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High ovulatory rates with use of troglitazone in clomiphene-resistant women with polycystic ovary syndrome

M.F.M.Mitwally, N.K.Kuscu and T.M.Yalcinkaya[1]

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, School of Medicine, West Virginia University Health Sciences Center, 830 Pennsylvania Avenue, Suite 304, Charleston, WV 25302, USA

[1]To whom correspondence should be addressed

This preliminary report reviews our experience with 18 infertile patients with clomiphene-resistant polycystic ovary syndrome (PCOS). In the first treatment cycle, troglitazone was administered alone. During cycles 2–5, clomiphene was added with increments of 50 mg (up to 200 mg/day) if the previous cycle was anovulatory. Basal body temperature charts and serum progesterone were obtained to confirm ovulation. In a total of 66 treatment cycles, ovulation occurred in 44 (67%) and pregnancy in seven (11%). There were no significant changes in body weight, waist:hip ratio or liver enzymes during treatment. Troglitazone, alone or with clomiphene, induced ovulation in 15 of 18 patients (83%) and seven (39%) of them achieved pregnancy. This is the first report on ovulatory rates in clomiphene-resistant women with PCOS when troglitazone was used alone or with clomiphene. Recently, metformin and clomiphene were successfully used in women with PCOS. However, our patients represent a more resistant population of women with PCOS, with each patient serving as her own historical control by previous resistance to clomiphene. Although the pregnancy rate (39%) was promising for clomiphene-resistant women with polycystic ovary syndrome, it does not seem to have a definite advantage over gonadotrophins.
Key words: clomiphene-resistant/ovulatory rate/polycystic ovary syndrome/troglitazone

Introduction

Polycystic ovary syndrome (PCOS) is thought to be the most common cause of anovulatory infertility and menstrual irregularities in women of reproductive age (Shoham and Weissman, 1998); it affects ~6% of these women (Franks, 1995). Clinically, PCOS manifests itself as hirsutism, oligomenorrhoea and anovulatory infertility. The anti-oestrogen clomiphene citrate (CC) is widely accepted as a first line drug for ovulation induction in PCOS. Some 50–80% of anovulatory patients ovulate and 40–50% conceive on CC at doses of 50–200 mg/day (Shepard *et al.*, 1979; Lobo *et al.*, 1982). However, in spite of administering high doses of CC, some patients may fail to ovulate; thus they are considered CC resistant.

For CC-resistant patients with PCOS, treatment with injectable gonadotrophins is the usual modality for ovulation induction. Such treatment can achieve ovulation in nearly all cases and a pregnancy rate of 40–70% (Dor *et al.*, 1980; March, 1987; Fluker *et al.*, 1994). However, these agents are expensive and carry the risk of serious complications such as multiple pregnancy and ovarian hyperstimulation syndrome, and require careful monitoring of the treatment using serum oestradiol measurements and/or transvaginal sonography.

Troglitazone is a new oral insulin-sensitizing agent that improves oral glucose tolerance and insulin resistance in individuals with impaired glucose tolerance. More recently, troglitazone was shown to increase total body insulin action and cause a concomitant trend towards normalization of steroidogenesis and sex hormone binding globulin in PCOS (Dunaif *et al.*, 1996; Ehrmann *et al.*, 1997a).

Because of the association of insulin resistance and hyperinsulinaemia with PCOS (Burghen *et al.*, 1980; Chang *et al.*, 1983; Espinosa de los Monteros *et al.*, 1995), insulin-sensitizing agents such as troglitazone and metformin have the potential as a useful primary treatment for women with PCOS (Ehrman *et al.*, 1997b). To date, studies of troglitazone use in PCOS women have reported only on improvements of hormonal and metabolic parameters. There are no published data on the ovulatory rates in women with PCOS using troglitazone (van Montraus *et al.*, 1998). Particularly, the utility of troglitazone in CC-resistant anovulation in PCOS has not been studied. At present, it is unknown whether treatments focusing on improving insulin sensitivity without weight loss will also improve the response to clomiphene-resistant women (Shoham and Weissman, 1998; van Montraus *et al.*, 1998).

The aim of this preliminary report is to review our experience in ovulation induction using troglitazone in PCOS women with CC-resistant anovulatory infertility.

Materials and methods

Patients

This study reviews our experience with 18 infertile patients with CC-resistant PCOS treated at an academic reproductive endocrinology and infertility clinic. Fifteen patients had primary infertility and three had secondary infertility. The duration of infertility was 5–8 years for patients with primary infertility and 3–7 years for patients with secondary infertility. Clomiphene citrate resistance was defined as failure to ovulate during a total of at least four cycles using doses of CC up to 200 mg/day on cycle days 3–7 after a withdrawal bleeding induced with medroxyprogesterone acetate (MPA), 10 mg daily for 10 days.

The diagnosis of PCOS was made according to NIH consensus criteria (Zawadzki and Dunaif, 1992): chronic anovulation with

Table I. Clinical and hormonal characteristics of patients (n = 18)

	Age (years)	BMI	W/H ratio	Insulin fasting (μU/ml)	Insulin 2 h (μU/ml)	DHEAS (ng/ml)	Total testosterone (ng/ml)
Mean ± SD	29 ± 4	36.31 ± 8.96	0.88 ± 0.05	31.9 ± 19	149.2 ± 115	1.82 ± 0.80	0.7 ± 0.31
Median	29	35	0.89	60	180	1.94	0.54
Range	23–39	17.5–57.7	0.82–0.93	13.7–60	50–361	0.68–2.81	0.42–1.36

BMI = body mass index; W/H = waist:hip; DHEAS = dehydroepiandrosterone sulphate.

hirsutism, and/or hyperandrogenaemia. Prolactin and thyroid disorders were excluded in all patients. All patients underwent basic metabolic screening with cholesterol profile and fasting and post-75 g Glucola glucose concentration. Male factor and tubal-uterine factor infertility were excluded with semen analyses and a hysterosalpingogram and/or laparoscopy.

Between May 1997 and May 1998, a total of 26 patients with CC-resistant PCOS were seen at our clinic. They were offered the options of ovulation induction with injectable gonadotrophins or with the aid of troglitazone. The 18 patients consenting for use of troglitazone were included in this report. All patients were Caucasian women; most of them stated to have Northern European ancestry. Body weight and waist:hip girth ratio were checked before and during treatment cycles.

Confirmation of ovulation

Basal body temperature charts (BBT) were kept by all patients and reviewed on day 28 of the cycle. Serum progesterone was measured on day 21–22 of treatment cycle and repeated if BBT showed a temperature rise later than day 21. A progesterone concentration ⩾5.0 ng/ml was considered as confirmatory of ovulation.

Troglitazone in ovulation induction

In the first treatment cycle, troglitazone (400 mg/day) was administered during days 1–28 of a spontaneous or induced menstrual cycle. Troglitazone was discontinued until a pregnancy was confirmed or excluded. During cycles 2–5, troglitazone was similarly administered; however, if the previous cycle was anovulatory, clomiphene citrate was added at 50 mg/day on days 3–7 after withdrawal bleeding induced with MPA. The clomiphene citrate was increased every cycle at increments of 50 mg/day (up to a maximum dose of 200 mg/day) until ovulation was achieved. Once ovulation was confirmed, the same treatment regimen was repeated until either a pregnancy occurred, or a maximum of six to seven troglitazone cycles was reached.

Liver function monitoring

After a change in the prescribing information for troglitazone in November 1997, liver function was assessed before starting troglitazone treatment and repeated every treatment cycle to detect any elevation of liver enzymes.

Results

The demographic, anthropometric and laboratory characteristics of the patients included in this review are shown in Table I. The insulin concentrations in the fasting state and during an oral glucose tolerance test were not routinely measured in these patients. There were no significant changes in body weight, or waist:hip ratio during treatment cycles (data not shown). Other parameters (dehydroepiandrosterone sulphate and total testosterone) were not reassessed during treatment. Troglitazone was well tolerated by the patients. Two patients discontinued their treatment after the first month of troglitazone for reasons not related to adverse drug effects. No liver enzyme elevation was observed during troglitazone treatment (data not shown).

Table II. Ovulation and pregnancy rates for each phase of treatment

	Total cycles No.	Cycles with ovulation No. (%)	Cycles with pregnancy No. (%)
Troglitazone alone	33	20 (61)	2 (6)
Troglitazone + CC 50 mg	16	11 (69)	1 (6)
Troglitazone + CC 100 mg	12	9 (75)	2 (17)
Troglitazone + CC 150 mg	4	2 (50)	1 (25)
Troglitazone + CC 200 mg	3	2 (67)	1 (33)
Total	68	44 (67)	7 (11)

CC = clomiphene citrate.

Table III. Number of patients who ovulated and conceived with different treatment conditions

Type of treatment	No. of patients	Cycles with ovulation No. (%)	Cycles with pregnancy No. (%)
Troglitazone alone	18	5 (28)	2 (11)
Troglitazone + CC 50 mg	11	6 (55)	1 (9)
Troglitazone + CC 100 mg	5	2 (40)	2 (40)
Troglitazone + CC 150 mg	3	1 (33)	1 (33)
Troglitazone + CC 200 mg	2	1 (50)	1 (50)
Total	18	15 (83)	7 (39)

CC = clomiphene citrate.

Table II shows a summary of treatment cycles for 18 patients. These patients were followed up for a total of 68 treatment cycles. Ovulation was documented in 44 cycles (65%) and pregnancy occurred in seven cycles (10%). The median serum progesterone concentration in the ovulatory cycles was 13.8 ng/ml (range: 5.7–27). Because of the decision to add CC to the treatment of patients who did not ovulate on one cycle of troglitazone, almost half of the treatment cycles (33 cycles) involved troglitazone alone, while CC was added in the other half of treatment cycles. CC 50 mg was used in 16 cycles, 100 mg in 12 cycles, 150 mg in four cycles and 200 mg in three cycles.

Table III shows number of patients who ovulated and conceived with different treatment conditions. Troglitazone, used alone or concomitantly with an appropriate dose of CC,

induced ovulation in 15 of 18 patients (83%) who had previously been resistant to a 200 mg dose of CC. Even though our patient population using troglitazone was small, addition of CC or stepwise increase in its dosage seemed to result in a 33–55% increment in the ovulation rate. During this limited period of treatment (three to four ovulatory cycles), seven of 18 (39%) patients achieved pregnancy. The frequency of conceptions was similarly distributed among different CC doses. Two patients have miscarried during the first trimester and the other five have delivered full-term healthy babies.

Discussion

This is the first report of ovulatory rates in CC-resistant women with PCOS when the insulin sensitizing agent troglitazone was used alone or in combination with CC. We observed a high ovulatory rate of 83% in a series of 18 patients. In most of the patients, ovulation was achieved with troglitazone alone or in combination with low doses (50–100 mg) of CC. Recently, another insulin-sensitizing agent, metformin, was used in 61 women with PCOS (Nestler *et al.*, 1998); 34 and 90% ovulatory rates were reported with metformin alone and metformin plus CC 50 mg respectively. However, our patients represent a more resistant population of PCOS by their previous failure to ovulate on CC.

Although we did not have any control groups receiving placebo or CC alone, each patient can serve as her own historical control by her previous resistance to 200 mg of CC. It is unlikely that troglitazone addition exerted a placebo effect in achieving such ovulatory rates. Cyclic use of MPA may have initiated some of the ovulatory cycles by modulating pituitary luteinizing hormone pulsatility (Homburg *et al.*, 1988; Berga and Yen, 1989); however, the lack of a similar ovulatory response to progestins prior to initiation of troglitazone in these women would make this an unlikely explanation.

In this clinical application of troglitazone to a group of CC-resistant women with PCOS, no tests of insulin sensitivity or serum levels were routinely performed before or during troglitazone administration. By their clinical diagnosis, all patients were presumed to have a certain degree of insulin resistance and were offered troglitazone. In fact, insulin resistance in PCOS appears to be heterogeneous among patients of different ethnicity (Dunaif *et al.*, 1993; Norman *et al.*, 1995), body mass index and body fat distribution (Holte *et al.*, 1994) and currently there are no sensitive tests to quantify it in the clinical setting. In our small series of CC-resistant patients, addition of CC or a stepwise increase in its dosage seemed to result in steady increments of 33–55% in the ovulatory rate, suggesting that an overall improvement of the underlying insulin resistance or other pathophysiological mechanism(s). This issue requires further studies of troglitazone with respect to its dose, effects on ovulatory response and metabolic and gonadotrophic parameters both in normo-ovulatory women and women with PCOS. Such studies may result in novel ovulation induction regimens and new dosages of thiazolidinediones for the treatment of PCOS.

In this small series, pregnancy occurred in 39% of patients. Accurate assessment of folliculogenesis and luteal phase adequacy was not attempted on our patients who did not conceive despite achieving levels of progesterone consistent with luteinization. Although promising for CC-resistant PCOS, the life-table analysis of pregnancy rates on such a regimen does not seem to have a definite advantage over those achieved by injectable gonadotrophins (Dor *et al.*, 1980; March, 1987; Fluker *et al.*, 1994). If supported by larger and randomized trials, this partial restoration of reproductive function would implicate other mechanisms, genetic and epigenetic, contributing to the pathophysiology of PCOS.

The safety of troglitazone use during pregnancy has not been determined, but it has been discussed (van Montfraus *et al.*, 1998) together with the risk of teratogenicity and hepatotoxicity (van Montfraus *et al.*, 1998). It is considered a category B drug by virtue of its lack of teratogenicity when used in pregnant rats during organogenesis. There are no adequate and controlled studies on its use in pregnant women. Since November 1997, there have been reports about liver toxicity associated with the use of troglitazone. It is recommended that troglitazone should not be started in patients with active liver disease and liver enzymes should be monitored during its use. If the concentration of ALT is >1.5 times the upper limit of normal, troglitazone should not be started. During troglitazone treatment, ALT should be monitored monthly for the first 8 months, every other month for the rest of the year and then periodically during treatment. If ALT level increased to 1.5–3 times the upper limit of normal, ALT level should be monitored weekly. If levels increase to a value more than three times the upper limit of normal, troglitazone should be discontinued (NIDDK News Briefs, 1998 and package insert for Rezulin).

In summary, we report high ovulatory response to troglitazone in infertile women with CC-resistant PCOS. Thus, as an insulin-sensitizing agent, troglitazone offers a new therapeutic option as well as an investigative tool into pathophysiology of PCOS. Nevertheless, more studies are needed about its safety and relative benefits over other treatment modalities for PCOS.

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