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Original Article

The Effect of Combined Oral Contraceptives on Metabolic and Cardiovascular Parameters in Patients with Polycystic Ovary Syndrome

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Objectives: To evaluate the effects of combined oral contraceptives (COC), containing 30 ㎍ ethinyl estradiol (EE)/ 3 mg drospirenone (DRSP) on metabolic and cardiovascular parameters in women with polycystic ovary syndrome.
Methods: Thirty patients diagnosed as PCOS according to Rotterdam criteria were included in this study. 30 ㎍ EE/ 3 mg DRSP was taken for 6 months. Follicle stimulating hormone (FSH), leutinizing hormone (LH), LH/FSH ratio, E2, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride (TG), LDL/HDL ratio, atherogenic index of plasma (AIP), total testosterone, sex-hormone binding globulin (SHBG), free androgen index (FAI), 17 hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulfate (DHEAS), fasting insulin, fasting glucose, homeostatis model assessment insulin resistance (HOMA-IR), homocysteine, and high-sensitivity C-reactive protein (hsCRP) were measured at baseline and at the end of treatment.
Results: STherapy with 30 ㎍ EE /3 mg DRSP significantly decreased LH/FSH ratio. The serum androgen levels including total testosterone, DHEAS, and 17 OHP decreased significantly and FAI was reduced significantly, accompanied by an increase of SHBG level. Total cholesterol, TG, LDL cholesterol, and HDL cholesterol increased significantly. The AIP and LDL/HDL ratio were not changed by COC treatment. HOMA IR, the glucose to insulin ratio and cardiovascular markers including hsCRP and homocysteine were not changed significantly.
Conclusion: Treatment with 30 ㎍ EE/3 mg DRSP in women with PCOS, without significant negative impact on cardiovascular and metabolic parameters, COC with 30 ㎍ EE/3 mg DRSP appears to be an effective drug in women with PCOS.

Key Words: Drospirenone, Oral Contraceptives, Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a common endocrine disorder of young women occurring globally in 6% to 10% of the population.[1] Combined oral contraceptives (COC) are most frequently used for long-term management and are recommended as the primary treatment of menstrual irregularity. The components of COC, estrogens and progestogens, are known to have various metabolic effects, including effects on lipid metabolism and, on the risk for cardiovascular disease.[2] Because of its possible deteriorating effect on carbohydrate metabolism and lipid profile, the use of COC in women with PCOS is still under scrutiny.[3] However, the metabolic effects of COCs are extremely variable, depending on the dose of ethinyl estradiol (EE) and the type of progestin associated.[4] A recently developed COC contains 30 ㎍

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EE and 3 mg drospirenone (DRSP), a new progestogen. This combination is known to have a high contraceptive efficacy in combination with an excellent cycle control and a low incidence of adverse effects.[5-6] Although there are few studies on effects of COC in women with PCOS, only a few trials have been done with drospirenone containing pills and more informations are needed to determine its metabolic and cardiovascular impacts. Therefore, this study was designed to evaluate the effects of COC, containing 30 μg ethinyl estradiol (EE)/3 mg drospirenone (DRSP) on metabolic and cardiovascular parameters in women with PCOS.

MATERIALS AND METHODS

Thirty patients diagnosed with PCOS who attended to the outpatient clinic of reproductive endocrinology of Yonsei University Health System between February 2009 and February 2010 were enrolled in the study. The study protocol was approved by the ethics committee of Severance Hospital and Yonsei University College of Medicine, and Institutional Review Board approval was obtained. PCOS was defined according to the Rotterdam criteria.[7] All subjects underwent transvaginal or transrectal ultrasound in the follicular phase, on 3rd day of menstrual cycle. Subjects with hypertension, diabetes mellitus, personal history of cardiovascular events or received treatment with COCs, insulin sensitizers, or drugs that might interfere with lipid profile, cardiovascular marker, or carbohydrate metabolism for the previous 6 months were excluded.

All subjects were studied at baseline, during the follicular phase of the menstrual cycle, on 3rd day of menstrual cycle and after six cycles of treatment. The blood sampling was obtained at baseline and after 6 months of treatment. Standing height and weight were measured and the mean BMI was calculated. Waist and hip circumferences were measured, and waist/hip ratio was also calculated. Blood samples were collected for fasting glucose, insulin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride along with hormonal parameters including follicular stimulating hormone (FSH), estradiol (E_2), leutinizing hormone (LH), total testosterone (T), sex-hormone binding globulin (SHBG), 17 hydroxyprogesterone (17-OHP) and dehydroepiandrosterone sulfate (DHEAS). The Free androgen index (FAI) was calculated: T (nmol/L) /SHBG (nmol/L) × 100. As for indicators of insulin sensitivity, the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: (blood glucose × insulin)/22.5. The glucose/insulin ratio (G/I) was also calculated.[4] Homocysteine and high sensitivity C-reactive protein (hsCRP) was also obtained as cardiovascular markers. Atherogenic index plasma was calculated using the following formula: log (TG/HDL-C).

After the baseline assessment, all patients were prescribed a monophasic COC containing 30 μg of EE plus 3 mg of DRSP (Yasmin; Schering AG, Berlin, Germany) for 6 months.

STATISTICAL ANALYSIS

Analysis was done using the SPSS software 16.0 (SPSS Inc, Chicago, IL, USA). Data are presented as mean±S.D. as appropriate. Paired *t* test was used to compare changes in follow-up values from baseline. A *P* value <0.05 was considered statistically significant.

RESULTS

Table 1 shows clinical and demographic characteristics of the study population. Among the enrolled women, 16.6% had all three criteria of PCOS, irregular menstruation, hyperandrogenism and polycystic ovary. The age of patients was 22.38±4.05 years.

Effects of treatment on lipid profile are shown in Table 2. There were significant rises in total cholesterol

(171.00±26.39 vs. 202.41±3 1.88, P<0.001), triglyceride (82.00±32.61 vs. 114.07±50.52, P=0.001), LDL cholesterol (97.67±27.98 vs. 112.09±31.11, P=0.001), and HDL cholesterol (57.77±14.27 vs. 71.13±15.21, P<0.001) from baseline and at the end of 6 months of treatment.

Table 1. Clinical characteristics in women with polycystic ovary syndrome

	Baseline characteristic (n=30)
Age (years)	22.38±4.05
Parity (%)	
Nulliparous	93.3
Multiparous	6.7
BMI (kg/m^2)	21.81±5.40
Waist circumference (cm)	74.83±12.86
Waist/hip ratio	0.79±1.57
Phenotypes of PCOS (%)	
IM+HA+PCO	16.7
IM+PCO	50
HA+PCO	33.3
Menstrual pattern (%)	
Oligomenorrhea	50
Amenorrhea	50
Modified FG scores	9.70±5.30
Ovarian volume (cm^3)	
Right	10.38±5.38
Left	7.93±3.30

BMI, body mass index; HA, Hyperandrogenism; IM, Irregular Menstruation; PCO, polycystic ovary; FG scores, Ferriman-Gallwey scale. Values are the mean±SD.

There was no change in glycemic profile at the end of 6 months treatment. None of the patients were found to be diabetic either at baseline or at the end of treatment.

As compared to the baseline, hormonal profile showed significant decrease after 6 months of treatment. LH (8.30±5.66 vs. 3.99±3.42, P<0.001), LH/FSH ratio (1.59±1.14 vs. 0.81±0.67, P<0.001), Total testosterone (53.84±25.09 vs. 37.78±19.07, P=0.001), 17-OHP (1.29±0.86 vs. 0.76±0.36, P=0.006), and DHEAS (199.40±72.81 vs. 160.86±68.82, P=0.026) were significantly decreased at the end of treatment, accompanied by an increase of SHBG levels (45.66±21.97 vs. 171.55±44.21, P<0.001). As a consequence the FAI (5.33±3.86 vs. 1.00±1.21, P<0.001) was significantly reduced. Indexes of cardiovascular risk did not differ

Table 2. Biochemical parameters at baseline and after treatment

	Baseline (n=30)	After treatment (n=30)	P value
LH (mIU/mL)	8.30±5.66	3.99±3.42	<0.001
FSH (mIU/mL)	5.38±1.50	5.75±2.70	0.422
LH/FSH ratio	1.59±1.14	0.81±0.67	<0.001
E_2 (pg/mL)	31.48±26.81	22.60±15.83	0.096
Total cholesterol (mg/dL)	171±26.39	202.41±31.88	<0.001
LDL cholesterol (mg/dL)	97.67±27.98	112.09±31.11	0.001
HDL (mg/dL)	57.77±14.27	71.13±15.21	<0.001
TG (mg/dL)	82.00±32.61	114.07±50.52	0.001
LDL/HDL ratio	1.87±0.95	1.67±0.62	0.055
AIP	0.13±0.24	0.18±0.25	0.271
Total testosterone (ng/dL)	53.84±25.09	37.78±19.07	0.001
SHBG (nmol/L)	45.66±21.97	171.55±44.21	<0.001
FAI	5.33±3.86	1.00±1.21	<0.001
DHEAS (mg/dL)	199.40±72.81	160.86±68.82	0.026
17-OH Progesterone (ng/mL)	1.29±0.86	0.76±0.36	0.006
Fasting glucose (mg/dL)	85.87±5.77	84.28±6.12	0.221
Fasting insulin (mg/dL)	9.91±5.76	8.81±4.17	0.540
Glucose/Insulin ratio	1.16±6.31	1.21±6.61	0.909
HOMA IR	2.08±1.39	1.85±0.92	0.600
hsCRP (mg/L)	1.88±3.23	1.04±0.78	0.252
Homocysteine (μmol/L)	12.13±3.20	12.26±2.39	0.634

AIP, atherogenic index of plasma; DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index; FSH, follicle stimulating hormone; HDL; high-density lipoprotein; HOMA IR, homeostatic model assessment insulin resistance; LDL, low-density lipoprotein; LH, leutinizing hormone; TG, triglyceride; SHBG, sex hormone-binding globulin; 17-OHP, 17 hydroxyrogesterone. Values are the mean±SD.

before and after the treatment.

DISSCUSSION

After 6 months of therapy, there was a significant improvement in the hormonal profile with falls in the level of total testosterone, LH, LH/FSH ratio, and DHEAS level and a rise in SHBG concentration.

DRSP is a unique progestin derived from 17 α -spironolactone; it shares progesterone's antiandrogenic and anti-mineralcorticoid properties, with no androgenic, estrogenic, glucocorticoid or antiglucocorticoid activity.[8-10] Although clinical manifestations of hyperandrogenism were not assessed in our study, Guido et al[11] reported improvement in F-G score and hirsutism, along with androgenic profiles. Similar results were found by Ibanez et al.[12] These results reflect the antiandrogenic activity of DRSP.

Several studies have reported that augmented LH pulse amplitude and increased expression of LH receptors in the ovaries of women with PCOS are considered to be central in the pathogenesis of the syndrome.[15-16] Therefore, decrease in LH would be beneficial in the treatment of PCOS. With this respect, similar to previous studies,[11,13] significant decrease in LH levels and LH/FSH ratio were observed in our study. With this finding, we could speculate a strong antigonadotropic activity of DRSP.

One of the issues concerning the use of COCs in women with PCOS is the increase of the insulin resistance and the induction of glucose intolerance, thereby affecting the carbohydrate metabolism. Conflicting data exist regarding this issue. According to Palep-Singh et al[14], EE/DRSP combined OC impairs insulin resistance as do other COCs, while Guido et al.[11] reported no deterioration in glucose tolerance. No significant impairment of carbohydrate metabolism occurred in our study.

Controversial data have been reported on the changes in the lipid profile with EE/DRSP therapy.[6,8,11-12] Triglycerides and HDL cholesterol levels were significantly increased in most studies with significant decrease in LDL.[11-13] As a result of increase in HDL cholesterol and a LDL cholesterol level, the HDL/LDL ratio increase after EE/DRSP treatment, which is considered beneficial with respect to cardiovascular disease risk reduction.[17] A significant increase in HDL cholesterol, Triglycerides, total cholesterol level and LDL cholesterol level was observed in our study, but with no shift in the HDL: LDL ratio. In this respect, the changes in the lipid profile with EE/DRSP therapy do not seem to have a negative impact on cardiovascular risk.

It is well known that PCOS patients have higher risk of cardiovascular events than normal healthy people. Among the surrogate markers of cardiovascular disease, homocysteine is an intermediate product formed by the breakdown of methionine[18] and hyperhomocysteinemia was shown to be a risk factor for atherogenesis and chronic vascular damage, especially when insulin levels increased.[19] After 6 months of therapy with EE/DRSP, no subjects showed an increase of homocysteine level, which is in agreement with Merki-Feld et al.[20] Highly sensitive C-reactive protein (hsCRP) is a chronic subclinical inflammation marker which is known as an another predictive marker of cardiovascular events. Its elevation in PCOS patients have been reported in many studies.[21-22] In this study, there was no significant change in hsCRP level after 6 months of therapy with EE/DRSP and this could be reflected by the report of Mohlig et al. that serum CRP levels are associated with obesity rather than with the presence of PCOS per se.[23]

In conclusion, a six months of treatment with 30 μ g of EE plus 3 mg of DRSP is efficacious in women with PCOS patients to improve hyperandrogenic hormonal profile, without negative impact both on metabolic and cardiovascular parameters. However, our results were obtained with a small sample size

and should be reconsidered with a large population and more long-term follow-up period to further assess the metabolic and cardiovascular parameters of PCOS and the relationship to COCs.

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▌국문초록 ▐

연구목적: 30 ㎍ estradiol (EE)과 3 mg drospirenone (DRSP)을 함유한 혼합 경구 피임약이 다낭성난소증후군 환자의 대사적 및 심혈관계 지표에 미치는 영향에 대하여 분석하였다.
연구대상 및 방법: Rotterdam 진단 기준에 합당한 전체 다낭성난소증후군 환자 30명을 대상으로 30 ㎍ EE/3 mg DRSP 경구 피임약을 6개월간 복용 하였다. 호르몬 검사, 총 콜레스트롤, 저밀도 지단백(LDL), 고밀도 지단백(HDL), 중성지방(TG), LDL/HDL 비 및 총 테스토스테론, 성호르몬 결합 단백(SHBG), 17 hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulfate (DHEAS)를 측정하여 Free androgen index (FAI)를 계산하였다. 공복 인슐린 및 혈당을 측정하고 homeostatic model assessment of insulin resistance (HOMA-IR)를 계산하였으며, 지질 검사, atherogenic index of plasma (AIP) 및 호모시스테인과 high-sensitivity C-reactvie protein (hs-CRP)를 약 복용 전과 6개월 뒤에 검사하였다.
결과: 30 ㎍ EE/3 mg DRSP 경구 피임약으로 치료한 결과 LH/FSH 비가 유의하게 감소하였으며, 총 테스토스테론, DHEAS, 그리고 17-OHP를 포함한 혈청 안드로겐 수치들이 유의하게 감소하였다. 또 FAI가 의미 있게 낮아졌고 SHBG가 증가하였다. 총 콜레스트롤, 중성지방, LDL, 그리고 HDL이 유의하게 증가한 반면, AIP와 LDL/HDL 비는 변화가 없었다. HOMA-IR과 당/인슐린 비 및 hs CRP와 homocysteine를 포함한 심혈관계 지표에는 유의한 차이가 없었다.
결론: 다낭성난소증후군 환자에서 30 ㎍ EE/3 mg DRSP 경구 피임약 치료는 대사 및 심혈관계 지표에 부정적인 영향을 미치지 않아 다낭성난소증후군 환자에게 사용함에 있어 안전할 것으로 사료된다.

중심단어: 드로스피레논, 경구 피임약, 다낭성난소증후군