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Research Paper

Comparative Study between Clomiphene Citrate plus Phytoestrogens and Clomiphene Citrate plus N-acetyl-Cysteine in Clomiphene Citrate Resistant Polycystic Ovary Syndrome

Medical Science

KEYWORDS : Polycystic ovary syndrome, clomiphene citrate, phytoestrogens and N-acetyl cysteine.

Mohamed Lofty — Department of Obstetrics and Gynecology, Faculty of medicine, Zagazig University

Walid A.Abdelsalam — Department of Obstetrics and Gynecology, Faculty of medicine, Zagazig University

Shymma Abdelazim — Department of Microbiology and Immunology, Faculty of medicine, Zagazig University

ABSTRACT

PCOS is the commonest endocrinopathy in reproductive age. Adjuvant agents with clomiphene citrate in C.C.resistant PCOS inducing good ovulatory rates and fewer side-effects. Patients and methods: Patients divided into two groups: group (A) (n=40) received C.C. 100mg/day for 5 days+Klimadynon,20 mg for 10 days; and group (B) (n=40) received C.C. 100 mg daily for 5 days+NAC 1.2 gm for 5 days. Monitoring of the patients on the 3rd day of the menstrual cycle include baseline TVS and hormonal changes. On the 12th day of the cycle, TVS was done to evaluate the follicular diameter and endometrial thickness. Serum progesterone was measured on cycle day 21 and b-hCG level was measured on the 14th day after hCG injection if menses not occurred. Results: Significant hormonal changes and endometrial thickness was greater in the Klimadynon group. Insulin sensitivity was increased in NAC group in all three treatment cycles.

Introduction

Polycystic ovarian syndrome (PCOS), is the most common endocrinopathy in reproductive age, with a prevalence of approximately 6.5%(Laven et.al; 2002). Diagnostic criteria for PCOS, as follows: 1) clinical and/or biochemical hyperandrogenism and exclusion of other etiologies 2) Oligo-ovulation and/or anovulation 3) polycystic appearing ovaries detected by ultrasound (Azziz et.al; 2006).

Clomiphene citrate (C.C.) resistance was defined as lack of ovulation after treatment with CC,100 mg, for 5 days in three consecutive cycles (Coelingh et.al; 1996).

A significant proportion PCOS patients have been found to suffer from insulin resistance (Venkatesan et.al; 2001) and compensatory hyperinsulinemia in more than 50% (Lanzone et.al; 1990). The homeostasis model assessment of insulin resistance (HOMA-IR) is a tool for evaluation of insulin resistance by using the fasting glucose and insulin levels (Matthews et.al; 1985).

Clomiphene citrate (C.C.) therapy has variable success rates in anovulatory women; however, it is the lowest in women with PCOS, particularly those with insulin resistance. There is increasing evidence that insulin sensitizers are particularly effective in inducing ovulation in PCOS patients (Nestler et.al; 1998). However, not all cases respond to insulin sensitizers (Malkawi et.al; 2003). Clomiphene citrate (C.C.) has many side effects, include undesirable anti-estrogenic effects in the endocervix, endometrium and ovary which explain the discrepancy between ovulation and pregnancy rates (Shams et.al; 2010). There is other adjuvant agents inducing good ovulatory rates and fewer side-effects including Cimicifuga racimosa extract and N-acetyl cysteine.

Cimicifuga racimosa is an alternative to hormonal therapy for the treatment of menopausal symptoms, although the evidence is mixed. The estrogenic effect of C. racimosa is evident, but its mechanism of action and its receptor selectivity have not been well studied. Accordingly, it may have an estrogen-like effect at a central level, and may therefore antagonize the endogenous estrogen. As such, it could be used for ovulation induction in PCOS patients (Wuttke et.al; 2006).

Another agent is N-acetyl cysteine (NAC), which is commonly used as a mucolytic drug, has been shown to influence both the insulin secretion in pancreatic b-cells and the regulation of insulin receptors in human erythrocytes (Santini et.al; 1997). NAC administration with C.C. associated with improving insulin sensitivity and better induction of ovulation in patients with C.C. resistant PCOS (Saghar et.al; 2012).

This is a comparative study aimed to evaluate the difference between C.C. plus phytoestrogens (Klimadynon) and C.C. plus N-acetyl cysteine in C.C. resistant PCOS in terms of hormonal profile, insulin sensitivity, ovulation and pregnancy rates.

Patients and methods

This prospective randomized study was conducted in the Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, Egypt from March 2011 to August 2014 following approval by the Department's Ethical Committee. Eighty patients with C.C. resistant PCOS were recruited from the attendees of the infertility clinic at Zagazig University Hospitals. Written informed consent was obtained from each woman prior to participation in the study. All infertile patients referred to infertility clinic with C.C. resistant PCOS, aged 20–35 years, infertility duration less than 10 years, body mass index (BMI) < 35 kg/m2, both patent tubes confirmed by hysterosalpingography or laparoscopy and with partner's normal seminogram results according to WHO guidelines 2010. Patients with thyroid dysfunction, hyperprolactinemia, hypercorticism, history of visual disturbance caused by C.C. and finally history of allergy to medications were excluded from the study. Patients who had received any hormonal medications (except progesterone for withdrawal bleeding) or medications affecting glucose metabolism for at least 3 months before the study were also excluded. Also, none of the patients or their male partners had any sexual dysfunction interfering with successful intercourse.

The women were randomly divided into two groups: group(A) (n=40) received C.C. 100mg/day for 5 days starting from the 3rd to 7th day of the cycle + Klimadynon, 20 mg twice daily orally for 10 days, starting from the 2nd day of the cycle; and group(B) (n=40) received C.C. 100 mg daily for 5 days, starting from the 3rd to 7th day of the cycle + NAC 1.2 gm from the 3rd to 7th day of the cycle. NAC was taken orally in two daily divided doses. This study was conducted during 3 successive cycles.

Monitoring of the patients on the 3rd day of the menstrual cycle (induced by 200 mg progesterone injection in amenorrheic patients) include baseline transvaginal ultrasound examination(TVS) and fasting venous blood sample was obtained after 8 hours of overnight fasting which used for the analyses of glucose, insulin, se-

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rum follicle-stimulating hormone (FSH), luteinizing hormone (LH), LH/FSH ratio and prolactin levels assessment (all measured by immunoreactive multianalysis) were performed for all patients who were candidates for ovulation induction. HOMA-IR was calculated as (Fasting glucose × Fasting insulin /405). Insulin resistence was defined as an elevated HOMA-IR value > 2.5 based on the original HOMA research (Matthews et.al; 1985).

On the 12th day of the menstrual cycle, patients were monitored by TVS examination to evaluate the mean follicular diameter and the endometrial thickness. In the presence of at least one follicle with 18–20 mm in size, 10,000 I.U. hCG was injected intramuscularly and timed intercourse was advised 36 hours after hCG injection. Serum progesterone was checked on cycle days 21.

Serum b-hCG level was measured on the 14th day after hCG injection if menses had not yet occured. Pregnancy was defined as an increase in the serum b- hCG level on serial determinations 2 days apart. Another TVS examination was performed on the 6th week of gestation to determine the clinical pregnancy.

Data were collected and tabulated using Excel Version 7 (Microsoft Corporation, New York, NY, USA), and analyzed using Statistical Package for the Social Sciences Version 11 (SPSS Inc., Chicago, IL, USA).

Results

Table (1): Clinical characteristics of the study group.

	Group(A)	Group(B)	P
Age (yrs)	29.21±5.34	29.40±5.23	NS
BMI (Kg/m2)	25.67±2.32	25.77 ±2.30	NS
Duration of infertility	4.29 ±1.64	4.39 ± 1.56	NS
Type of infertility Primary type Secondary type	24 (60 %) 16 (40 %)	22 (55 %) 18 (45 %)	NS NS

Table 1, shows that the clinical characteristics of the study group were comparable between the Klimadynon group and the NAC group in terms of age , type of infertility, body mass index (kg/m2) and duration of infertility. There was no statistically significant difference as regard age, BMI, type and duration of infertility.

Before treatment, no statistical differences were found between the two groups in terms of FSH, LH, FSH/LH ratio, insulin resistance, mid-luteal serum progesterone level and endometrial thickness (Table 2). Following treatment, significant hormonal changes were seen in the Klimadynon group, particularly in LH level and LH/FSH ratio, with a marked reduction in LH level and this significant difference was present in all three treatment cycles (Table 3).

Table (2): Hormonal changes in study groups before treatment:

	Before treatment		
	Group (A)	Group (B)	P value
FSH IU/ml	4.8 ± 0.23	4.3 ± 0.79	NS
LH (IU/ml)	9.4± 0.73	9.6±0.70	NS
LH/FSH ratio	1.6±0.44	1.75±0.33	NS
P level (ng/ml)	7.63±0.570	7.56±0.430	NS
HOMA-IR	3.78±1.70	3.88±1.20	NS
Endometrial thickness (mm)	4.1	4.3	NS
Pregnancy rate	0	0	NS

Table (3): Hormonal changes in study groups after treatment

	After treatment						P value
	1st cycle		2nd cycle		3rd cycle		
	Group (A)	Group (B)	Group (A)	Group (B)	Group (A)	Group (B)	
FSH IU/ml	5.4±0.46	5.2±0.47	5.4±0.36	5.2±0.47	5.56±0.27	5.24±0.29	0.001
LH (IU/ml)	7.4±0.23	8.6±0.20	6.5±0.28	7.2±0.65	4.45±0.22	5.23±0.15	0.0001
LH/FSH ratio	1.02±0.98	1.6±0.46	1.06±0.34	1.4±0.67	0.675±0.21	0.934±0.73	0.007
P level (ng/ml)	10.23±0.16	9.67±0.17	11.20±0.567	11.10±0.413	11.65±0.317	11.45±0.233	0.002
HOMA-IR	3.76±1.37	2.73± 0.66	3.25±1.36	2.23±.89	3.20±1.33	1.98±56	0.001
Endometrial thickness (mm)	8.59	6.66	9.22	7.32	9.33	7.22	0.0003
Pregnancy rate	1	0	2	1	3	2	0.04

The progesterone level was higher in the Klimadynon group than the NAC group, especially in the first cycle. Endometrial thickness was greater in the Klimadynon group than the NAC group in all treatment cycles. The pregnancy rate was higher in the Klimadynon group than the NAC group, this difference was statistically significant (6 vs. 3 pregnancies). Our results showed that HOMA-IR was non-significant difference between the Klimadynon group and NAC group before treatment. After treatment the mean HOMA-IR rates of NAC group were significantly higher than klimadynon group.

Discussion

This study compared two treatment modalities, CC -Klimadynon versus CC-NAC for ovulation induction in women with C.C. resistant PCOS. Klimadynon treatment resulted in a significant reduction in LH level and LH/FSH ratio. This was evident in the first treatment cycle and continued throughout all treatment cycles. This is in accordance with Wuttke et al.,2006 who reported that C. racimosa extract acted directly on the hypothalamus to reduce the release of gonadotrophin-releasing hormone, and therefore reduce the LH level. Wuttke et al.,2006 ruled out a direct effect of C. racimosa extract on the pituitary, as C. racimosa extract had no direct effect on LH release in pituitary tissue of ovariectomized rats in vitro. A reduction in LH has a remarkable effect on the symptoms of excessive androgens experienced by PCOS women , allowing better ovulation and implantation rates. In addition, reduction of the LH level increases the sensitivity of ovarian tissue to circulating FSH, improving follicular growth, ovulation and implantation. This study found good ovulation rates from the first treatment cycle with Klimadynon. Endometrial thickness increased in response to C.C. + Klimadynon combination due to either endogenous induced estrogen or the direct effect of Klimadynon on the endometrium, which improves the implantation and pregnancy outcome. This finding was in agreement with Casper, 2004 and Unfer et.al; 2004 who reported a significant increase in endometrial thickness among women receiving phytoestrogens with clomiphene citrate.

Shaheen et.al;(2008) showed that treatment PCOS women with C. racimosa extract led to higher pregnancy rate compared with C.C. treatment, but this difference was not significant. A higher pregnancy rate was also evident in a study that used C. racimosa extract as adjuvant therapy with C.C. in patients with unexplained infertility.

In this study N-acetyl cysteine associated with improvement of insulin sensitivity in women with C.C. resistant PCOS. This is in agreement with study of Fulghesu et.al; (2002) who reported that NAC administration in C.C. resistant PCOS associated with improvement of insulin circulating levels and insulin sensitivity in hyperinsulinemic PCOS patients. Also Rizk et.al; (2005) showed that NAC adjuvant therapy for PCOS patients. It is a simple, well-tolerated, and inexpensive agent. It could be used as an alternative to other insulin-sensitizing agents.

Further studies are needed in the future to document the agonistic/antagonistic actions of C. racimosa extract on different estrogenic receptors in different body systems, and to confirm the direct and indirect effects of C. racimosa extract on these receptors. Also, there is a need to study the effect of C. racimosa extract on cervical mucus when used alone or as adjuvant therapy with CC.

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