Study to Assess Clomiphene and Metformin for Infertility in the Polycystic Ovary Syndrome

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ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) is a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries. Clomiphene citrate (CC) is an antioestrogen and competes for receptor binding sites with endogenous oestrogens. Metformin and other insulin sensitising agents are thought to help correct this and therefore increase ovulation and pregnancy rates in women with PCOS. Hence, the present study was undertaken for assessing the efficacy of clomiphene and metformin for infertility in the polycystic ovary syndrome.

Material and methods: A total of 90 subjects who fulfilled the diagnostic criteria of PCOS were included in the present study. All the subjects were randomly divided into three study groups as follows: Group A: CC group, Group B: Metformin group and Group C: Combination of metformin and CC. All the subjects received medications according to their respective study groups. On day eight, transvaginal sonography for follicular monitoring was carried out. Timed intercourse advice was given if ovulatory and same dose of medicine was repeated as per their study groups. In the CC group, women who failed to ovulate were termed as CC resistant. The protocol was maintained till subjects were pregnant or CC resistant occurred or until 6 months as applicable independently. All pregnant women were followed up till delivery.

Results: Ovulation occurred in 53.33% of subjects of group A, 60 percent of the subjects of group B and 86.67% of the subjects of group C. Pregnancy rate was 30 percent, 50 percent and 53.33 percent among the subjects of group A, group B and group C respectively. Live birth rate was 23.33 percent, 33.33 percent and 43.33 percent among the subjects of group A, group B and group C respectively. Non-significant results were obtained while comparing the live birth rate in between the subjects of all the three study groups.

Conclusion: Best results are obtained in terms of live birth rate when combination of CC and metformin is given. However; individuals results obtained when CC and metformin are given individually are also promising.

Keywords: Clomiphene citrate, Polycystic, Ovary, Metformin

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries. The disorder can be morphological (polycystic ovaries) or predominantly biochemical (hyperandrogenemia). Hyperandrogenism, a clinical hallmark of PCOS, can cause inhibition of follicular development, microcysts in the ovaries, anovulation, and menstrual changes. Anovulation (or oligo-ovulation) in women with PCOS is one of the commonest causes of infertility. High circulating androgen levels results in women with PCOS experiencing hirsutism and acne.[1-3]

Women with this syndrome have hyperandrogenism, morphologic changes in the ovary (polycystic), inappropriate gonadotropin secretion (elevated levels of circulating luteinizing hormone), and insulin resistance with accompanying compensatory hyperinsulinemia. Targeting these metabolic abnormalities has been noted to improve ovulation and fertility in women with this syndrome. Clomiphene citrate (CC) is an antioestrogen and competes for receptor binding sites with endogenous oestrogens. Metformin and other insulin sensitising agents (e.g. troglitazone, rosiglitazone, pioglitazone, and D chiro inositol) are thought to help correct this and therefore increase ovulation and pregnancy rates in women with PCOS.[4-6] Hence, under the light of above mentioned data, the present study was undertaken for assessing the efficacy of clomiphene and metformin for infertility in the polycystic ovary syndrome.

MATERIAL AND METHODS

The present study was conducted for 1 year (2017-2018) with the aim of assessing the efficacy of clomiphene and metformin for infertility in the polycystic ovary syndrome. Evaluation of women who reported to the department of gynaecology and obstetrics with chief complaint of infertility and oligomenorrhea for PCOS was done. Diagnosis of PCOS was done based on the criteria – Rotterdam, as described previously in the literature.[6] LH has been omitted from both diagnostic criteria as unnecessary (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2003).[6] LH has been assessed as a diagnostic test to discriminate between women with PCOS and healthy controls, and the LH/FSH ratio in particular was found to be predictive (Turhan et al., 1999).[7] A total of 90 subjects who fulfilled the diagnostic criteria of PCOS were included

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Outcome	Group A (n=30)		Group B (n=30)		Group C (n=30)	
	n	%	n	%	n	%
Ovulation	16	53.33	18	60	26	86.67
Pregnancy	9	30	15	50	16	53.33
Early pregnancy loss	2 (out of 9)	22.22	5 (out of 15)	33.33	3 (out of 16)	18.75
Live birth rate	7	23.33	10	33.33	13	43.33

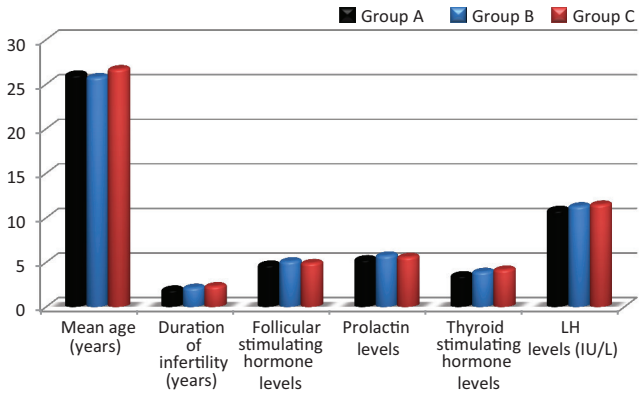
Table-1: Outcome

Group Versus Group		p- value
Group A Versus Group B	Ovulation rate	0.34
	Live birth rate	0.89
Group A Versus Group C	Ovulation rate	0.00*
	Live birth rate	0.91
Group B Versus Group C	Ovulation rate	0.48
	Live birth rate	0.62
*: Significant		

Table-2: Comparison between individual study groups

Variable	Group A	Group B	Group C
LH levels (IU/L)	10.9	11.3	11.5

Table-3: LH levels



Graph-1: Demographic and clinical results

Comparison	p- value
Group A Versus Group B	0.36
Group A Versus Group C	0.11
Group B Versus Group C	0.82

Table-4: Comparison of LH levels

in the present study. Diabetic and hypertensive subjects and subjects with negative history of any other systemic illness were excluded from the present study. All the subjects were randomly divided into three study groups as follows:

Group A: CC group,

Group B: Metformin group and

Group C: Combination of metformin and CC

All the subjects received medications according to their respective study groups. On day eight, transvaginal sonography for follicular monitoring was carried out. Timed intercourse advice was given if ovulatory and same dose of medicine was repeated as per their study groups. In the CC group, women who failed to ovulate were termed as CC resistant. Enrolment of all women was done for a time period of six months. The protocol was maintained till subjects were pregnant or CC resistant occurred or until 6 months as applicable independently. All pregnant women were followed up till delivery. All the results were recorded in Microsoft excel sheet and were analysed by SPSS software. Chi-square test and student t test were used for evaluation of level of significance.

RESULTS

Mean age of the subjects of group A, group B and group C was found to be 26.1 years, 25.8 years and 26.7 years respectively. Mean duration of infertility among subjects of group A, group B and group c was found to be 1.96 years, 2.16 years and 2.33 years respectively. Mean LH among the subjects of group A, group B and group C was found to be 10.9 IU/L, 11.3 IU/L and 11.5 IU/L respectively. At baseline, mean levels of follicular stimulating hormone, prolactin levels, and levels of thyroid stimulating hormone were comparable among the three study groups. In the present study, ovulation occurred in 53.33% of subjects of group A, 60 percent of the subjects of group B and 86.67% of the subjects of group C. Pregnancy rate was 30 percent, 50 percent and 53.33 percent among the subjects of group A, group B and group C respectively. Live birth rate was 23.33 percent, 33.33 percent and 43.33 percent among the subjects of group A, group B and group C respectively. In the present study, non-significant results were obtained while comparing the live birth rate in between the subjects of all the three study groups.

DISCUSSION

The female hypothalamic–pituitary–ovarian (HPO) axis is a meticulously synchronized and tightly regulated network ultimately responsible for reproductive competence and survival of the species. The HPO axis responds to internal signals (i.e., hormonal and neuronal) and external factors (i.e., environment influences). Polycystic ovary syndrome (PCOS), a disorder primarily characterized by signs and symptoms of androgen excess and ovulatory dysfunction, disrupts HPO axis function. The polycystic ovary syndrome is a disorder that is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphologic features.[7, 8] PCOS is characterized by excessive ovarian and/or adrenal androgen secretion. Intrinsic ovarian factors such as altered steroidogenesis and factors external to the ovary such as hyperinsulinemia contribute to the excessive ovarian androgen production.[9] Hence; under the light of above mentioned data, the present study was undertaken

for assessing the efficacy of clomiphene and metformin for infertility in the polycystic ovary syndrome.

In the present study, at baseline, mean levels of follicular stimulating hormone, prolactin levels, and levels of thyroid stimulating hormone were comparable among the three study groups. Mean LH among the subjects of group A, group B and group C was found to be 10.9 IU/L, 11.3 IU/L and 11.5 IU/L respectively. The possibility of using LH as a diagnostic test for oligo-/ amenorrhoeic PCOS does not directly imply that it should be used. The current Rotterdam criteria give rise to four different phenotypes of PCOS patients, and introducing an extra criterion would only increase the diversity, which would be undesirable. Due to the heterogeneity of the syndrome, no single criterion of the Rotterdam consensus, or LH, can be used as a single test to diagnose PCOS. Limited data demonstrated no evidence of difference in effect between metformin and the OCP on hirsutism and acne. Metformin was less effective than OCP in reducing serum androgen levels. Metformin was less effective than OCP in improving menstrual pattern. Metformin resulted in a higher incidence of gastrointestinal, and a lower incidence of non-gastrointestinal, severe adverse effects requiring stopping of medication.[9, 10]

In the present study, ovulation occurred in 53.33% of subjects of group A, 60 percent of the subjects of group B and 86.67% of the subjects of group C. Pregnancy rate was 30 percent, 50 percent and 53.33 percent among the subjects of group A, group B and group C respectively. Live birth rate was 23.33 percent, 33.33 percent and 43.33 percent among the subjects of group A, group B and group C respectively. Legro RS et al randomly assigned 626 infertile women with the polycystic ovary syndrome to receive clomiphene citrate plus placebo, extended-release metformin plus placebo, or a combination of metformin and clomiphene for up to 6 months. Medication was discontinued when pregnancy was confirmed, and subjects were followed until delivery. The rates of first-trimester pregnancy loss did not differ significantly among the groups. However, 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). With the exception of pregnancy complications, adverse-event rates were similar in all groups, though gastrointestinal side effects were more frequent and vasomotor and ovulatory symptoms less frequent, in the metformin group than in the clomiphene group. Clomiphene was superior to metformin in achieving live birth in infertile women with the polycystic ovary syndrome, although multiple births were a complication.[11]

In the present study, non-significant results were obtained while comparing the live birth rate in between the subjects of all the three study groups. Dasari P et al assessed the ovulatory and pregnancy rates in infertile PCOS subjects who receive Clomiphene citrate (CC) alone and a combination of metformin and CC. Twenty-four infertile PCOS women received CC alone at incremental doses of 50 mg up to 150 mg for three cycles and then at a dose of 150 mg for another three cycles (control group). The study group (16 PCOS) received the same dose of CC along with 1500mg of metformin. The metformin and clomiphene combination resulted in a significantly higher rate of ovulation (P = 0.0016). The pregnancy rate was 8% with CC and 24% with metformin and CC. The CC failure group also ovulated at a similar rate as that of the study group. The ovulatory rate and the pregnancy rate with the metformin–CC combination was found to be higher when compared with CC alone.[12] Zhang J et al evaluate the therapeutic effects of metformin and clomiphene in combination with lifestyle adjustment on infertility in women with obese polycystic ovarian syndrome (PCOS). The authors concluded that lifestyle adjustment combined with metformin and clomiphene can improve the reproductive endocrine and lipid metabolism of obese PCOS patients, decrease the volumes of left and right ovaries, and increase the menstrual recovery, ovulation and pregnancy rates.[13]

CONCLUSION

From the above results, the author conclude that highest and best results are obtained in terms of live birth rate when combination of CC and metformin is given. However, individuals results obtained when CC and metformin are given individually are also promising. Hence, further studies are recommended.

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