Comparison of efficacy of metformin and oral contraceptive combination of ethinyl estradiol and drospirenone in polycystic ovary syndrome

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Abstract

Objective: The 2013 Endocrine Society guidelines state that hormonal contraceptives should be used for treating both menstrual irregularity and hirsutism in patients with polycystic ovary syndrome (PCOS). Metformin should be reserved for the treatment of women presenting with only menstrual irregularity because it has limited benefits in treating hyperandrogenism associated with PCOS. A high prevalence of insulin resistance is noted among the South Asians, and these guidelines may not hold good for this population. Thus, this study was conducted to investigate and compare the effects of metformin and an oral contraceptive containing drospirenone on menstrual pattern, body mass index, serum testosterone levels, and dehydroepiandrosterone sulfate (DHEAS) levels at baseline to 6 months of therapy in the treatment groups.

Material and Methods: This was a prospective observational study that was conducted over a year in patients visiting the Endocrinology outpatient department at a tertiary care center in a south Indian city. Forty-six subjects diagnosed with PCOS as per the Rotterdam criteria were included. They received either metformin twice daily or an oral contraceptive containing drospirenone once daily as a monthly regimen for 6 months.

Results: Metformin regularized menstrual cycles in 72% of patients who were followed up at 6 months. No significant difference was observed between the two treatment groups with respect to decreasing the body mass index, serum testosterone levels, and DHEAS levels ($p=0.40$, $p=0.65$, and $p=0.22$, respectively).

Conclusion: Metformin is effective in regularizing menstrual cycles, decreasing body mass index, and treating hyperandrogenism in Indian women diagnosed with PCOS. (J Turk Ger Gynecol Assoc 2016; 17: 6-9)

Keywords: Polycystic ovary syndrome, metformin, oral contraceptive containing drospirenone, menstrual cycle, testosterone

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder with a prevalence of 15%–20% (1) and is characterized by oligomenorrhea, hyperandrogenism, and ultrasonographic evidence of PCOS (2).

Combined oral contraceptives have been the traditional choice for patients not desirous of conception (3) and patients who have a major component of hyperandrogenism. Metformin for treating insulin resistance has also been found to be beneficial in restoring ovulation in women suffering from PCOS (4), and thus, can be used as a therapeutic option. However, there are not many studies demonstrating its benefit in treating hyperandrogenism (5).

Guidelines released by the Endocrine Society state that metformin has limited or no benefit in treating hyperandrogenism and should be used if patients presenting with menstrual irregularity as the chief complaint (6). The applicability of these guidelines in South Asia, particularly India, is uncertain because of the high prevalence of insulin resistance amongst

this population (7). The relevance of this observation concerning therapy for patients with PCOS is highlighted by a study where patients with PCOS of the South Asian ethnicity had more severe symptoms, higher fasting insulin concentrations, and lower insulin sensitivity compared with Caucasians (8). Thus, insulin-sensitizing drugs may have a more beneficial role to play in this population. Hence, this study was conducted to compare the efficacy of metformin and oral contraceptive containing drospirenone on menstrual pattern, body mass index (BMI), serum testosterone levels, and dehydroepiandrosterone sulfate (DHEAS) levels in Indian women with PCOS.

Material and Methods

This study was conducted at a tertiary care hospital in a south Indian city among patients visiting the Endocrinology outpatient department over a 1-year period. The study was approved by the Institutional Ethics Committee.

Patients aged between 18 and 45 years who were diagnosed with PCOS as per the Rotterdam criteria (2) with a modified

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Ferriman–Gallwey score of >8 were included. Patients with contraindications to oral contraceptives; patients desirous of conception within 6 months of inclusion in the study; patients with a diagnosis of concomitant hypothyroidism, hyperprolactinemia, diabetes mellitus, renal, or adrenal insufficiency; history of drug use for PCOS before inclusion in the study, and history of smoking and substance abuse were excluded from the study.

Forty-six patients were included, and informed consent was obtained. Demographic data, baseline parameters, such as menstrual pattern and BMI, were recorded. Baseline laboratory parameters, such as serum testosterone and DHEAS levels were recorded. The patients at the physician's discretion received either $30\text{ }\mu\text{g}$ ethinyl estradiol+3 mg drospirenone (one tablet daily) as a monthly regimen of 21 days for 6 months or 2 g metformin sustained release tablet in two divided doses daily for 6 months.

The patients were followed up at 3 and 6 months of treatment, and changes in menstrual pattern, BMI, and serum androgen levels (testosterone and DHEAS) were recorded and compared between the two groups.

A priori sample size calculation was performed using a priori sample size calculator for Student's t-tests (software) version 3.0 (9) and considering an α value of 0.05, β value of 0.20, and an anticipated effect size of 0.85. The total sample size required was calculated to be 46 with 23 patients in each group. Student's t-test (two tailed, independent) was used to determine the significance of study parameters on a continuous scale between the two groups and chi-square test was used to determine the significance of study parameters on a categorical scale between the two groups. Student's t-test (two tailed, dependent) was used to determine the significance of study parameters on a continuous scale within each group. The analyses were performed using the Statistical Package for Social Sciences software version (SPSS) software version 17 (SPSS Inc.; Chicago, USA).

Results

Forty-six patients (23 in each group) were enrolled in the study, with 72% follow-up at 3 months and 48% follow-up at 6 months (Figure 1).

The baseline characteristics of patients in both the groups were comparable (Table 1). Regarding the menstrual pattern, nine of the 16 patients in the metformin group and all 17 patients who were analyzed in the oral contraceptive containing drospirenone group had attained regular menstrual cycles at the 3-month follow-up ($p=0.002$ between the two groups), and eight of the 11 patients in the metformin group and all 11 patients in the oral contraceptive containing drospirenone group had attained regular menstrual cycles at the 6-month follow-up ($p=0.06$ between the two groups). BMI, serum testosterone levels, and serum DHEAS levels significantly declined within the individual groups, but no significant difference was observed between the two groups at the 6-month follow-up (Table 2).

Both the drugs were well tolerated with no serious adverse events being recorded during the study period.

Discussion

Therapy for patients with PCOS is targeted toward regularization of menstrual cycles and suppression of ovarian testosterone production, which is conventionally, achieved using combined oral contraceptives. However, side effects, such as increased risk of venous thrombosis and weight gain, make the use of combined oral contraceptives inappropriate in obese women and women with prediabetes. Thus, alternative options are explored. Metformin is an insulin-sensitizing drug that has demonstrated promise in therapy for patients with PCOS. This study assessed the efficacy of metformin and oral contraceptive containing drospirenone in patients with PCOS.

All patients enrolled in the study had oligomenorrhea. As expected, oral contraceptive containing drospirenone regularized menstrual cycles in all patients. However, 72% of patients receiving metformin also had regular menstrual cycles after 6 months of therapy, with no significant difference being observed between

Figure 1. Patient recruitment chart

Table 1. Baseline characteristics of patients

Baseline characteristics	Metformin group (n=23)	Oral contraceptive containing drospirenone group (n=23)	p
Age (years)	24.52±4.37	23.52±6.04	0.52
BMI (kg/m ²)	27.72±5.04	26.48±4.56	0.25
Patient symptoms and clinical signs			
1. Oligomenorrhea	23 (100%)	23 (100%)	1.00
2. Hirsutism (FG score >8)	23 (100%)	23 (100%)	1.00
3. Infertility	4 (17.39%)	2 (8.69%)	0.33
4. Acne	6 (26.08 %)	6 (26.08%)	0.85
USG for PCOS features			
1. Present	19 (82.60%)	19 (82.60%)	1.00
2. Absent	4 (17.39%)	4 (17.39%)	

BMI: body mass index; FG score: modified Ferriman-Gallwey score; USG: ultrasonography; PCOS: polycystic ovary syndrome

Table 2. Comparison of efficacy of metformin and oral contraceptive containing drospirenone on body mass index, serum testosterone and DHEAS levels at baseline, 3 and 6 months of treatment

Parameters	Baseline (Mean±SD)			3 months of therapy (Mean±SD)			6 months of therapy (Mean±SD)		
	Met	Drosp	p	Met	Drosp	p	Met	Drosp	p
BMI (kg/m ²)	27.72± 5.04	26.48± 4.56	0.38	26.27± 4.60***	25.57± 4.30**	0.65	25.61± 3.19 **	24.28± 3.98 **	0.40
Serum Testosterone (ng/dL)	56.52± 11.70	62.23± 13.59	0.15	51.75± 10.43***	53.94± 15.40***	0.68	49.67± 13.68 **	52.57± 14.17***	0.65
Serum DHEAS (mcg/dL)	197.30± 60.35	227.16± 66.34	0.30	175.00± 50.02	200.61± 47.03*	0.37	166.50± 43.12	195.45± 32.73*	0.22

SD: standard deviation; Met: metformin; Drosp: oral contraceptive containing drospirenone; BMI: body mass index; DHEAS: dehydroepiandrosterone sulphate

*, ** and *** denote statistical significance at $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively within the individual group (Met versus Met; Drosp versus Drosp) for decline in BMI, serum testosterone and serum DHEAS levels from baseline at 3 and 6 months of treatment.

The p-values mentioned in the table denote the p-values between the two treatment groups (Met versus Drosp) for BMI, serum testosterone and serum DHEAS levels at baseline, 3 and 6 months of treatment.

the two groups. Bobde et al. (10) reported a significant regularization of menstrual cycle in patients who received oral contraceptive containing drospirenone compared with those who received metformin ($p=0.001$). This is also reported in a review by Costello et al. (11), where 18 of 21 patients on metformin and 20 of 24 patients on oral contraceptives had oligomenorrhea. Metformin was less effective compared with oral contraceptives in improving menstrual pattern ($p=0.004$). In this study, the results observed at 3 months are consistent with earlier studies. The mechanism for regularization of cycles in oral contraceptive containing drospirenone users is withdrawal bleeding that occurs because of the hormone-free interval in the monthly cycle. In this study, the delayed effect of metformin on the menstrual cycle is possibly because of the lag period of 4–6 months that is required for the plasma luteinizing hormone (LH) levels to return to normal following decreased LH pulse secretion when the patient is initiated on metformin therapy (10).

There was no significant difference in BMI observed between the two groups at 6 months. Cinar et al. (12) reported no decline in BMI among 25 patients who received oral contraceptive containing drospirenone alone, whereas a decline in BMI was observed among 20 patients who received metformin along with an oral contraceptive. In another study by Ibáñez et al. (13), oral contraceptive containing drospirenone alone was ineffective in reversing dysadipocytokinaemia, hypertriglyceridemia, and adiposity, whereas patients who received add-on metformin demonstrated reversal of the aforementioned features. Weight loss because of metformin observed in this study could be because of its anorexic property and its ability to counteract adipose tissue expansion through direct inhibition of adipogenesis (14). Moreover, Oelkers et al. (15) reported reduction in body weight because of its anti-mineralocorticoid properties of drospirenone in healthy young menstruating women who received oral contraceptive containing drospirenone. The results of this study re-instate that weight loss is observed with oral contraceptive containing drospirenone. The

problem of weight gain experienced with the use of conventional combined oral contraceptives is, thus, reduced with oral contraceptives containing drospirenone.

In this study, no significant difference is observed between the two groups in decreasing serum testosterone and DHEAS levels. A review by Jakubowicz et al. (16) reported a 44% decrease in serum androgens in obese women diagnosed with PCOS. A decline in serum androgens is also reported in lean women diagnosed with PCOS who were on metformin therapy. However, Bobde et al. (10) and Cosma et al. (17) reported oral contraceptive containing drospirenone to be more effective in improving hirsutism in patients with PCOS. Drospirenone being a 17- α spironolactone derivative exhibits anti-androgenic property. This property is also exhibited by metformin in this study probably because of its ability to treat insulin resistance in this inherently insulin-resistant population. Insulin resistance is postulated as a mechanism in the pathogenesis of PCOS (18, 19) because of the following hypotheses. First, hyperinsulinemia is hypothesized to increase ovarian testosterone production by stimulating insulin receptors present on the ovarian theca cells, which act by a signaling pathway different from that mediating the metabolic effects of insulin. Second, hyperinsulinemia results in decreased synthesis of sex hormone-binding globulin in the liver, and thus, free testosterone levels are increased. Third, insulin facilitates local activity of insulin-like growth factor-binding protein-1 (IGF-1) in the ovary, which stimulates ovarian androgen production. Both the drugs were well tolerated with no serious adverse events being recorded.

The results of this study suggest that the universal guidelines released by the Endocrine society may not be applicable to this population; hence, ethnicity-wise modifications may be required. Good response to metformin on hyperandrogenism in this patient subset proves that it may be beneficial for South Asians who are more insulin resistant compared with Caucasians. Further studies are required.

The limitations of the study are that the study design was observational, and there was loss to follow-up of patients. Li et

al. (20) also reported a 25.6% treatment compliance and follow-up rate among patients with PCOS in the 6-month study period. Non-compliance and subsequent failure to return for review was observed among patients with an increased BMI, and the contributing factors included the long duration of therapy, delayed beneficial effects of drug treatment, and concern regarding adverse drug reactions. This study depicts a similar scenario, and thus, reinforces the need to develop educational tools and materials to strengthen treatment education and intervention in the clinic. Moreover, drug treatment for patients with PCOS is provided on an outpatient basis. In this age of advancing technology, the development of mobile applications to provide reminders to patients to take their pill daily at home and go to the clinic for regular reviews can be a simple, yet effective step to ensure treatment compliance.

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Informed Consent: Informed consent was obtained.

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