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Metformin as an Adjuvant Therapy with Clomiphene Citrate for Ovulation Induction in Clomiphene Citrate Resistant PCOS Patients

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ABSTRACT

Objective: *The aim of the study was to identify whether metformin pretreatment and co-administration increases the ovulation and pregnancy rate in response to clomiphene citrate (cc) in women who are resistant to clomiphene alone.*

Methods: *This prospective study was conducted in a private tertiary infertility care center during the period between June 2002 and November 2003. Thirty two anovulatory women with polycystic ovarian syndrome who were resistant to clomiphene citrate were subjected to this investigation. Patients who did not response to 150 mg CC daily for 5 days in at least two consecutive cycles were declared as CC resistant. The non obese (BMI <30) participants received metformin 500mg thrice daily with meal and obese (BMI >30) participants received 850mg twice daily for a period of 6 months. For first 6 weeks only metformin was given to determine resumption of menstruation. Women who resumed menstruation spontaneously within this period were administed with CC at a lower dose (100 mg daily for 5 days). This dosage was increased if necessary in subsequent cycle by 50 mg up to 150 mg daily. For the other patients, CC was started after progesterone withdrawal bleeding. Ovulation was documented by serial transvaginal ultrasonograpy and D_{21} serum progesterone. Patients who developed follicle ≥18 mm received injection HCG 10,000 IU intramuscularly. Treatment was terminated when patients achieved pregnancy, completed six ovulatory cycles or on completion of 6 months metformin therapy. The main outcome measures observed were ovulation and pregnancy rates.*

Results: *Following the completion of 6 months trial 20/32 (62.5%) patients ovulated using CC at 100-150 mg daily dose. Seventy percent (14/20) of patients ovulated and in the whole study population, l4/32 (43.75%) achieved pregnancy. One patient aborted at 7 weeks and she conceived again 3 months after abortion. One patient conceived only afler taking metformin and two from the ovulating group conceived spontaneously afler completion of six months of therapy.*

Conclusion: *In CC resistant PCOS women metformin use improved menstrual cyclicity, ovulation and pregnancy rate in a significant number of such women.*

Key words: PCOS, CC Resistant, Metformin

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INTRODUCTION

Anovulation is the most common cause of female infertility and it comprises 40% of female causes. Polycystic ovarian syndrome (PCOS) is the most common hormonal disorder in women of reproductive age and about 80% of all causes of anovulatory infertility is attributed to PCOS. It is characterized by irregular or absent menstruation, obesity, excess hair growth and infertility. When patients are diagnosed with anovulatory infertility, induction of ovulation is first line of treatment. In these women clomiphene citrate (CC) remains the primary therapy to induce ovulation. Approximately 75% of patients ovulate in response to CC treatment [1] and 70% of them respond at a dose of 50-100 mg/day [2]. Although the maximum dose of CC is usually 250 mg/d, most of the infertility specialists consider patients who do not ovulate while receiving the 150 mg dose of CC to be resistant to the drug [3]. An alternative ovulation-inducing agent for these CC resistant patients is gonadotropin injections. Laparoscopic ovarian drilling is another option to increase the sensitivity of the ovaries to any ovulation inducing agents. Gonadotropins are expensive and there is risk of hyperstimulation and multiple pregnancy in comparison to CC. On the other hand laparoscopic ovarian drilling is an invasive procedure and effects revert after a few months. In this regard, relatively inexpensive and non-invasive option should be made available for CC resistant patients.

Insulin resistance is the pivotal defect in PCOS and the women have compensatory hyperinsulinemia [4-8]. Hyperinsulinemia plays a pathologic role in PCOS and appears to contribute to both chronic anovulation [9-16] and hyperandrogenism [15-18]. Evidence suggests that this elevated insulin level directly stimulates the ovary to produce excess androgens [l9,20]. Since both obese and lean women with PCOS have insulin resistance and from the clinical point of view it is safe and reasonable to regard all women with PCOS as being insulin resistant [19,21]. Metformin reduces insulin resistance in PCOS patients by various mechanisms and they increase menstrual cyclicity, improves spontaneous ovulation and promote fertility [3,9,1 1,14-16, 23-30].

The purpose of this study was to investigate whether in CC resistant PCOS patients the use of metformin in addition to CC treatment would improve the rates of ovulation and pregnancy.

Materials and methods

This study was conducted in a private setting between June 2002 and November 2003. We decided to enroll the patients of age 18-35 years with the primary cause of infertility being anovulation due to PCOS. We recruited women with PCOS who did not produce any mature follicle in response to 150 mg CC per day for a course of 5 days at least for two consecutive cycles. These patients were referred to in this study as clomiphene resistant. PCOS was diagnosed by history of oligomenorrhoea (6-7 cycles per year), hirsutism, obesity, ultrasonographic polycystic ovaries, and day 3 altered FSH:LH ratio.

We excluded all other hormonal factors, which might be the cause of infertility. Other infertility factors for both partners also were excluded. Hysterosalpingogram was limited only to secondary infertility and for patients with a history of pelvic infection and pelvic surgery. In other cases it was performed after failure of three ovulatory cycles. We did not explore insulin resistance as PCOS patients both lean and obese were confirmed having with intrinsic insulin resistance [19,31] and patients with PCOS may benefit from the insulin sensitizer.

PROTOCOL

The patients were divided in two groups for dose scheduling according to BMI. Those patients' BMI < 30 were given metformin 500 mg three times daily and those BMI was >30 were given 850 mg two times daily. All obese patients were counseled for weight loss by exercise and dieting. In both groups metformin was scheduled for a period of 6 months. In first 6 weeks we gave metformin alone to improve ovarian sensitivity and awaited for spontaneous menstruation within 6 weeks. Women who did not establish menstruation spontaneously were given progesterone for withdrawal bleeding. After resumption of menstruation either spontaneously or after progesterone withdrawal we started CC with a lower dose (100mg daily) in first cycle. The dose was further increased to 150 mg daily if there was no response to previous dose. Ovulation was documented by serial transvaginal sonography from, D_{12}. to D_{16} as necessary. Observations recorded were the number and size of follicles and sign of impending ovulation. Follicles were considered as mature when average measurement of inner two diameters of each follicle was ≥18mm. Ovulation was triggered by injecting hCG 10,000 IU intramuscularly when at least one follicle achieved maturity. Observing the disappearance or collapsing of the previous follicles and collection of fluid in POD ascertained signs of ovulation. A D_{21} serum progesterone measurement supplemented this finding and a level of ≥4ng/ml was considered as ovulatory. Patients were counseled for timed sexual intercourse after giving hCG. A pregnancy test was done after 7 days of missing the period and if it was positive pregnancy was diagnosed by ultrasonography on the 15th day. Metformin was

discontinued thereafter. In other cases this protocol was discontinued after completion of 6 months, or after failure of ovulation using CC at 150mg/day for two consecutive cycles or after failure of pregnancy after 6 ovulatory cycles. Regular menstruation and spontaneous pregnancy after 6 months of metformin was considered as the result of this therapy. The patients who did not achieve pregnancy were given other options of fertility treatment.

RESULTS

Thirty-two CC resistant PCOS patients were evaluated in this study and the baseline characteristics of the patients are given in Table 1. With the exception of one woman, all patients presented with primary subfertility. The patients were in the age range of 20-34 years with a duration of infertility from 1-12 years. Serum FSH value was 2-5 mIU/ml with a mean value 4.42 mIU/ml and serum LH value was 3.1-39.1 mIU/ml with a mean value 14.7 mIU/ml. The ratio of LH:FSH was 3.32. Twenty of the 32 patients (62.5%) ovulated in response to metformin and CC. Fourteen among 20 ovulatory women (70%) conceived Table 2. Ovulatory responses and pregnancy outcome was shown in Table 3. Among the 20 patients, 9 ovulated when given a dose of 100 mg CC per day and 10 ovulated at the dose of 150 mg per day. One patient ovulated and conceived after treatment with metformin only. During this observation period 72 ovulatory cycles occurred among the 20 ovulating women. In two cases, the patients stopped taking CC after completion of 6 ovulatory cycles and they conceived spontaneously in next cycle. One patient aborted at 7 weeks of pregnancy and again conceived 3 months after abortion folowing the same treatment regime.

DISCUSSION

In insulin resistance body's insulin is unable to perform its job effectively and induces high androgen production in both the ovary [32] and the adrenal [33]. As the researchers strongly suggest that insulin resistance is a important metabolic disturbance in PCOS, we would expect the drugs that reverse insulin resistance to reverse hyperandrogenism, restore normal menses and help eliminate the infertility associated with PCOS. At the top of the drug is metformin, which reduces insulin resistance of peripheral tissue without causing hypoglycemia [34].

We sought to test the hypothesis that metformin administration would restore responsiveness to CC in women with CC resistant PCOS. In this study we found after administration of metformin 62.5% patients ovulated in response to CC by which they did not ovulate beforehand. Among them 9/20 (45%) ovulated at a lower dose than before and 10/20 (50%) ovulated at the same dose of CC which was given before administration of metformin. One patient ovulated and got pregnant with metformin alone. She waited for spontaneous menstruation then took progesterone for withdrawal bleeding. Without having withdrawal bleeding she came for next suggestion and by ultrasonography she was detected 7 weeks pregnant 3 months after starting of metformin. Among ovulated women 14/20 (700/O) women became pregnant.

Different randomized and double blind study showed that addition of metformin with CC increased the rate of ovulation and pregnancy in CC resistant PCOS patients [3,33]. But the same was not true for another investigator who failed to show the benefits of metformin along with CC in CC resistant PCOS [34]. Another three studies also failed to show any improvement in reducing hyperinsulinaemia and hyperandrogenism with metformin in markedly obese (35-39 kg/m^2) and suggested that drug will not benefit PCOS patient suffering from morbid obesity [35-37]. So weight reduction by exercise and dieting should be the prerequisite for treatment in these cases. In our study maximum BMI was 34 and that patient did not ovulate in response to metformin 850 mg twice daily along with CC 150 mg/day for two cycles. We did not look for hormonal and BMI response to treatment in this study since the main outcome measure was ovulation and pregnancy.

Researchers showed that metformin alone significantly improved the hormonal milieu and menstrual cyclicity and 3/26 (11.54%) became pregnant [22]. After 5 weeks treatment of metformin 34% patients ovulated and ovulatory rate was increased to 90% after addition of CC [15]. So for fertility treatment metformin alone is not effective but it increased sensitivity of ovaries to CC and gonadotropins also. It reduces the chances of ovarian hyperstimulation syndrome in gonadotropin stimulated cycles [10]. Women with PCOS are at increased risk of miscarriage. First trimester pregnancy loss in PCOS patients is reported to be 30% to 50% in comparison to 10%-15% in normal population [10,34,35]. Hyperinsulinaemia is considered a risk factor for early pregnancy loss. Insulin increases the plasminogen activator inhibitor (PAI), which causes placental insufficiency and miscarriage. Metformin reduces PAI activity and rate of spontaneous abortion [22,38,39]. In our study one patient aborted at 7 weeks of pregnancy and again became pregnant 3 months after abortion with the same treatment. We did not continue metformin beyond viability test (She came during 8 weeks).

It is noteworthy that insulin resistance with resultant

hyperinsulinaemia is a prominent feature of PCOS, and it is seen both in obese and normal weight women [4, 20]. Moreover, obese women develop a greater degree of insulin resistance as their body mass increase [40].

Hyperinsulinaernia plays a key role in development of ovarian hyperandrogenism[41,42]. Insulin stimulates androgen synthesis in the ovary and inhibits SHBG synthesis in the liver [43 44], with the result being an increased bioavailability of free androgens. This increased intra-ovarian androgen production leads to altered gonadotrophin secretion and impaired folliculogenesis [45], and these women present with anovulation and infertility. Ovulation induction with clomiphene citrate is the treatment of choice, though about 20% of these women do not respond. Obesity and hyperinsulinaemia are well correlated with clomiphene citrate resistance [46].

Although as indicated, ovulation induction with gonadotrophins is the standard treatment for clomiphene-resistant women. This approach is associated with complications and has the added disadvantage of high cost and need for careful monitoring. Hence, there is a clear need for an alternative, less expensive therapy.

In this regard metformin has been shown to have beneficial effects on ovarian function and hormonal milieu. In an uncontrolled study PCOS women were treated with metformin and showed improved menstrual cycles and hormonal parameters[22]. Subsequently, other studies using metformin in PCOS women have show improved clinical parameters and variable changes in hormonal levels. Placebo-controlled, randomized trials with metformin have shown improved menstrual function[15,46], and improved insulin levels and insulin sensitivity in anovulatory PCOS women[47,48]. The improved insulin levels were associated with variable changes in testosterone, SHBG and BMI[49,50]. Two studies reported no significant change in hormonal levels with metformin therapy[36,37].

Two randomized, placebo-controlled trials in clomiphene-resistant women showed improved ovulatory rates with sequential therapy of metformin and clomiphene citrate [3, 51]. However, another study in a similar group of women could not demonstrate better ovulatory rates in spite of improved hormonal levels [34].

In the present study, metformin pre-treatment followed by clomiphene citrate has indicated a beneficial effect in our series of women with PCOS. It is preferable but clinically difficult to select only those women who are insulin-resistant, as there is no ideal screening test to detect insulin sensitivity. Use of the euglycaemic clamp is possible only in a research setting, and the insulin tolerance test is also difficult to conduct in clinical practice. A single fasting insulin level is unreliable, and monitoring the fasting glucose to insulin ratio is useful mainly in obese women[52]. Consequently, all clomiphene resistant, women were included in these investigation. Metformin is considered a category B drug, which means that sufficient human data are available. Mouse embryos exposed to metformin have shown no major malformations in the offspring[53]. Although metformin had been used by some clinicians to determine whether metformin-therapy reduced development of gestational diabetes in women with POCS [54] or to treat diabetes [55] in a small number of women throughout their pregnancies, no adverse effects were observed in their infants. There are at present no adequate and well-controlled studies on its use in pregnant women. For this reason, we discontinued the administration of metformin on the day of hCG injection.

The predictors of success of metformin have not been established, although there is some evidence that patients who are substantially overweight do not respond as well. Side effects to metformin include nausea, vomiting, diarrhea and other forms of gastrointestinal intolerance. Serious side effects such as lactic acidosis are rarely seen in younger patients, but patients should be warned about the interaction between metformin and alcohol. Metformin and lifestyle modification seem to work effectively together and the addition of clomiphene citrate to metformin also appears to be more effective than clomiphene alone [26, 25].

What is the most effective therapy for an anovulatory patient with PCOS who wishes to become pregnant? It is clear that lifestyle modification with caloric restriction and execise is extremely important in the first stage of any intervention. This should be considered active medical therapy and not as an alternative to other medical intervention. Once the patient has establislled adequate lifestyle change, ovulation will either occur spontaneously with subsequent pregnancy or additional intervention will be required. Clomiphene citrate is still considered to be a cheap, safe, and easy alternative and would probably be considered thefirst-line therapy for anovulatory PCOS.

In summary findings of different studies suggest that metformin restores responsiveness to CC in PCOS patients who had remained anovulatory despite maximum dose of CC. It increased the rate of ovulation and pregnancy in CC resistant PCOS patients. We also found that patients who did not ovulate at a maximum dose of CC became

responsive to either the same dose or to a lower dose after treatment with metformin. Thus our results provide a rationale for a combination of metformin and CC treatment for PCOS patients resistant to CC.

Patients who do not respond to this regime can proceed to ovulation induction with the more expensive gonadotrophins as well as ovarian drilling.

Table 1 Characteristics of CC resistant anovulatory women

Characteristics	Range	Mean	SD
Age (Years)	20-34	24.66	2.54
BMI	22-34	25 87	3.45
Duration of marriage	1.5-12	4.78	3.47
Duration of infertility	1-12	3.44	3.38
Serum FSH (mlU/ml)	2-5	4.42	1.23
Serum LH (mlU/ml)	3.1-39.13	14.68	9.52

Table 2 Ovulatory and pregnancy outcomes in response to CC

Outcome	Number	Percentage
No of women who ovulated	20	62.5
No of women who conceived in all groups	14	43.8
No of women who conceived among ovulated women	14	70

Table 3 Ovulatory response to treatment with metformin and CC

No of patients	Ovulatory cycles		Pregnancy
	100mg CC	150mg CC	
9	2-6	X	3 in 2nd cycle 2 in 3rd cycle 1 in 4th cycle 1 after 6 ovulatory cycles
10	X	2-6	3 in 2nd cycle 2 in 3rd cycle 1 after 6 ovulatory cycles
1	X	X	Only with metformin (after 5 weeks)

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