Combined oral clomiphene citrate with pioglitazone hydrochloride improves outcome of treatment of PCOS women: A comparative Study versus oral clomiphene citrate with metformine

Hesham Abou Ragab MD and Hany El-klaf MD

Department of Obstetrics & Gynecology, Faculty of Medicine, Benha University, Egypt
Abouragab@yahoo.com

Abstract: Objectives: To evaluate the ovulatory outcome of combined clomiphene citrate (CC) stimulation with pioglitazone hydrochloride (ACTOS) versus metformin treatment in conjunction with weight reduction dieting program. Patients & Methods: 80 polycystic ovary syndrome (PCOS) women diagnosed according to the Rotterdam criteria underwent transvaginal ultrasonography (TVU), anthropometric measurements and estimation of fasting blood glucose (FBG), plasma insulin (FPI) and insulin resistance (IR) was measured by homeostasis model assessment (HOMA) and hormonal profile. CC (50 mg twice daily) was given on Days 2–6 of a menstrual cycle in combination with either ACTOS (15 mg tablets once daily) or metformin (0.5 gm tablets trice daily). Estimated serum progesterone ≥25 nmol/l on Day 21 of the cycle indicates ovulation. The frequency of women got follicles >16 mm was considered as ovulation success rate. At the end of 3 months, HOMA-IR score was re-evaluated. Results: At the end of 3-months therapy, all women showed significant reduction of BMI and HOMA-IR scores compared to pre-treatment scores with non-significant difference between studied groups, but the percentage of change of HMOA-IR score was significantly higher with ACTOS compared to metformin. Ovulation was assured in 65 patients (81.3%); 36 patients (90%) received ACTOS and 29 patients (72.5%) received metformin with significant difference in favor of ACOTS. ROC curve analysis to predict the oncoming effect of insulin sensitizing drugs on ovulatory function defined the pre-treatment HOMA-IR score as a significant screening parameter. Conclusion, for PCOS women, combined CC and ACTOS therapy in association with weight reduction provides the best chance for getting regular ovulation with better biomilieu and promises for higher chances for getting pregnant.

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1. Introduction

The polycystic ovary syndrome (PCOS) which is one of the most common endocrinological disorders seen not only in women in reproductive age but also in female adolescents nowadays with incidence estimated at 5–10% and is associated with reproductive, metabolic and cardiovascular problems (Yii et al., 2009).

The PCOS is undoubtedly one of the most confusing diseases, probably due to various manifestations of the disorder and lack of uniformly accepted diagnostic criteria. Despite being heterogeneous in nature, the hallmarks of the disease are constant and involve chronic anovulation, hyper-androgenism, infertility, increased first trimester miscarriage rate, dyslipidemia and insulin resistance, all of which appear mainly in obese patients but may be also present in lean women (Benjamins and Barratt, 2009).

Three different diagnostic classifications have been proposed to define PCOS; the first one, published in 1990, known as the "NIH criteria" requires the simultaneous presence of hyperandrogenism and menstrual dysfunction in order to diagnose PCOS. Later on, in 2003, the presence of polycystic ovarian morphology detected by transvaginal ultrasonography was added to the previous criteria so as to include women with oligomenorrhea and PCO without hyper-androgenism or hyperandrogenism and PCO without menstrual dysfunction. Finally, the Androgen Excess Society, published in 2006 defined new diagnostic criteria which required the presence of clinical or biochemical hyperandrogenism, with either PCO or menstrual dysfunction to diagnose PCOS (Artini et al., 2010).

In comparison to the general population, women with PCOS more frequently experience impaired glucose tolerance (35–40%) and diabetes (7.5–10%). Such frequency emphasis the special attention given to insulin resistance associated with dyslipidemia and metabolic syndrome in women with PCOS and the potential utility of insulin sensitizers in management of the syndrome. The benefit and utmost importance of lifestyle modification for the long-term health of these women is stressed as well (El-Mazny et al., 2010).

Targeting insulin resistance may result in a list of benefits for women with PCOS, including hormonal, metabolic and ovulatory (and fertility) improvements. The therapeutic strategy to treat PCOS should however depend on the clinical situation, the phenotype, the degree of androgen excess, age, the presence of infertility and the woman's desire to conceive, the presence of obesity

and, finally, the spectrum of metabolic abnormalities and the need to treat or prevent long-term associated co-morbidities.

ACTOS (pioglitazone hydrochloride) is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. ACTOS is used in the management of type 2 diabetes mellitus. Pharmacological studies indicate that ACTOS improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. ACTOS improves glycemic control while reducing circulating insulin levels. Pioglitazone (thiazolidinedione monohydrochloride) belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibitors (Kroese et al., 2009, Iwanishi et al., 2009).

This prospective comparative study aimed to evaluate the ovulatory outcome of combined clomiphene citrate stimulation with ACTOS versus metformin treatment in conjunction with weight reduction dieting program.

2. Patients and Methods

The present study was conducted at AGH, Dammam, KSA since June 2008 till Jan 2010. After obtaining written fully informed patients' consents, women with PCOS who had a chief complaint of irregular menstrual cycles and/or clinical hyperandrogenism and able to undergo vaginal ultrasound, were recruited in the study. Diagnosis of PCOS was based on the Rotterdam criteria, in which at least two of the following three criteria were met: Oligomenorrhea (<8 spontaneous menstrual cycles per year for at least 3 years before enrollment) or amenorrhea, biochemical hyper-androgenemia (serum total testosterone level >0.8 ng/ml), and polycystic ovaries (>12 follicles in the 2–9 mm range and/or an ovarian volume >10 ml per ovary by vaginal ultrasound) (Chen et al., 2006, 2007). Patients with hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, adrenal tumor or ovarian tumor, current or previous pregnancy within 1 year of enrollment, autoimmune disease, malignancy, central nervous system disease, current or previous use of oral contraceptives within 6 months of enrollment were excluded from the study.

All patients underwent transvaginal ultrasonographic examination and anthropometric measurements were recorded including body height measured to the nearest 0.5 cm using a wall-mounted stadiometer and weight to the nearest 0.1 kg using a balance beam scale. BMI was calculated as body weight in kg divided by square body height in meter (Khosla and Lowe, 1967) according to definitions provided by WHO expert consultation (2004) as over-weight was defined as BMI ≥25-<30 kg/m^2, obesity as BMI ≥30-<35 kg/m^2, morbid obesity as BMI of ≥35. Overnight fasting blood samples were collected randomly from PCOS subjects with amenorrhea exceeding 3 months without hormone-induced withdrawal bleeding. Blood was processed within 30 min of collection for estimation of the concentration of plasma glucose, and insulin levels and the hormone profiles including FSH, LH, estradiol and progesterone.

Insulin resistance (IR) was measured by homeostasis model assessment (HOMA). The HOMA-IR score was calculated as (fasting serum insulin (μU/ml) x [fasting plasma glucose (mg/ml)/18])/22.5 (Matthews et al., 1985), considering an abnormal HOMA-index >2 (Ascaso et al., 2001). All enrolled women, irrespective of their BMI or HOMA-IR scores, were instructed to follow a 3-ms weight reduction dietary program.

Oral clomiphene citrate was given in dose of 50 twice daily starting on Days 2–6 of a menstrual period or after a progestogen withdrawal bleeding. Patients were randomly, using closed envelops, allocated into 2 equal study groups: Group A: included patients assigned to receive ACTOS oral 15 mg tablets once daily and Group M: included patients assigned to receive metformin oral 0.5 gm tablets trice daily. Ovulation was monitored by measuring the serum concentration of progesterone on Day 21 of the menstrual cycle. A serum progesterone level of ≥25 nmol/l was used to indicate ovulation that was assured using TVU for evident ovulation with a dominant follicle size >16 mm and the frequency of women got these follicles was considered as ovulation success rate. At the end of 3 months, HOMA-IR score was evaluated as an index for the impact of the study drugs on insulin resistance.

Statistical analysis

Results were expressed as mean±SD, range, numbers and percentages. Intra-group data was statistically analyzed using paired t-test and Chi-square test, and inter-group analysis of variance was examined using one-way ANOVA test. ROC curve analysis was applied for assurance of sensitivity and specificity of studied parameters as predictors for oncoming ovulation using area under curve (AUC) tested against the null hypothesis that true AUC=0.5. Statistical analysis was conducted using SPSS statistical program, (Version 10, 2002). P value <0.05 was considered statistically significant.

3. Results

The study included 80 women fulfilling the inclusion criteria; 52 were primary infertile, while 28 were secondary infertile of which only 2 were para-two and 5 were para-one. Mean age of enrolled women was 28.1±3.1; range: 21-34 years. Only 3 women were overweight, while 77 women were obese. Thirty-nine women were glucose intolerant with HMOA-IR ≥2, while 41 women were glucose

tolerant with HOMA-IR <2. There was non-significant (p>0.05) difference between women enrolled in both study groups as regard constitutional data, (Table 1). Mean serum levels of evaluated hormones showed non-significant among studied patients, (Table 2).

Table (1): Patients' data recorded at time of study enrollment

			ACTOS	Metformin
Age (years)			27.8±2.5	28.4±2.9
Type of infertility	1ry		27 (67.5%)	25 (62.5%)
	2ry	para-0	9 (69%)	12 (80%)
		Para-1	3 (23%)	2 (13%)
		Para-2	1 (8%)	1 (7%)
		Total	13 (12.5%)	15 (37.5%)
BMI parameters	BW (kg)		86.7±4	88.8±5
	BH (cm)		162±6	161.7±5
	BMI (kg/m^2)		32.5±2	34±1
HOMA data	FBG		127±11	127±12
	FPI		6.4±4.4	5.4±1.5
	IR index		1.7±0.53	1.8±0.52

Data are presented as mean ±SD, numbers; ranges & percentages are in parenthesis
FBG: fasting blood glucose FPI: fasting plasma insulin
IR: insulin resistance BW: body weight
BH: body height BMI: body mass index

Table (2): Patients' data recorded at time of study enrollment

	ACTOS	Metformin
LH (IU/L)	14.2±3.3	13.5±3
FSH (IU/L)	5.98±1.34	5.74±1.19
Testosterone(ng/ml)	0.78±0.26	0.75±0.23
Estorgen (pg/ml)	141.5±37.9	148±37.9

Data are presented as mean ±SD

At the end of 3-months therapy, diet regimen combined with insulin sensitizing drugs induced significant reduction of BMI and HOMA-IR scores compared to pre-treatment scores with non-significantly lower scores with ACTOS compared to metformin. However, the percentage of change of HMOA-IR score was significantly higher (F=28.404, p=0.035) with ACTOS compared to metformin, (Table 3).

Ovulation was induced and assured in 65 patients with a total ovulation induction success rate of 81.3%; 36 patients (90%) received ACTOS and 29 patients (72.5%) received metformin with significantly higher levels (X^2=5.888, p<0.05) with ACOTS compared to metformin.

Using ROC curve analysis judged by the AUC compared versus the null hypothesis of AUC=0.5 for evaluation for the best screening constitutional parameter to predict the oncoming effect of insulin sensitizing drugs on ovulatory function defined the pre-treatment HOMA-IR score as a significant screening parameter irrespective of the BMI or its constituents or the patient's age, (Fig. 1).

Table (3): BMI and HOMA-IR scores determined at 3-months after initiation of induction therapy compared to baseline data

	ACTOS	Metformin	F	p
BMI score				
Baseline	32.5±2 (27.3-34.4)	34±1 (31.5-35.3)	1.080	>0.05
At 3-m	30.6±1.4 (26.3-33.2)	32.1±1.2 (29.8-33.8)	0.806	>0.05
T	20.782	24.865		
P	<0.001	<0.001		
% of change	6.3±1.9 (2.4-10.8)	5.8±1.6 (2.3-9.5)	0.565	>0.05
HOMA-IR score				
Baseline	1.8±0.52 (1.12-2.63)	1.71±0.53 (0.98-2.61)	4.419	>0.05
At 3-m	1.33±0.39 (0.77-2)	1.35±0.44 (0.65-2.2)	2.987	>0.05
t	17.814	12.862		
p	<0.001	<0.001		
% of change	26.3±4.6 (16.85-37.1)	21.2±7.2 (9.6-37.5)	28.404	=0.035

Data are presented as mean ±SD & ranges are in parenthesis

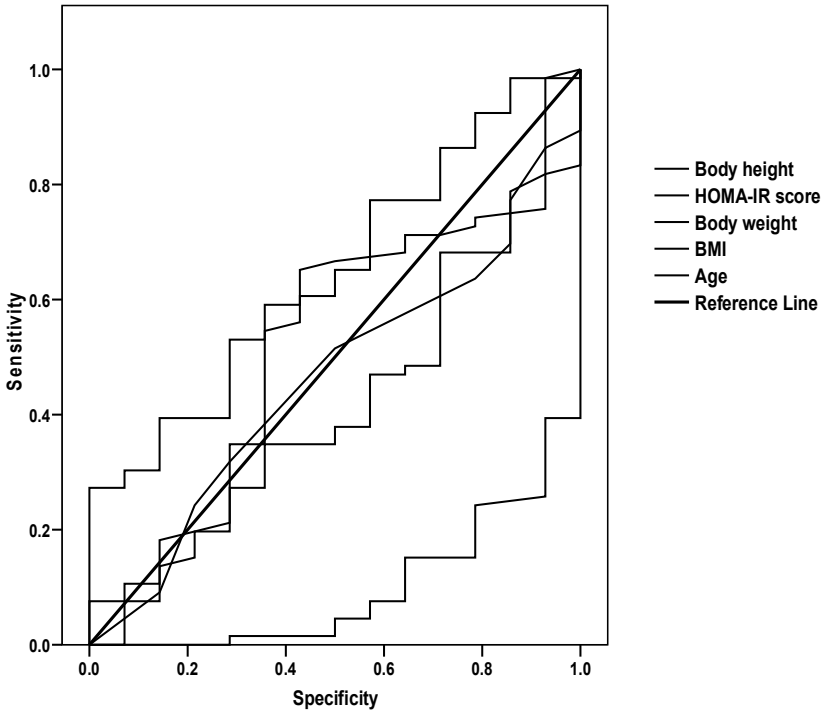

Figure (1): ROC curve analysis for the best screening constitutional parameter to predict the oncoming effect of insulin sensitizing drugs on ovulatory function

4. Discussion

Polycystic ovary syndrome is of clinical and public health importance as it is very common, affecting up to one in five women of reproductive age. It has significant and diverse clinical implications including reproductive (infertility, hyperandrogenism, hirsutism), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, adverse cardiovascular risk profiles) and psychological features (increased anxiety, depression and worsened quality of life) (Teede et al., 2010). Importantly, PCOS has unique interactions with the ever increasing obesity prevalence worldwide (Demerath et al., 2009) as obesity-induced insulin resistance significantly exacerbates all the features of PCOS. Polycystic ovary syndrome is a heterogeneous condition and, as such, clinical and research agendas are broad and involve many disciplines (Farrell and Antoni, 2009).

The present study reported an ovulatory rate of 81.3% with the use of insulin sensitizing drugs combined with CC and diet regimen applied for 3-months. Such figure of ovulation goes in hand with various previous studies evaluated insulin sensitizing drugs as a line for PCOS management either alone or in combination with CC (Palomba et al., 2005 & 2007, Johnson, 2006, Neveu et al., 2007, Legro et al., 2007).

Ovulation was induced and assured in 65 patients; 36 patients (90%) received ACTOS and 29 patients (72.5%) received metformin with significantly higher ovulation rate with ACOTS compared to metformin. These data go in hand with that reported in literature; Glueck et al. (2003) in women with PCOS who failed to respond optimally to metformin, when pioglitazone was added, insulin, glucose, IR, insulin secretion, and DHEAS significantly fell and sex hormone-binding globulin significantly rose, and menstrual regularity improved 2-fold higher than on metformin. Brettenthaler et al. (2004) compared effect of pioglitazone (30 mg/d) administration versus placebo for periods of 3 months and found that pioglitazone significantly increased serum SHBG, resulting in a significant decrease in the free androgen index and treatment with pioglitazone was also associated with higher ovulation rates.

Gambineri et al. (2008) found treatment with pioglitazone resulted in progressive amelioration of insulin resistance, hyper-insulinaemia and hyperandrogenaemia; menses also improved, with restoration of a eumenorrhoeic pattern, and the framework of ultrasound PCO was in complete remission. Aroda et al. (2009) also,

found pioglitazone treatment in PCOS was associated with improvements in insulin action and glucose homeostasis and ameliorated the hyperandrogenic ovarian response. Narsing et al. (2009) reported that administration of pioglitazone for 6 months in obese adolescents and young adult women with PCO results in significant improvements in menstrual frequency. Kim et al. (2010) found pioglitazone therapy reduced intraovarian stromal blood flow and might be beneficial in improving both the response to ovarian stimulation and IVF outcome in PCOS patients.

Insulin sensitizing therapy combined with diet regimen induced significant decrease of BMI score, irrespective of drug used, compared to pre-treatment BMI. These data goes in hand with Pasquali and Gambineri (2009) who found that according to the needs, therapeutic options include, alone or in combination, management of obesity, the use of insulin sensitizers, metformin and thiazolidinediones, antiandrogens or estro-progestins. Kazerooni et al. (2009) who found that BMI and percentage of participants with insulin resistance were significantly decreased in PCOS patients pre-treated with metformin.

These findings spot light on the necessity of trials of weight reduction in association with the use of insulin sensitizing drugs that optimize insulin uptake by its exposed and active receptor thus improving fuel utilization. In support of such explanation, Vigouroux (2010) found that in lipodystrophic syndromes, the endocrine deficiency of adipose tissue has been shown to play important pathophysiological roles in metabolic alterations; in particular leptin is decreased, contributing to the ectopic lipid storage in non-adipose cells, which inhibits insulin signaling (lipotoxicity), this is in favor of an aggravating role of post-receptor insulin resistance on ovary dysfunctions.

The additive beneficial effect of insulin sensitizers was manifested as significant reduction of HOMA-IR, despite the non-significant difference between both study drugs, indicated the favoring outcome of the combined use of insulin sensitizers change with dieting on the blood glucose and insulin levels. Associated ovulation induction with reduction of these parameters finalizes the impact of glycemic control on ovarian function. These data go in hand with Marsh et al. (2010) who reported a significant diet-metformin interaction with greater improvement in oral glucose tolerance test among women prescribed both metformin and the low-glycemic index diet and compared with women who consumed the conventional healthy diet, more women who consumed the low-glycemic index diet showed improved menstrual cyclicity.

In support of this assumption estimation of HOMA-IR score prior to initiation of ovulation induction was found to be a significant screening tool for responders compared to age, body weight or BMI as documented by ROC curve analysis. Also, ovarian non-responders were found to still have high HOMA-IR at 3-months after initiation of therapy with minimal percentage of HOMA-IR reduction. These data supported that previously reported by Ma et al. (2008) who found HOMA-IR is a clinic , simple and practical and sensitive Index for assessing the ovulation failure, meanwhile, after anti-IR treatment, HOMA-IR is also a reliable and simple for accessing the recovering ovulation function.

ACTOS induced significantly higher percentage of HOMA-IR control than that reported with metformin; such finding spots light on the fact that ACTOS, being a pioglitazone with different metabolic and pharmacological actions, improves insulin sensitivity more favorably than metformin. In support of this assumption, Basu et al. (2009) reported pioglitazone significantly increased insulin-stimulated glucose disappearance, increased insulin-induced suppression of glucose production through gluconeogenesis and glycogenolysis than metformin and concluded that pioglitazone improves both the hepatic and the extrahepatic action of insulin than metformin. Also, van der Meer et al. (2009) found pioglitazone versus metformin significantly improved the early peak flow rate; the left ventricular compliance, increased myocardial glucose uptake and fatty acid oxidation with subsequent increased cardiac work, and only pioglitazone reduced hepatic triglyceride content with no effect of metformin on such function.

In conclusion, for PCOS women, combined CC and ACTOS therapy in association with increased daily physical activity and weight reduction provides the best chance for getting regular ovulation with better biomilieu and promises for higher chances for getting pregnant.

Corresponding Author:
Dr. Hesham Abou Ragab
Department of Obstetrics & Gynecology
Faculty of Medicine, Benha University
Benha, Kaluobia, Egypt
E-mail: Abouragab@yahoo.com

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