

Role of Letrozole and Metformin Vs Letrozole Alone in Ovulation Induction in Patients of Polycystic Ovarian Syndrome

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ABSTRACT

Aim: To compare letrozole and metformin with letrozole alone, in ovulation induction in terms of pregnancy rate in infertile polycystic ovarian syndrome patients.

Study Design: Randomized Controlled Trial from March-2018 to Jan-2019.

Setting: Obstetrics and Gynaecology Department of CMH Multan.

Methods: A total number of 100 females with diagnosis of polycystic ovarian syndrome (PCOS) having age 20-35 years were included in this study. In group A; tablet metformin along with letrozole (LE; 2.5 mg) was given 500 mg three times daily with meals starting from the first day of cycle and continuous for three cycles and to be stopped when pregnancy is achieved. In both group; 2.5 mg twice daily LE was administered on 3rd day of menses and then every day for 5 days. Patients were followed for 3 months to evaluate pregnancy.

Results: Mean age of patients was 28.51±4.63 years. Mean duration of infertility in(PCOS patients was 3.13±1.20 years. On comparison of pregnancy between the groups, the pregnancy was achieved in 41 patients in who letrozole alone was given versus 56 in females in whom letrozole plus metformin was given (p-value 0.03).

Conclusion: Combination of letrozole plus metformin is superior as compared to letrozole alone for induction of pregnancy in female patients with polycystic ovarian syndrome.

Keywords: Polycystic ovarian syndrome (PCOS), Letrozole, Metformin, Ovulation Induction, Pregnancy.

INTRODUCTION

Female infertility is a frequent problem and 40 % is due to ovulatory dysfunction and polycystic ovarian syndrome is one of the main cause¹. Polycystic ovarian syndrome is the most common endocrinopathy of reproductive age and its prevalence is as high as 15 to 20%. The development of safe and effective treatment for infertility in PCOs is an important public health goal².

Ovulation induction is recognized as the main therapeutic procedure for patients with polycystic ovarian syndrome wanting to get pregnant³.

The first line of treatment for ovulation induction is clomiphene citrate but 15 to 40 % do not achieve ovulation and it is referred as clomiphene citrate resistance. Clomiphene citrate is an antiestrogen⁴.

Second choice is using insulin sensitizers such as metformin alongwith clomiphene citrate. Metformin a biguanide is used for ovulation induction in patients with PCOs whose main disturbance is insulin resistance and hyperinsulinemia. Compiled analysis indicates that long term metformin is associated with 30 % improvement in ovulation frequency as compared to placebo⁵.

Letrozole (LE) is considered to be second line drug in ovulation induction. It is a selective third generation aromatase inhibitor which can selectively block estrogen without disturbing other steroidogenic pathways⁶.

Previous studies show that there was a significant percentage of patients who used letrozole after failure of ovulation by clomiphene citrate and had successful ovulation. According to reports ovulation rate in women with CC resistance PCOs is between 54.6 % to 84.4%³.

Some studies have shown that addition of metformin to letrozole is an efficient procedure in ovulation induction with pregnancy rate of 20.6%.¹ In another study the pregnancy rate with letrozole alone was 35%².

Previously most of the studies were performed on international level, showing comparison of clomiphene citrate and letrozole in ovulation induction. According to my knowledge no local study regarding this topic has been done in Pakistan, while few studies have been done at international level up till now. This study aims to determine the efficiency of letrozole with metformin and letrozole in inducing ovulation. This study will help in improving the treatment modalities in polycystic ovarian syndrome infertility patients and achieving better results.

METHODS

A total number of 100 patients with diagnosis of subfertility due to PCOS with Normal hysterosalpingogram (HSG) having age 18-35 years were included in this study. Women having hormonal disorders such as hyperprolactinemia, hypo or hyperthyroidism diabetic patients and cushings syndrome were excluded. All patients were admitted through OPD after complete evaluation with history, examination, investigation and verbal informed consent for inclusion in the study.

Patients were randomized using computer generated sequence of randomnumbers to either of the two treatment arms— letrozole and metformin and letrozole alone. Letrozole and metformin was administered as oral preparation.

In group A tablet metformin was given 500 mg three times daily with meals starting from the first day of cycle and continuous for three cycles and to be stopped when pregnancy is achieved and in both groups, 2.5 mg twice

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daily LE was administered on 3rd day of menses and then every day for 5 days. Treatment was repeated for 3 cycles if the patient fails to ovulate, patients would be followed for 3 months after the treatment in both groups. In groups, pregnancy rate was measured. All patients were reviewed and findings were noted in the SPSS v23.

RESULTS

Mean age of females was 28.51±4.63 years (28.44±4.78 in group A versus 28.28±4.48 in group B). Mean BMI was 25.75±3.65 Kg/m² (25.49±3.60 in group A v/s 26.01±3.68 in group B). Mean duration of infertility in polycystic ovarian syndrome (PCOS) patients was 3.13±1.20 years (3.11±1.16 in group A v/s 3.15±1.26 in group B). On comparison of pregnancy between the groups, the pregnancy was achieved in 41 patients in whom LE alone was given versus 56 in females in whom LE plus metformin was given (p-value 0.03).

Table 1. Comparison of Study Variables

	Group A	Group B	P-value
Age	28.74±4.78	28.28±4.48	0.44
BMI	25.49±3.60	26.01±3.68	0.26
Duration of infertility	3.11±1.16	3.15±1.26	0.83
Successful Pregnancy			
Yes	56	41	0.03
No	44	59	

DISCUSSION

PCOS is a very major risk factor for ir-regular periods or amenorrhea with incidence rate of 4-8% in fertile women globally. Many of the effected females aresub-fertile and can conceive in some part of life and only a few needs fertility treatment⁷⁻¹⁰.

Because PCOS is associated with impaired insulin sensitivity so the treatment with insulin sensitizers is given for ovulation. A recent review has proven the use of insulin sensitizers alone has limited efficacy in ovulation induction in PCOS patients¹¹.

In present study, we evaluated the efficacy of letrozole plus metformin for induction of pregnancy in patients of polycystic ovary syndrome (PCOS).

In present study, mean age of patients was 27.51±4.63 years and the mean duration of infertility was 3.13±1.20 years. Mean age of patients in the study of Elgafor et al. was 24.7±1.8 years, while mean duration of infertility was 3.4±0.9 years¹². While mean age of the patients in the study of Liu et al. was 27.2±3.3 yrs and mean duration of infertility was only one years¹³. While mean age of the patients in the study of Davar et al was 28.54±3.13 yrs & mean duration of infertility was 3.76 yrs¹⁴.

We found significantly high success rate of induction of pregnancy in patients receiving letrozole plus metformin versus letrozole alone, with success rate of 56% in LE+ metformin group and 41% in letrozole group alone. Liu et al. reported a pregnancy rate of 57.9% in letrozole plus metformin group and only 46.8% in patients who received letrozole alone¹³.

Another study conducted by Elgafore et al. reported that LE+metformin combination can have a success rate of 90.57% and successful pregnancy in 34.50% females¹².

While Davar et al. reported a pregnancy rate of only 8.3% in PCOS women. These authors found a very lower rate of pregnancy induction after letrozole and metformin combination that is contrary to the results of our and other published studies¹⁴.

CONCLUSION

Combination of letrozole plus metformin is superior as compared to letrozole alone for induction of pregnancy in female patients with polycystic ovarian syndrome.

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