

# Effects of drospirenone pill in Indian women with polycystic ovary syndrome

## *Polikistik over sendromlu Hintli kadınlarda drospirenon hapının etkileri*

Sudhindra Mohan Bhattacharya<sup>1</sup>, Mainak Ghosh<sup>2</sup>, Nupur Nandi<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynaecology, KPC Medical College, Kolkata, India

<sup>2</sup>Department of Pharmacology, Calcutta Medical College, Kolkata, India

### Abstract

**Objective:** To study the effects of treatment with a drospirenone pill (DRSP) (with ethinyl oestradiol, EE) in Indian women with polycystic ovary syndrome (PCOS).

**Material and Methods:** Fifty-one women with PCOS (Androgen excess society criteria, 2006), with preset inclusion-exclusion criteria, treated with a combination of EE 30 mcg and DRSP 3 mg cyclically in the traditional (21+7) regimen, were evaluated at baseline and after six and twelve cycles of treatment. Parameters studied were - body mass index (BMI), abdominal circumference (AC), Ferriman Galwey (FG) score, presence of acne and acanthosis nigricans, serum testosterone, sex hormone binding globulin (SHBG), fasting glucose and fasting insulin levels. Free Androgen Index (FAI) and Glucose: Insulin ratio (G:I) were calculated.

**Results:** Significant improvements in clinical and biochemical hyperandrogenic parameters were found at the two points of study. There were no significant changes in BMI, AC, incidence of acanthosis, or metabolic parameters studied.

**Conclusion:** EE/DRSP improves hyperandrogenic parameters significantly without affecting the insulin resistance adversely in Indian women with PCOS. (J Turkish-German Gynecol Assoc 2011; 12: 144-7)

**Key words:** Drospirenone pill, polycystic ovary syndrome, androgenic parameters, insulin resistance, Indian women

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### Özet

**Amaç:** Polikistik over sendromu (PKOS) olan Hintli kadınlarda drospirenon (DRSP) hapı ile (etinil estradiol, EE ile birlikte) tedavinin etkilerini çalışmak.

**Gereç ve Yöntemler:** Önceden belirlenmiş dahil etme-dışlama kriterlerine göre seçilen, geleneksel (21+7) rejimde EE 30 mcg ve DRSP 3 mg kombinasyonu ile döngüsel olarak tedavi edilen PKOS'lu (Androjen fazlalığı topluluğu kriterleri, 2006) 51 kadın başlangıçta ve tedavinin 6. ve 12. döngüsünde değerlendirildi. Çalışılan parametreler; vücut kitle indeksi (VKİ), karın çevresi (KÇ), Ferriman Galwey (FG) skoru, akne ve akantozis nigrikans varlığı, serum testosteron, seks hormonu bağlayan globulin (SHBG), açlık glukozu ve açlık insülin düzeyleri idi. Serbest Androjen İndeksi (SAI) ve Glukoz: İnsülin oranı (G:I) hesaplandı.

**Bulgular:** Çalışmanın iki noktasında klinik ve biyokimyasal hiperandrojenik parametrelerde önemli iyileşmeler bulundu. VKİ, KÇ, akantozis insidansı veya çalışılan metabolik parametrelerde anlamlı bir değişiklik yoktu.

**Sonuçlar:** EE/DRSP PKOS'lu Hintli kadınlarda insülin direncini olumsuz olarak etkilemeksizin hiperandrojenik parametreleri anlamlı olarak iyileştirmektedir.

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**Anahtar kelimeler:** Drospirenon hapı, polikistik over sendromu, androjenik parametreler, insülin direnci, Hintli kadınlar

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### Introduction

Polycystic ovary syndrome (PCOS) is one of the most common gynaecological endocrinological disorders. Ethnic background of women with PCOS may affect the clinical, hormonal and metabolic characteristics of this condition. Response to treatment of PCOS in Asia may be different from those in Western countries (1). Indians are an ethnic group at particularly high risk for central obesity, type 2 diabetes mellitus and dyslipidaemia, all resulting from a state of insulin resistance (IR). Interaction of environmental factors (obesity) with the

genetic factors finally results in the characteristic metabolic and menstrual disturbances and the final expression of the PCOS phenotype (2).

For a long time, combined oral contraceptives containing ethinyl oestradiol (EE) and a progestogen, have been used to treat these women. This combination can suppress the pituitary-ovary axis, increase sex hormone binding globulin (SHBG) level and can cause lowering of "free" androgen level (3).

The new progestogen drospirenone (DRSP) derived from 17-alpha-spironolactone is found to have a pharmacological profile similar to that of natural progesterone with clinically relevant antimineralocorticoid activities and antiandrogenic

activities and has been claimed to have the potential to reduce body weight and blood pressure (BP) (4). Many studies have shown that oral contraceptives can cause deterioration of IR (5, 6).

This study was performed to evaluate the effects of EE/DRSP on various hyperandrogenic (clinical and biochemical) and metabolic parameters in Indian women with PCOS.

## Materials and Methods

This was a prospective, open label, single arm study. The Ethics committee of S.C. Das Memorial medical and research center approved the study protocol and subject consent was obtained at study initiation.

Fifty-one unmarried women (age ranges 15-32 years) presenting with the complaints of oligomenorrhoea ( $\leq$  six menses per year), with clinical evidence of hyperandrogenism (hirsutism and /or acne) were studied at the gynaecology clinic of the first author. PCOS was diagnosed as per the Androgen Excess Society 2006 criteria (7). Detailed clinical and hormonal tests were done, as per the said criteria. Secondary causes of hyperandrogenism such as 21-hydroxylase deficiency, Cushing's syndrome, hypothyroidism, hyperprolactinaemia, and androgen-secreting tumors were excluded by appropriate clinical and /or laboratory tests. All patients underwent ultrasonographic examination of the lower abdomen to note the status of their ovaries. In India, transvaginal ultrasonography cannot be performed in unmarried girls. All women had an ovarian volume of more than 10 cc.

Exclusion criteria included adolescent girls with a gynecologic age (age since menarche) less than three years; those who had used oral pills in the preceding three months, those with known diabetes or hypertension or having treatment known to affect glucose metabolism such as corticosteroids.

During clinical examination, the height, weight, abdominal circumference (AC), blood pressure (BP) were recorded. The procedures followed have been reported previously (8). Body mass index (BMI) (as kg / m<sup>2</sup>) was calculated in each case from height and weight measurements.

BP was measured in each case by Korotkoff sound (stage V was used to determine the diastolic pressure). Hirsutism scoring was done as per the modified Ferriman- Galwey score (mFG score) (9). Patients using cosmetic measures were requested not to depilate for at least one month before evaluation. To avoid interobserver error, the first author (SMB) himself graded the degree of hirsutism. The mFG score of  $\geq 6$  was considered as hirsutism. 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.

The following biochemical tests were carried out on the second/third day of a progestogen-induced bleeding - Serum total testosterone (TT); sex hormone binding globulin (SHBG); fasting insulin and plasma glucose levels (after 8-10 hours fasting).

"Free Androgen Index" (FAI) was calculated as per the following formula

$$\text{FAI} = \frac{\text{Testosterone (nmol/l)}}{\text{SHBG (nmol/l)}} \times 100.$$

Serum testosterone was measured by Electrochemiluminescence Immunoassay, Roche Lot. No. 181371-01. Insulin was measured by Elecsys 2010, Roche Lot No. 179-202-01. SHBG was measured by ELISA technique (EIA-2996) [DRG instruments GmbH, Germany]. Plasma glucose was measured by 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. After initial clinical and laboratory evaluation, each patient was advised to take a combination of EE (30 mcg) / DRSP (3 mg) (Yasmin<sup>®</sup>, Bayer Scherring Pharma, Berlin, Germany) 1 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. Each patient was advised to continue the tablet for 6 cycles, then to repeat the tests as done at the beginning and clinically evaluated at the first follow-up visit at the first author's clinic. The final review was performed with another set of the same tests and clinical assessments after 12 months of treatment at the second follow-up visit.

## Statistical analysis

**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 of 0.25 at baseline and 0.22 at study end, based on previous samples. Assuming a correlation coefficient of zero, for 5% level of Significance and 80% power, for a one-sided test, the study required 42 patients.

**Analysis:** A per-protocol analysis was done at study end using Graphpad Instat version 5.0. Repeated measures ANOVA with Tukey's post-test was used for parametric variables, Friedman ANOVA with Dunn's post-test for non-parametric variables. Dichotomous parameters were analyzed with Chi-square test.

## Results

At study initiation, the participants were aged  $22.2 \pm 5.4$  years (mean  $\pm$  SD). Table 1 shows the mean  $\pm$  SD values of BMI in kg / M<sup>2</sup> (minimum 21 to maximum 35), AC (cm), presence of acne and AN (in %), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting sugar (mg%), fasting insulin (mcu /ml) and G: I ratio of the subjects at the three points of study, namely at baseline (0 month), 6 month and 12 months. It shows that there are no significant changes in the values of BMI, AC, presence of AN, SBP, DBP between 0 months and 6 months and 6 months and 12 months. However, the percentage of patients having acne was reduced significantly from baseline to 12 months ( $p < 0.05$ ).

Table 2 shows the results for FG score, serum testosterone, serum SHBG and the free androgen index (FAI). It is found that with EE/DRSP, there is significant improvement in the FG score ( $p < 0.005$ ). The testosterone level reduced significantly after 6 months of treatment and this reduction was maintained at 12 months ( $p < 0.001$ ). Serum SHBG showed a very signifi-

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

Time points	BMI (kg/M <sup>2</sup> )	AC (cm)	A.N present n (%)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Acne Present n (%)	FBS (mg %)	Fasting insulin (mcu / ml)	G:I ratio
0 month (n=51)	26.2 (4.3)	78.3 (9.5)	32 (62.7)	122.7 (11.7)	77.8 (9.9)	28 (54.9)	89.3 (7.3)	17.3 (10.9)	8.0 (6.6)
6 month (n=51)	26.1 (4.0)	77.5 (8.8)	31 (60.8)	126.0 (8.0)	81.0 (10.5)	16 (31.4)*	87.5 (6.4)	19.6 (9.6)	5.9 (3.8)
12 month (n=51)	26.1 (4.0)	77.5 (8.6)	31 (60.8)	125.3 (8.0)	80.3 (9.8)	15 (29.4)*	87.6 (7.1)	20.1 (10.6)	5.9 (3.9)

\*significant compared to corresponding value at 0 month (p<0.05); G: I ratio- fasting glucose- insulin ration, n=Number, BMI: Body Mass Index, AC: Abdominal circumference, BP: Systolic and diastolic blood pressure, FBS: Fasting blood Sugar, G:I: Glucose-Insulin ratio, SD: Standard deviation

**Table 2. Values of Ferriman-Gallwey score, serum testosterone, sex hormone binding globulin levels and free androgen index of the study subjects at various time-points [all expressed as mean (SD)]**

Time Points	F: G score	Testosterone (ng / ml)	SHBG (nmol / l)	FAI
0 month (n=51)	6.7 (5.2)	0.51 (0.3)	31.4 (15.9)	6.4 (4.2)
6 month (n=51)	4.8 (3.1)	0.30 (0.16)**	155.1 (67.0)**	0.94 (1.2)**
12 month (n=51)	4.6 (2.9)*	0.28 (0.16)**	157.6 (68.7)**	0.81 (0.89)**

\*significant comparing with corresponding value at 0 months (p<0.05), \*\*very significant comparing with corresponding value at 0 months (p<0.001), F: G: Ferriman-Gallwey score, SHBG: Sex hormone binding globulin, FAI: Free androgen index, SD: Standard deviation

cant rise (p<0.001) after 6 months of treatment with EE/DRSP and remained significantly high at 12 months. The FAI similarly showed a very significant fall at 6 months (p<0.001) and remained suppressed at 12 months.

## Discussion

In this study the authors report their clinical experience on the use of EE/DRSP in Indian women with PCOS. Yu Ng et al (1) had stressed that it is important to take into consideration the ethnic background of patients in future studies related to PCOS.

Table 2 shows that the trend in improvement in various hyperandrogenic manifestations are also maintained even after 6 months of treatment. Darney (10), Cerel-Suhl et al. (11) reported that EE/DRSP combination can help to obviate the common adverse effects found with the use of pills containing nortestosterone derivatives.

DRSP possesses a strong antigonadotropic activity per se. Muhn et al. (12, 13) in animal studies has shown that DRSP can cause significant reduction of plasma LH levels. This LH lowering effect of DRSP may be one of the mechanisms by which the hyperandrogenic manifestations are reduced. Our study has shown a significant reduction of testosterone level by 6 months of treatment and also after 12 months of treatment. Krattenmacher (14) has shown that EE/DRSP combination can inhibit the steroidogenic enzymatic activities at the ovarian level. Our study has also shown significant improvement in cosmetically unacceptable signs of hyperandrogenism namely, acne, hirsutism. Hirsutism is in part ethnically determined, being more common in women with dark skin (15). Zarger et al. (16)

in a study from Kashmir, India found that 10.1% had mild hirsutism (F: G score 6-9) and 0.4% had moderate hirsutism (F: G score 10-14). DRSP has been reported to have antiandrogenic effects even in the peripheral level also, by repression of androgen receptor-mediated transcription. DRSP can competitively bind to androgen receptors, because of its intrinsic molecular structure (17).

Low SHBG level in PCOS may be an intrinsic feature of the syndrome and this cannot always be explained by obesity alone because low SHBG has been reported in lean PCOS women also. Our study shows that there is a significant rise in SHBG level by 6 months of treatment and this trend is maintained even after 12 months of treatment. Consequently, FAI level shows the same trend. This stimulatory effect is due to the EE content of the medication. This shows that DRSP does not antagonize this stimulatory effect of EE on SHBG level in contrast to the progestogen derived from 19-nortestosterone. This action can also explain the significant amelioration obtained in the various manifestations of hyperandrogenism (14).

Our study did not find any change in BMI, AC, and BP (both SBP and DBP). EE activates the Renin-Angiotensin-Aldosterone system, leading to fluid and electrolyte retention. This in turn can raise the body weight and BP. DRSP on the other hand, because of its unique antimineralocorticoid activity, induces sodium excretion and a compensatory rise in rennin secretion, plasma rennin activity, angiotensin II, and plasma aldosterone (18).

Our study found that EE/DRSP does not alter serum glucose or insulin level even after 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. Guido et al (19), Gaspard et al. (20) stated that EE/DRSP might be considered neutral with respect to insulin resistance. Pehlivanov et al. (21) reported that in Europe, the most widely used combined oral pill in women with PCOS is a combination of EE (35 mcg) and 2 mg cyproterone acetate. However, the present study shows that the EE/DRSP can be a reasonable alternative. Lack of a control group is a major limitation of the study. A larger study will help to establish whether this combination has any effect on insulin resistance and compare the same with similar agents. The originality of the study is that it has been carried out among the Indian population. Considering the unique Indian population structure with strictly defined endogamous and genetically homogeneous populations, the result of this present study is an enriching experience for any clinician, particularly in the Indian subcontinent interested in the treatment of the polycystic ovary syndrome. Further, this study shows that the response to treatment is the same as that in Western countries.

#### Conflict of interest

No conflict of interest was declared by the authors.

#### References

1. Yu Ng EH, Ho PC. Polycystic Ovary Syndrome in Asian Women. *Semin Reprod Med* 2008; 26: 14-21. [\[CrossRef\]](#)
2. Bhatia V. IAP National Task Force for Childhood Prevention of Adult Diseases: Insulin Resistance and Type 2 Diabetes Mellitus in Childhood. *Indian Paed* 2004; 41: 443-57.
3. Practice Bulletin ACOG Clinical management guidelines for obstetrician-gynecologist: number 41. *Obstet Gynecol* 2002; 100: 1389-402. [\[CrossRef\]](#)
4. Mansour D. Experiences with Yasmin: the acceptability of a novel oral contraceptive and its effects on well-being. *Eur J Contracept Reprod Health Care* 2002; 7: 35-41.
5. Skouby SO, Anderson O, Saurbrey N, Kuhl C. Oral contraception and insulin sensitivity: in vivo assessment in normal women and women with previous gestational diabetes. *J Clin Endocrinol Metab* 1987; 64: 519-23. [\[CrossRef\]](#)
6. Godsland IF, Walton C, Felton C, Prondler A, Patel A, Wynn V. Insulin resistance, secretion and metabolism in users of oral contraceptives. *J Clin Endocrinol Metab* 1992; 74: 64-70. [\[CrossRef\]](#)
7. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Androgen Excess Society. Position statement: criteria for defining Polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab* 2006; 91: 4237-45. [\[CrossRef\]](#)
8. Bhattacharya SM. Insulin resistance and overweight-obese women with polycystic ovary syndrome. *Gynecol Endocrinol* 2010; 26: 344-47. [\[CrossRef\]](#)
9. Lewis V. Polycystic ovary syndrome: a diagnostic challenge. *Infert Reprod Med Clin N Amer* 2003; 14: 497-516. [\[CrossRef\]](#)
10. Darney AD. The androgenicity of progestins. *Am J Med* 1995; 98: 104s-10s. [\[CrossRef\]](#)
11. Cere!-Suhl L, Yeager BF. Update on oral contraceptive pills. *Am J Obstet Gynecol* 1999; 179: 577-82.
12. Muhn P, Krattenmacher R, Beier S, Elger W, Schillinger E. Drospirenone: a novel progestogen with antimineralocorticoid and antiandrogenic activity: pharmacological characterization in animal models. *Contraception* 1995; 51: 99-110. [\[CrossRef\]](#)
13. Muhn P, Fuhrmann U, Fritzscheier KH, Krattenmacher R, Schillinger E. Drospirenone: a novel progestogen with antimineralocorticoid and antiandrogenic activity. *Ann NY Acad Sci* 1995; 761: 311-35. [\[CrossRef\]](#)
14. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. *Contraception* 2000; 62: 29-38. [\[CrossRef\]](#)
15. Carmina E, Koyama T, Chang L, Stanczyk FZ, Lobo RA. Does ethnicity influence the prevalence of adrenal hyperandrogenism and insulin resistance in polycystic ovary syndrome? *Am J Obstet Gynecol* 1992; 167: 1807-12.
16. Zarger AH, Wani AI, Masoodi SR, Laway BA, Bashir MI, Salahuddin M. Epidemiologic and etiologic aspects of hirsutism in Kashmiri women in the Indian subcontinent. *Fertil Steril* 2002; 77: 674-8.
17. Fuhrmann U, Krattenmacher R, Slater EP, Fritzscheier KH. The novel Progestin drospirenone and its natural counterpart progesterone: biochemical profile and antiandrogenic potential. *Contraception* 1996; 54: 243-51. [\[CrossRef\]](#)
18. Oelkers W, Foidart JM, Dombrovicz N, Welter A, Heithecker R. Effects of new oral contraceptive containing an antimineralocorticoid progestogen, drospirenone, on the rennin-aldosterone system, body weight, blood pressure, glucose tolerance and lipid metabolism. *J Clin Endocrinol Metab* 1995; 80: 1816-21. [\[CrossRef\]](#)
19. Guido M, Romualdi D, Giuliani M, Suriano R, Selvaggi L, Apa R, et al. Drospirenone for the Treatment of Hirsute Women with Polycystic Ovary Syndrome: A Clinical, Endocrinological, Metabolic Pilot Study. *J Clin Endocrinol Metab* 2004; 89: 2817-23. [\[CrossRef\]](#)
20. Gaspard U, Scheen A, Endrikat J, Buicu C, Lefebvre P, Gerlinger C, et al. A randomized study over 13 cycles to assess the influence of oral contraceptives containing ethinyl oestradiol combined with drospirenone or desogestrel on carbohydrate metabolism. *Contraception* 2003; 67: 423-9. [\[CrossRef\]](#)
21. Pehlivanov B, Mitkov M. Efficacy of an oral contraceptive containing drospirenone in the treatment of women with polycystic ovary syndrome. *The Eur J Contracept Reprod Health Care* 2007; 12: 30-5. [\[CrossRef\]](#)