

Effects of Metformin on Ovulation and Pregnancy Rate in Women with Clomiphene Resistant Poly Cystic Ovary Syndrome

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Abstract

Background: To evaluate the effect of metformin on ovulation and pregnancy rate in clomiphene citrate resistant women with polycystic ovary syndrome (PCOS).

Material & Methods: In this clinical trial each patient, regarding her previous resistance to Clomiphene, served as her own control. A total of 35 clomiphene citrate resistant PCOS patients, referring to Royan institute were studied. Clomiphene citrate resistance was defined as having failure of ovulation during at least three cycles using clomiphene citrate doses up to 200 mg/day on cycle days 3-7 after a withdrawal bleeding with progesterone. Metformin was used alone or in combination with clomiphene citrate. First, the patients received metformin up to 1500 mg/day for 8 weeks. During the next 2-3 cycle if the patients did not become pregnant, clomiphene was added with increments of 100 mg (up to 150 mg/day). Follicular development and ovulation were monitored by ultrasound scans and mid-luteal progesterone level. Menstrual pattern, ovulation, and pregnancy rate were evaluated during the two stages of treatment.

Results: After 8 weeks of metformin monotherapy, ovulation occurred in 23 cases (65.7%) and 7 patients (20%) became pregnant. Among other patients (28/35) who were treated with Clomiphene Citrate and metformin for 64 cycles, 19 patients (67.8%) had proper ovulation and five of them (17.8%) became pregnant. Totally, metformin induced ovulation in 31 of 35 patients (88.6%) and twelve (34.3%) of them achieved pregnancy.

Conclusion: Metformin alone or in combination with clomiphene is a very effective treatment in inducing ovulation and pregnancy in clomiphene resistant women with PCOS.

Keywords: PCOS, Clomiphene Citrate Resistant, Metformin, Ovulation

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common disorders, affecting approximately 5-10% of pre-menstrual women (1, 2). It is a syndrome with unknown etiology characterized by hyperandrogenism and chronic anovulation (2, 3). However, PCOS includes a wide spectrum of signs and symptoms (obesity, polycystic ovary), pathology, and laboratory findings.

Recent studies have shown that women with PCOS are frequently insulin resistant and at increased risk of developing glucose intolerance or non insulin-dependant diabetes mellitus (NIDDM) in the third and fourth decades of their life (2, 4).

The anti-estrogen clomiphene citrate (CC) is widely accepted as a first line medication for

ovulation induction in PCOS, but unfortunately 10-20% of the women are clomiphene resistant with no response to the drug (5, 6).

For CC resistant patients with PCOS, treatment with injectable gonadotropin is the usual modality for ovulation induction. However, these agents carry the risk of serious complications such as multiple pregnancy and ovarian hyperstimulation syndrome (7, 8).

Some studies have reported that hyperinsulinemia is the main cause of clomiphene resistance in PCOS patients (9-12). Hyperinsulinemia appears to lead to hyper production of ovarian androgens and to an increase in serum free-testosterone concentration and peripheral androgen action by decreasing the serum sex-hormone-binding-globulin concentration (SHBG) (9-12).

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Several insulin-sensitizing agents have shown to improve insulin resistance and therefore, reduce circulating insulin levels in women with PCOS (13). Among these, metformin chloride, an oral biguanide for type 2 diabetes mellitus, is a safe and effective drug that is recently used for the treatment of PCOS patients (12-15). The administration of metformin improves clinical and biochemical features of PCOS and induces ovulation cycles in anovulatory CC-resistant or nonresistant patients with PCOS (16-18).

This study was conducted to examine the effects of metformin on ovulation and pregnancy rate in women with clomiphene resistant PCOS.

Material and Methods

This clinical trial study was conducted on 35 infertile patients with clomiphene resistant PCOS referring to Royan Institute (Infertility research center) from November 1999 up to November 2000.

The patients were healthy infertile women aged 20-35 years, with oligomenorrhea (interval between menstrual periods from 35 days to 6 months), normal serum FSH level (1-10 IU/L), and spontaneous menses or positive progesterone-induced withdrawal bleeding (19,20). All patients with hyperprolactinemia, diabetes and thyroid disorders were excluded. Male factor and tubal-uterine factor infertility were excluded with semen analysis and hysterosalpingography.

The criteria for PCOS were chronic anovulation with hirsutism, and/or hyperandrogenaemia (NIH consensus criteria) (20).

Clomiphene citrate resistance was defined as having failure of ovulation during at least three cycles using clomiphene citrate doses up to 200 mg/day on cycle days 3-7 after a withdrawal

bleeding with progesterone.

Body weight and waist/hip ratio was checked before and during treatment cycles. Also FBS, OGTT, Fasting insulin, FSH, LH, and total testosterone were measured on cycle day 3 before and after treatment.

First, the patients received metformin (metformin hydrochloride, Tab; 500mg, Pars minoo Co.) alone, 1500 mg/day for 8 weeks. During the next 2-3 cycles, clomiphene was added with increments of 100 mg (up to 150 mg/day) if the patients did not have successful pregnancy. Follicular development was monitored by transvaginal ultrasound scans [Aloka 1000, 7.5 M.H.Z, Probe] and when dominant follicles (≥ 18 mm), were seen, HCG 10,000 IU was injected intra muscularly. Ovulation was determined by mid-luteal serum progesterone level (≥ 5 ng/ml). To confirm pregnancy β HCG test was done twice (12 and 14 days after HCG injection). Menstrual pattern, ovulation, and pregnancy rate were evaluated during the two stages of treatment. Data analysis was performed by SPSS software utilizing student t-test (or Mann Whitney test if needing non parametric analysis), Levin test, χ^2 , and logistic regression. P value ≤ 0.05 was considered as statistically significant.

Results

Demographic and laboratory results of the patients are summarized in table 1.

Mean (\pm SD) age, duration of infertility, and BMI were similar in ovulatory and non-ovulatory patients using students t-test ($p > 0.05$). There were no statistically significant changes in LH and total testosterone levels before and after treatment. A significant decrease in mean serum insulin level was detected after 8 weeks of Metformin treatment ($p \leq 0.05$).

Table 1: Demographic, anthropometrics and laboratory findings of the studied patients

	Age (Year)	BMI Before Treatment (kg/m ²)	Insulin level Before Treatment (mIU/ml)	Insulin level After Treatment (mIU/ml)	LH level Before Treatment (mIU/ml)	LH level After Treatment (mIU/ml)	Total Testosterone Before treatment (ng/ml)	Total Testosterone After treatment (ng/ml)
Mean \pm SD	25.8 \pm 4.06	29.89 \pm 5.17	19.20 \pm 7.55	16.18 \pm 7.97	9.78 \pm 8.65	8.1 \pm 6.45	1.3 \pm 1.11	0.98 \pm 0.3
Range	21-36	23-42.35	3.5-34.5	4.4-38	0.7-24.8	0.8-28.6	0.1-2	0.04 – 0.8

Table 2: Ovulation and pregnancy rates of each phase of treatment

Type of treatment	Total Cycles No.	Cycles With Ovulation No (%)	Cycles With Pregnancy No.(%)
Metformin Alone	66	39(59.1%)	7(10.6%)
Metformin+CC 100+150mg	64	44(68.8%)	5(7.8%)
Total	130	83(63.8%)	12(9.2%)

CC=Clomiphene Citrate

Table 3: Number of patients who ovulated and conceived with different treatment conditions

Type of treatment	No of patients	Cycles with ovulation no.(%)	Cycles with ovulation no.(%)
Metformin alone	35	23(65.7%)	7(20%)
Metformin +CC (100-150g)	28	19(67.8%)	5(17.8%)

CC=Clomiphene Citrate

Table 2 demonstrates a summary of treatment cycles with Metformin monotherapy and Metformin in combination with Clomiphene Citrate. Of 66 treatment cycles with Metformin alone, ovulation was documented in 39 cycles (59.1%) and pregnancy occurred in seven cycles (10.6%). Of 64 treatment cycles with Metformin and Clomiphene Citrate (100-150 mg), ovulation was recorded in 44 cycles (68.8%) and pregnancy occurred in five cycles (7.6%). Table 3 shows the number of patients who ovulated and conceived with different treatment. Totally, Metformin induced ovulation in 31 of 35 patients (88.6%) and twelve (9.2%) of them achieved pregnancy.

Discussion

For many years, it was suggested that a correlation exists between, insulin resistance and PCOS (9-12).

Several studies have demonstrated the effect of an insulin sensitizing agent like metformin and troglitazone on PCOS patients. These agents have been reported to result in restoration of menstrual cycle, ovulation, and pregnancy (21). Several reports on treatment with insulin sensitizing agents suggest that metformin reduces LH/FSH, LH, free testosterone, and increases SHBG (22-25).

We observed a high ovulation rate (88.6%) in a series of 35 patients. In most of the patients ovulation was achieved with metformin alone or in combination with low dose (100-150mg) clomiphene citrate. Metformin has been used in many recent studies. For example Nestler et al (21) reported 90% ovulation rate with metformin alone or metformin plus 50 mg/day clomiphene citrate.

In two studies, conducted by Acbay et al and Eframann et al high dose of metformin (850 mg-twice or three times a day) was administered and no significant change was observed (26-27).

However our patients represent a more resistant population of PCOS with previous failure of ovulation with CC.

In another study, Mitwally et al evaluated the effect of troglitazone on Clomiphene citrate resistant PCOS women and reported 83% ovulation and 30% pregnancy (28). Comparison of our results with the Mitwally study showed no statistically significant difference (88.5% ovulation and 34.2% pregnancy). But in some patients troglitazone leads to hepatic toxicity and liver function tests during treatment is required. Therefore, it seems that metformin offers the best therapeutic option in CC-resistant PCOS women.

In this study, serum insulin level showed a significant reduction after 8-weeks of treatment. This fact supports the hypothesis suggested by Velasques et al (24).

However we observed no significant reduction in BMI after treatment and therefore BMI has no effect on metformin response (p=0.1).

It is well documented that metformin reduces serum insulin level and results in ovulation (24).

Regarding the fact that the number of CC resistant PCOS patients are considerable and that usual treatments are expensive and have more serious documented complications, we highly suggest metformin alone or in combination with CC as a new therapeutic option.

Conclusion

In our study metformin was considered a very effective drug in restoration of normal menstrual cycle, ovulation, and pregnancy in CC-resistant PCOS patients and it remarkably reduced serum insulin level. Also BMI and LH level had no significant effect on response to metformin.

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