



Efficacy of sequential treatment of metformin and clomiphene citrate in clomiphene resistant women with polycystic ovary syndrome

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OBJECTIVE(S) : To determine whether metformin increases ovulation rate and pregnancy rate in women with polycystic ovary syndrome (PCOS) resistant to clomiphene citrate.

METHOD(S) : A randomized placebo-controlled trial was conducted on 36 clomiphene citrate resistant women with PCOS. Eighteen women each were randomly allocated to receive either metformin or placebo for 3 months. Pretreatment baseline hormonal assays were obtained and repeated after 3 months. Clomiphene citrate was added in women who were still ovulatory after 3 months. Six ovulatory cycles, pregnancy or anovulation even on a daily clomiphene citrate dose of 200 mg were considered end point of the study. Paired t test and Fisher's exact test were used for statistical analysis.

RESULTS : Fasting insulin levels and serum testosterone and androstenedione decreased significantly after 3 months of metformin therapy. Ovulation and pregnancy rates were significantly higher in women who had received metformin pretreatment ($P < 0.001$).

CONCLUSION(S) : Metformin-clomiphene citrate therapy in clomiphene citrate resistant polycystic ovary syndrome women significantly increases ovulation and pregnancy rates ($P < 0.001$).

Key words : polycystic ovary syndrome, clomiphene resistance, metformin

Introduction

Polycystic ovary syndrome (PCOS) affects approximately 6% women of reproductive age¹. Insulin resistance with compensatory hyperinsulinemia, a prominent feature of the syndrome², can adversely affect folliculogenesis and ovulation by increasing intraovarian androgen production, altering gonadotropin secretion or directly affecting follicular development³.

This study was undertaken to determine whether reduction of hyperinsulinemia with metformin has any beneficial effects on ovulation and pregnancy rates in women with clomiphene citrate resistant PCOS. Hormonal levels before and after

treatment with metformin were assayed in order to determine any beneficial affect.

Methods

Thirty-six clomiphene resistant PCOS women were enrolled in the study at our teaching hospitals in Gangtok and Pokhara between 2004 and 2006. All women had oligomenorrhea and clinical or biochemical features of hyperandrogenism, along with either raised LH/FSH ratio or raised LH or ultrasound features of polycystic ovaries⁴. All patients had normal serum prolactin concentrations and normal thyroid function tests and none had diabetes mellitus. All women had normal renal and liver function tests and had no other factor causing infertility. All women gave their informed consent before being enrolled into the study.

These women were evaluated prospectively and randomized to two groups of 18 each using computer generated tables, to receive orally either metformin 500 mg or placebo thrice daily for 3 months. Body mass index (BMI) and waist-to-hip ratio were documented at the time of entry into the study

Paper received on 09/05/2006 ; accepted on 01/12/2006

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and repeated at the end of 3 months of treatment. Blood samples for hormonal assays were obtained during the follicular phase before starting metformin or placebo and at the end of 3 months of treatment. Fasting levels of insulin and glucose were obtained similarly. Serum progesterone was measured between day 21 and day 28 and ovulation was presumed to have occurred if the value exceeded 8 ng/dL on either of these days. In the second phase of the study, women who did not ovulate were given 50 mg clomiphene citrate (CC) from day 3 to day 7 for 5 days, while continuing to receive metformin or placebo. With ovulation, the CC dose was not changed, but with anovulation it was increased by 50 mg for the next cycle, up to a maximum of 200 mg per

day. Patients were asked to maintain a menstrual calendar throughout and instructed to carry on their usual lifestyle and dietary habits during the study.

Outcome measures were any change in hormonal profile after treatment with metformin, resumption of menses, presumptive ovulation, and pregnancy. Six ovulatory cycles, pregnancy or anovulation despite taking 200 mg of CC were considered end points of the study. Baseline and posttreatment hormonal levels were compared using a paired t-test. Fisher's exact test was used to analyze the difference in ovulation and pregnancy rates between metformin and placebo groups.

Table 1. Baseline profile of women with polycystic ovary syndrome and profile 3 months after treatment.

Characteristic	Metformin Group (n=18)		Placebo Group (n=18)	
	Baseline	After 3 months	Baseline	After 3 months
Age (years)	28 ± .62	28.2 ± .62	28.2 ± .4	28.2 ± .4
Body mass index (kg/m ²)	25.7 ± .3	25.3 ± 0.3	25.4 ± .3	25.6 ± .3
Waist-to-hip ratio	0.89 ± 0.01 ^a	0.80 ± 0.01 ^a	0.89 ± .01	0.89 ± .01
Serum FSH (miu/mL)	7.1 ± .25 ^b	7.5 ± 0.2 ^b	6.3 ± .2	6.3 ± 0.2
Serum LH (miu/mL)	15.4 ± 1.09 ^c	12.9 ± 1.0 ^c	13 ± .7	13.2 ± 0.8
Fasting serum insulin (µu/dL)	17.8 ± 1.0 ^d	13.2 ± 0.43 ^d	17.3 ± 1.04	18.1 ± 0.9 ^d
Fasting serum glucose (mg/dL)	96.8 ± 0.5	96 ± 0.6	96.9 ± .8	98 ± 0.3
Serum progesterone (ng/mL)	0.7 ± .02	0.7 ± 0.2	0.6 ± 0.3	0.61 ± .03
Serum estradiol (pg/mL)	44.1 ± 1.2 ^e	52.1 ± 1.0 ^c	55.8 ± 1.5	52.4 ± 1.2
Serum testosterone (ng/dL)	62.3 ± 1.2 ^f	52.3 ± 0.4 ^f	62.8 ± 1.02	63 ± 1 ^f
Serum DHEAS (ug/dL)	197 ± 3.4	184.1 ± 5.8	212 ± 3.5	207 ± 2.4
Serum androstenedione (ng/dL)	213 ± 2.4 ^g	198.2 ± 2.7	211 ± 5.6	213 ± 1.7 ^g

All values are means ± SE. a – P<0.001; b – P<0.001; c – P < 0.05; d – P<0.001; e – P = 0.241; f – P<0.05; g – P<0.001

Results

At entry into the study, the metformin and placebo groups did not differ with respect to history of CC treatment, anthropometric variables and biochemical values (Table 1).

After 3 months of treatment with either metformin or placebo there was a small but significant decrease in the waist-to-hip ratio (0.89 ± 0.01 , $P<0.001$) in the metformin group, but not in the placebo group. There was no change in the BMI or glucose concentration during fasting; but fasting serum insulin levels decreased significantly in the group treated with metformin (17.8 ± 1 vs 13.2 ± 0.43 µu/mL, $P<0.001$). Serum testosterone, serum androstenedione and serum LH fell

significantly and serum FSH increased significantly in the group treated with metformin, while there was no change in the placebo group (Table 1).

In the metformin group at the end of 3 months of treatment ovulation rate was 33.3% and pregnancy rate 16.7% whereas in the placebo group only 5.5% women ovulated and conceived. These differences were, however, not statistically significant (Table 2).

Twelve women in the metformin group and 17 in the placebo group, who were anovulatory at the end of 3 months, continued into the second phase of the study, during which they received concurrent CC treatment. 83.3% women

Table 2. Ovulation and pregnancy rates.

	Metformin n=18	Metformin clomiphene citrate n=12	Total n=18	Placebo n=18	Placebo - clomiphene citrate n=17	Total n=18
Ovulation rate	6 (33.3%)	10 (83.3%) ^a	16 (88.9%)	1 (5.5%)	2 (11.8%)	3 (16.7%)
Pregnancy rate	3 (16.7%)	7 (58.3%) ^b	10 (55.5%)	1 (5.5%)	1 (5.9%)	2 (11.1%)

^a and ^b P < 0.001

ovulated in the metformin-clomiphene group and 58.3% conceived, whereas 11.8% in the placebo-clomiphene group ovulated and 5.9% conceived. These differences in the ovulation and pregnancy rates were statistically significant (P<0.001). Overall, ovulation rate was 88.9% and pregnancy rate 55.5% in the metformin-clomiphene group, compared to 16.7% and 11.1% respectively in the placebo-clomiphene group. These differences were statistically significant (P<0.001).

At the end of 3 months of metformin therapy, 33.3% women had resumed cyclical menses, and at the end of 6 months of combined metformin-clomiphene therapy 61.1% had resumed cyclical menses. Four patients (22.2%) had gastrointestinal side effects and the dose of metformin had to be decreased to 500 mg twice daily. No serious side effects were observed with metformin and no patient discontinued therapy.

Discussion

Insulin stimulates androgen synthesis in the ovary⁵ and inhibits serum hormone binding globulin (SHBG) synthesis in the liver⁶, resulting in increased levels of free androgens along with increased intraovarian androgen production. These in turn lead to altered gonadotropin secretion and impaired folliculogenesis with resultant anovulation and infertility. Though CC is the drug of choice for anovulation hyperinsulinemia and obesity have been associated with CC resistance⁷.

Several studies have shown metformin to have beneficial effects on ovarian function and hormonal profile and it is a less expensive drug. Moghetti et al⁸ have reported improved menstrual function, insulin levels, and insulin sensitivity in anovulatory PCOS women in a placebo-controlled, randomized trial. The improved insulin levels were associated with variable changes in testosterone, SHBG and BMI. Ehrmann et al⁹ have reported no significant change in hormonal levels with metformin therapy.

We found that treatment with metformin but not placebo

significantly improved ovarian function. No change was observed in the BMI, though waist-to-hip ratio decreased in a small, but significant way in the metformin clomiphene group and 33.3% women resumed regular menstrual cycles. Metformin also decreased levels of androgenic hormones and fasting insulin significantly. These findings support the idea that hyperinsulinemia impedes ovulation and by decreasing insulin secretion, metformin facilitates not only spontaneous ovulation, but also ovulation induction by CC.

Pregnancy rate in the metformin-clomiphene group was 55.5%, significantly higher than 11.1% in placebo-clomiphene group. Vandermolen et al¹⁰ have reported similar rates whereas Heard et al¹¹ have reported lower rates of conception.

The duration of pretreatment with metformin has varied in different studies^{12,13}. We chose to give metformin for 3 months and found that 33.3% had resumed cyclical menses and at the end of 6 months of combined metformin-clomiphene this figure increased to 61.1%. Therefore, metformin pretreatment should be given for at least 3 months.

Metformin is classified as a category B drug, with no teratogenic effects in vitro and is a good option in developing countries where costlier gonadotropins are not affordable.

Conclusion

In a high percentage of clomiphene resistant patients with PCOS treatment with metformin is followed by regularization of menstrual cycles, reduction in hyperandrogenism, and improvement in rates of ovulation and conception.

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