was achieved in 58% of patients while treated with clomiphene citrate alone.

In a recent multi-center randomized trial²³ CC proved to be superior to metformin. Clinical pregnancy rate were 40% with metformin 39% with CC, 54% with combination metformin plus CC.

However a number of studies carried out establishing a role of metformin in achieving pregnancy when combined with CC. Ayisha Raja¹⁶ Tang T et al²⁵ Creanga et al,²⁶ were of this opinion and favoured use of metformin.

Our study is a single center study with a small sample size, so results cannot be generalized. Large randomized clinical trials are required to further investigate the role of metformin in achieving conception in PCOS women.

CONCLUSIONS

Conception rate 72.2% with Clomiphene Citrate alone and 50.0% when metformin is combined suggest that metformin does not have a role in achieving higher rates of pregnancy. Role of metformin is therefore controversial.

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