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Effects of ethinyl estradiol and desogestrel on clinical and metabolic parameters in Indian patients with polycystic ovary syndrome

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Abstract

Aim: The aim of this study was to examine the therapeutic effects of an ethinyl estradiol (EE) and desogestrel (DSG) combination pill in polycystic ovary syndrome (PCOS).

Methods: A total of 42 women with PCOS were treated with an EE 30 mcg and DSG 150 mcg (EE/DSG) combination pill for 12 cycles. The following parameters were studied at 0, 6, and 12 months: body mass index, abdominal circumference, Ferriman–Gallwey score, presence of acne and acanthosis nigricans, serum testosterone and sex-hormone-binding globulin levels, fasting glucose and fasting insulin levels. Free androgen index and glucose : insulin ratio were calculated.

Results: There were significant improvements in Ferriman–Gallwey score, incidence of acne, serum testosterone and sex-hormone-binding globulin levels and free androgen index values at the 6-month follow up. But there were no further beneficial changes in the above parameters at the 12-month follow up. There were no significant changes in body mass index, abdominal circumference, incidence of acanthosis nigricans, fasting glucose and insulin levels and glucose : insulin ratio during treatment.

Conclusion: Significant improvements in hyperandrogenic parameters were seen only in the first 6 months of treatment with EE/DSG in PCOS. Further continuation with this pill did not produce any significant improvement. There were no adverse effects on insulin sensitivity.

Key words: androgenic parameter, desogestrel, insulin resistance, oral pill, polycystic ovary syndrome.

Introduction

Polycystic ovary syndrome (PCOS) is characterized by various symptoms and signs, which include menstrual disorders, evidences of hyperandrogenism (clinical and/or biochemical) and ultrasonographic features. Mode of treatment is mainly guided by the main complaint of the patient.

Ethinyl estradiol (EE) combined with a progestogen, has been used for many years to treat these women. This combination not only helps in cycle control, but also suppresses the pituitary-ovary axis, increases the sex-hormone-binding globulin (SHBG) level, and lowers the 'free' androgen level.

Desogestrel (DSG) is a third-generation progestogen, and is considered lipid-friendly and relatively less androgenic. Many PCOS women are now believed to have insulin resistance (IR), and many studies have shown that oral contraceptives can cause deterioration of IR and several other metabolic,

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cardiovascular and inflammatory parameters.[1–3] Androgens themselves and the androgenic progestogen in many oral pills can induce or increase IR.[4,5]

Pills containing antiandrogens, such as cyproterone acetate or drospirenone, are already available, but they are costly compared to the DSG-containing pill. Here lies the importance of using a cheaper pill of low androgenicity in a resource-poor setting. To the best of our knowledge, there are few studies where EE and DSG have been used together for more than 6 months. Therefore, this study was performed to evaluate the effects of EE/DSG on clinical and selected endocrinal and metabolic parameters in Indian women with PCOS.

Materials and Methods

This prospective, open label, single-arm study was conducted at the gynecology clinic of the first author at S.C. Das Memorial Medical and Research Center, after obtaining permission from the Institutional Ethics Committee. Informed consent was obtained at study initiation.

A total of 42 women (age range 17–31 years) who reported to the first author's clinic consecutively with the complaints of oligomenorrhea (≤six menses per year), with clinical evidences of hyperandrogenism (hirsutism and/or acne), were studied. All patients underwent detailed clinical examination and hormonal tests, as mentioned below, for the diagnosis of PCOS, as per the Androgen Excess Society (2006) criteria.[6] All women were unmarried.

During clinical examinations, all patients had measurements of their height, weight and abdominal circumference (AC). Blood pressure (BP) was recorded. The procedures followed have been reported already.[7] Body mass index (BMI) (as kg/m^2) was calculated in each case from height and weight measurements. Hirsutism scoring was done as per the modified Ferriman–Gallwey score (mFG score). Patients using cosmetic measures were requested not to depilate for at least 1 month before evaluation. To avoid interobserver error, the first author (S.M.B.) graded the degree of hirsutism in all cases. A mFG score of ≥6 was considered as hirsutism.[8] Presence of acne and acanthosis nigricans (AN) was noted in each case, and reported as 'Yes/No'. The number of cases having acne and AN were expressed at each time-point as % of patients with acne and AN present.

Ultrasonography (USG) was done to note the status of the ovaries. Transabdominal ultrasonography was carried out in unmarried girls due to social reasons. All women had an ovarian volume of more than 10 cc.

Assay methods

The following biochemical tests were carried out: serum total testosterone level (TT); sex-hormone-binding globulin (SHBG) level; and insulin level and plasma glucose level (after 8–10 h fasting). These hormonal tests were done on the second–third day of a progestogen-induced bleeding.

Free androgen index (FAI) was calculated as per the following formula:

$$\mathrm{FAI} = \frac{\mathrm{Testosterone\,(nmol/L)}}{\mathrm{SHBG\,(nmol/L)}} \times 100.$$

Serum testosterone was measured with Electrochemiluminescence Immunoassay, Roche Lot. no. 181371–01. Insulin was measured with Elecsys 2010, Roche Lot no. 179–202-01. SHBG was measured with the enzyme-linked immunosorbent assay technique (EIA-2996). Plasma glucose was measured using the glucose oxidase method. All tests were done at Ashok Laboratory, Jodhpur Park, Kolkata, India. As it was an open-label study, the laboratory test values were available at each point of study.

Exclusion criteria (appropriate clinical and/or biochemical tests were performed for the following)

1 Cases with hyperprolactinemia/hypothyroidism
2 Secondary causes of androgen excess
3 Women who had any hormone treatment in the preceding 3 months (to avoid inaccuracy in the assessment of circulating androgen/ SHBG levels)
4 Women older than 40 years of age with irregular periods
5 Women on medications known to affect carbohydrate metabolism (like corticosteroids in the preceding month or oral contraceptive pill use in the preceding 3 months) or known to have diabetes mellitus
6 Patients with impaired renal or hepatic function
7 Patients diagnosed to be hypertensive and/or taking any antihypertensive medication
8 Patients clinically diagnosed to have cardiac diseases or on medication for the treatment of cardiac diseases.

After initial clinical and laboratory evaluation, each patient was advised to take a combination of EE (30 mcg)/DSG (150 mcg): one tablet daily from the first day of her menstruation for 21 days, then a 7-day gap, and

again for 21 days, and so on cyclically. After six cycles of treatment, each patient was clinically evaluated at the first author's clinic as before, and the above-mentioned tests were repeated. Each patient was advised to continue the drug for six more cycles, and a final review was performed, with another set of the same tests and clinical assessments, after 12 months of treatment (second follow-up visit).

Statistical calculation

Sample size calculation: The primary outcome to be measured was a drop in the mean serum testosterone level of 0.15 ng/mL. The study assumed a standard deviation (SD) of 0.28 at baseline and 0.25 at study end based on previous samples. Assuming a correlation coefficient of zero, for a 5% level of significance and 80% power, for a one-sided test, the study required 41 patients. While the study could be conducted for a larger sample, due to resource constraints in India, the present study attempts to capture a more attainable sample size.

Recruitment period

From the previous registration rates at the study centre, a recruitment period of 6 months was proposed to the ethics committee, and all patients meeting the study inclusion/exclusion criteria within this period were offered enrolment. A total of 42 patients volunteered to participate in the study. The study was proposed for 6 months with a follow-up visit at 12 months.

Dropouts

If a patient did not appear for the first follow-up visit, she was excluded from the study. For single missing observations after first follow up, the last observation was carried forward to compensate for dropouts, provided the last observation carried forward did not significantly change the mean observations of the group. This meant that despite dropouts after 6 months, the study could assume the drug effect persisting and could analyze for the initial sample size. By 12 months, nine patients had dropped out. The inclusion of the previous data (from 6 months) for these nine patients did not significantly change the group mean of 33 patients who completed the study at 12 months but allowed the power analysis to remain valid till the end of the study.

An intention-to-treat analysis was performed for 42 patients with parametric data analyzed using repeated measures ANOVA with Tukey's post-test; non-parametric data were analyzed using Friedman repeated measures ANOVA with Dunn's post-test, dichotomous variables were analyzed using the χ^2-test and odds ratio was calculated for significant changes.

Results

At study initiation, the participants were aged 22.4 ± 5.53 years (mean ± SD). Table 1 shows the mean ± SD values of BMI, AC, presence of acne and AN (in %), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting sugar, fasting insulin and glucose : insulin ratio of the subjects at the three points of study, namely at baseline (0 months), at 6 months and at 12 months. It shows that there were no significant changes in the values of BMI, AC, presence of AN, SBP or DBP between 0 months and 6 months, and 6 months and 12 months. However, the reduction in acne from baseline to 6 months of treatment was significant ($P < 0.0001$). After the initial 6 months of treatment, there was no further improvement in acne.

Table 1 Values of body mass index, abdominal circumference, systolic and diastolic blood pressure, percentage positive for acanthosis nigricans, acne, fasting blood sugar, fasting insulin and glucose : insulin ratio of the subjects at various time-points (values are mean [standard deviation] or [%] as the case may be)

Time-points	BMI (kg/m^2)	AC (cm)	AN present *n* (%)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Acne present *n* (%)	Fasting sugar (mg%)	Fasting insulin (mcu/mL)	G : I ratio
0 months (*n* = 42)	25.02 (4.3)	77.5 (9.7)	12 (28.5)	119.25 (13.1)	77.7 (9.1)	21 (54.1)†	88.5 (7.4)	14.9 (9.2)	10.2 (9.1)
6 months (*n* = 42)	24.8 (3.9)	77.5 (8.8)	12 (28.52)	123.1 (11.6)	79.1 (7.3)	6 (23.4)†	87.1 (8.5)	14.4 (8.1)	8.7 (8.5)
12 months (*n* = 33)	24.9 (3.9)	77.5 (6.1)	10 (30.3)	120.3 (11.6)	77.6 (7.4)	6 (18.1)†	86.4 (8.5)	14.7 (8.7)	8.2 (6.5)

†Significant change in the first 6 months (χ^2-test, $P < 0.0001$). AC, abdominal circumference; AN, acanthosis nigricans; BMI, body mass index; BP, blood pressure; G : I ratio, fasting glucose : insulin ratio.

Table 2 Values of FG score, serum testosterone, SHBG and FAI of the study subjects at various time-points (all expressed as mean [standard deviation])

Time-points	FG score	Testosterone (ng/mL)	SHBG (nmol/L)	FAI
0 months ($n = 42$)	6.4 (5.0)	0.94 (0.2)	31.03 (22.2)	8.4 (9.7)
6 months ($n = 42$)	4.6 (3.6)†	0.34 (0.2)†	141.9 (78.7)†	1.11 (1.1)†
12 months ($n = 33$)	3.7 (3.4)	0.37 (0.2)	143.4 (75.3)	1.61 (2.0)

†Significant at only first 6 months compared with corresponding value at 0 months ($P < 0.0001$). FAI, free androgen index; FG, Ferriman–Galway; SHBG, sex-hormone-binding globulin.

Table 2 shows the results for FG score, serum testosterone, serum SHBG and the FAI. It reveals that with EE/DSG, there was significant improvement in FG scores, testosterone level, SHBG level, and the value of FAI in the initial 6 months of treatment ($P < 0.0001$) and this improvement was sustained at 12 months ($P < 0.0001$ compared to baseline). However, there was no significant change in the parameters studied between 6 months and 12 months.

Discussion

In this study, the authors report their clinical experience on the use of EE/DSG in Indian women with PCOS. PCOS patients need long-term treatment.[9] The American College of Obstetricians and Gynecologists considers combined oral contraceptive pills to be the mainstay of medical treatment of PCOS women who do not wish to become pregnant.[10] The present study shows that 6 months of therapy with this combination of EE/DSG can cause significant improvements in acne and biochemical hyperandrogenic parameters and is especially relevant in an Indian context because of the higher cost of antiandrogenic progestogen-containing pills. Table 2 shows that this improvement in hyperandrogenism, as observed in the initial 6 months, is not maintained after continuing treatment for 12 months.

Morreale *et al*.[11] studied the effects of EE/DSG-containing pills in PCOS for six cycles only. They stressed the need for long-term study of this third-generation pill in PCOS. They found significant improvements in insulin sensitivity, without changes in weight or BMI. Pasquali *et al*.[12] found that long-term treatment with oral pills in women with PCOS prevented the deterioration in insulin sensitivity, found in untreated women. The authors did not replicate these findings.

Low SHBG level in PCOS may be an intrinsic feature of the syndrome. It may not be related to obesity always, because low SHBG has been reported in lean PCOS women also. As SHBG rises, FAI level decreases. Our study shows that there is a significant rise in SHBG level by 6 months of treatment, but there is no change after the initial 6 months of treatment. Consequently, the FAI level shows the same trend. Our study also shows a similar trend with testosterone level. The stimulatory effect on SHBG may be due to the EE content of the medication. DSG is a progestogen derived from 19-nortestosterone. It may be the intrinsic androgenic activity of DSG that finally counteracts the stimulatory effects of EE on SHBG. In a recent study, De Leo *et al*.[13] found that testosterone (total and free form) dropped by 40–60% but the rise in SHBG level was less with DSG compared to pills containing other antiandrogens. They stressed the need to perform clinical studies to determine the effects of oral pills upon clinical signs of hyperandrogenism. In a randomized trial, Kriplani *et al*.[14] found a rise of BP and BMI with DSG-containing pills. The progestogen component may have an intrinsic androgenic action, but it was speculated that this might be negligible. DSG blocks the estrogen-induced increase of SHBG to a lesser degree than older combined oral pills.[15] DSG can inhibit LH-mediated androgen production.[16,17] Further studies are needed to assess the intrinsic androgenic effects of the DSG-containing pill.

EE activates the renin-angiotensin-aldosterone system, leading to fluid and electrolyte retention.[18] This in turn can increase bodyweight and BP. Our study did not find any change in BMI, AC, and BP (both SBP and DBP) even by 12 months of treatment. Again, Morreale *et al*.[11] did not find any change in BMI after 6 months of treatment, although they reported improvement in insulin sensitivity.

Our study finds that EE/DSG does not alter serum glucose or insulin level, even by 12 months of treatment. Consequently, there is no change in fasting glucose : insulin ratio, or in other words, there is no

deterioration of insulin sensitivity. EE/DSG combination may be considered neutral with respect to insulin resistance. Morreale *et al*.[11] also reported no deterioration of insulin sensitivity, detected by fasting insulin level, and homeostasis model assessment. In their study of frequently sampled IV glucose tolerance test in PCOS patients taking EE/DSG, Cagnacci *et al*.[19] found that this combination caused a decrease in insulin sensitivity and an increase in glucose utilization (SG), independent of insulin. A reduction of SG has been reported in PCOS patients.[20] Therefore its improvement during EE/DSG treatment might be beneficial. This may be due to the highly estrogenic equilibrium of this pill, which can amplify pancreatic beta cell response to glucose, leading to more efficient glucose control. This can counterbalance the reduction in insulin sensitivity induced by EE/DSG. Further studies are needed to evaluate whether this EE/DSG pill can reduce or delay the onset of diabetes in these women.

This study shows that the significant antiandrogenic effects of a combination of EE/DSG in polycystic ovary syndrome occur only in the first 6 months of treatment. Further continuation of this pill does not help in amelioration of hyperandrogenism. There is no significant adverse effect on insulin sensitivity.

Lack of a control group and not using any insulin sensitizers in addition are major limitations of this study. In spite of the limitations, the originality of the study is that it has been done among an Indian population.

More studies are needed comparing this combination pill with pills containing other progestogens. After 6 months of treatment with an EE/DSG combination pill, the clinician may need to change over to other pills with more antiandrogenic effects. The results of the present study are informative for any clinician interested in the treatment of PCOS.

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