Comparison of Norgestrel- *Versus* Cyproterone Acetate-Containing Hormone Replacement Therapy on Lipid - Lipoprotein Metabolism

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Abstract

To compare the effects on the lipid profile of estradiol valerate with norgestrel to a regimen of estradiol valerate with cyproterone acetate. Sixty-four healthy women in their perimenopause or early postmenopause, aged between 40-55 years, were randomized to one of the two 21-day sequential regimens: estradiol valerate 2 mg/day for 21 days and combined with either norgestrel 0.5 mg/day or cyproterone acetate 1 mg/day from day 12 to 21, with 7 days of drug–free interval, for 12 cycles. Lipid profiles were followed at baseline, 6 and 12 cycles. Sixty-one subjects completed the study, 30 in the norgestrel group and 31 in the cyproterone group. During 12 cycles of study, serum HDL cholesterol levels decreased significantly in the norgestrel group ($p<0.01$) and were unchanged in the cyproterone group. The levels were significantly lower in the norgestrel group than in the cyproterone group ($p<0.05$). No differences were found between groups as regards LDL cholesterol and total cholesterol levels. Triglyceride levels decreased significantly in the norgestrel group ($p<0.01$), remained unchanged in the cyproterone group and the levels were significantly different between groups ($p<0.01$). In conclusion, the study demonstrated that sequential regimen of estradiol valerate with norgestrel produced less favorable HDL cholesterol but more favorable triglyceride levels than the regimen of estradiol valerate with cyproterone acetate.

Key word : Hormone Replacement Therapy, Lipid Metabolism

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There is an increased incidence of coronary heart disease after menopause[1]. The decline of estrogen at this time induces changes in serum lipid and lipoproteins by increasing levels of low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglycerides. However, the effect on high-density lipoprotein (HDL) cholesterol is not as striking[2]. These changes have a strong causal role in the pathogenesis of coronary heart disease[3].

Postmenopausal women who use estrogen therapy have lower rates of coronary heart disease than those who do not[4]. The important mechanism is consistent with the ability of estrogens to reverse the lipoprotein pattern back to the premenopausal levels,[5] by increasing HDL-cholesterol and decreasing LDL-cholesterol[6,7]. With respect to triglycerides, the effect seems to be potentially adverse[7]. Estrogen treatment has been shown to increase hepatic triglyceride production[8].

The use of unopposed estrogen has been shown to increase the risk of endometrial carcinoma[9]. The addition of progestogen in sufficient quantity may reduce this risk. Two main types of progestogen, derivatives of 19-nortestosterone and 17α-hydroxyprogesterone have been used. The documented effect of the androgenic action of 19-nortestosterone type (e.g. norgestrel) is decreased HDL cholesterol and triglyceride levels[10]. However, some studies have demonstrated that low doses of this type of progestogen may have little effect on HDL cholesterol[7,11].

Cyproterone acetate is a 17α-hydroxyprogesterone derivative with antiandrogenic property [12]. It has been reported that this progestogen may retain the increased HDL cholesterol seen with unopposed estrogen, lower the levels of LDL cholesterol and does not influence the total cholesterol and triglyceride[7]. However, some studies showed that these effects are inconsistent especially with respect to the HDL cholesterol and triglyceride levels[7,13].

There is a shortage of studies regarding the lipid profile after use of different types of progestogen among postmenopausal Thai women. Hence, we conducted a prospective study to describe pairwise differences of lipid profile particularly HDL cholesterol by comparing two combined hormone replacement regimens containing different progestogens in women in their perimenopausal or early postmenopausal periods.

MATERIAL AND METHOD

Sixty-four women attending the menopause clinic, Chulalongkorn Hospital, aged between 40-55 years, were recruited for the study. Women were eligible to participate if they had a body mass index between 19-30 kg/m^2, suffered from menopausal symptoms (e.g. hot flushes, sweating) and were in the perimenopausal or early postmenopausal period. The term "perimenopause" is defined as having had irregular vaginal bleeding during the previous 12 months and serum follicle stimulating hormone (FSH) level above 10 IU/L, "early postmenopause" is defined as natural menopause, having had no vaginal bleeding for 1 to 5 years retrospectively and serum FSH level above 30 IU/L. Exclusion criteria were: pregnancy, surgical menopause, history of severe systemic disease (e.g. hepatic, renal, cardiac), blood pressure ≥ 160/95 mmHg, smoking, regular alcohol consumption, treatment with any medication that could have an influence on lipid metabolism, hyperlipidemia: LDL cholesterol ≥ 190 mg/dl or triglycerides ≥ 500 mg/dl, current or past history of estrogen related tumors and taking of hormone replacement therapy within the previous three months. The study protocol was approved by the Ethics Committee of Chulalongkorn University Hospital. All women gave written informed consent to participate in the study.

All subjects were randomly allocated to one of two treatment groups. There were 32 patients in each group, both groups received a 28 days/cycle hormone regimen for 12 cycles. Under both regimens, 2 mg/day of estradiol valerate was administered for 21 days and a progestogen was added sequentially for 10 days and followed by a 7-day drug-free period in each cycle. The progestogen used was either norgestrel 0.5 mg/day (CycloProgynova®) or cyproterone acetate 1 mg/day (Climen®). Subjects were considered to have good compliance if they had taken at least 80 per cent of their medication. Women were scheduled to be seen at 1, 3, 6, 9 and 12 cycles. At every visit, vital signs, body weight, adverse events and medication compliance were assessed. Serum lipids and lipoproteins were measured at baseline, 6 and 12 cycles. All samples were taken between day 25 and 28 of the cycle.

Serum total cholesterol levels were measured using an enzymatic colorimetric test with cholesterol esterase, cholesterol oxidase and 4-aminophenazone[14]. Triglyceride levels were measured using an enzymatic colorimetric test with

glycerol phosphate oxidase and 4- aminophenazone[15]. HDL cholesterol levels were measured after precipitated LDL cholesterol and very low density lipoprotein (VLDL) cholesterol with phosphotungstic acid and magnesium choride[16]. The LDL cholesterol levels were calculated by the Friedewald formula[17]. The intra-and interassay coefficients of variation were as follows; 2.9-4.7 per cent for total cholesterol, 3.3–5.4 per cent for triglycerides and 1.2-2.0 per cent for HDL cholesterol. Between-group statistical analyses were performed using student's *t*-test for independent groups. The general linear model for repeated measures was used where it was appropriate. When the overall comparison of data at different cycles was significant, the differences between pairs of groups were made by Bonferroni method. Rates of incidence of adverse events were compared using the Chi-square and Fisher's Exact test. The level of significance was $p<0.05$.

RESULTS

Sixty-one women completed the study. There were 30 women in the norgestrel group and 31 women in the cyproterone group. Two subjects in the norgestrel group were withdrawn because of headache (1) and breast pain (1). One patient in the cyproterone group discontinued therapy because of poor compliance. Population characteristics are shown in Table 1 which shows no significant difference between the two treatment groups.

Table 2 shows values of the lipid profile. Baseline values were comparable between the two treatment groups. Serum HDL cholesterol levels significantly decreased from the baseline at 6 and 12 cycles in the norgestrel group ($p<0.01$), whereas the levels were unchanged in the cyproterone group. In the norgestrel group, HDL cholesterol levels were significantly lower at 6 and 12 cycles than in the cyproterone group ($p<0.05$). LDL cholesterol, and total cholesterol levels decreased significantly in the cyproterone group at 6 cycles ($p<0.01$) but showed no significant changes from the baseline at 12 cycles. In the group receiving norgestrel, LDL cholesterol levels showed no significant changes throughout 12 cycles. The between group differences were not significant at both 6 and 12 cycles. Triglyceride levels showed a significant decrease during norgestrel treatment ($p<0.01$). There was a trend to higher levels of triglycerides during cyproterone treatment but the difference did not reach statistical significance. Comparing between groups, the differences were significant at 6 cycles ($p<0.05$) and 12 cycles ($p<0.01$). Fig. 1 reveals mean per cent change of lipid profile from baseline.

Adverse events reported by the subjects are presented in Table 3. There were no significant differences as to the incidence of adverse events between both groups.

DISCUSSION

Several studies[18] have revealed that serum total cholesterol, LDL cholesterol and triglycerides increase after menopause, whereas HDL

Table 1. Baseline population characteristics (mean ± SE).

Characteristics	Norgestrel (N=30)	Cyproterone (N=31)
Age (y)	48.7±0.6	49.8±0.6
Body mass index (kg/m^2)	23.6±0.6	23.7±0.6
Mean arterial pressure (mmHg)	87.6±1.9	90.4±1.9
Follicle stimulating hormone (IU/L)	55.2±9.9	55.7±10.2

Table 2. Lipid-lipoprotein profile (mean ± SE) at baseline and after six and 12 treatment cycles.

Parameters (mg/dl)	Cycle	Norgestrel (N=30)	Cyproterone (N=31)
HDL cholesterol	0	59.2 ± 2.3	57.5 ± 1.2
	6	53.6 ± 1.8* +	60.2 ± 2.0*
	12	52.9 ± 2.3* +	60.6 ± 2.0*
LDL cholesterol	0	143.3 ± 7.2	155.1 ± 5.9
	6	141.5 ± 7.1	136.0 ± 5.7+
	12	146.4 ± 7.0	145.8 ± 6.2
Total cholesterol	0	220.0 ± 7.8	232.2 ± 6.0
	6	210.5 ± 7.9	217.6 ± 6.1+
	12	213.5 ± 7.7	224.3 ± 6.3
Triglycerides	0	89.2 ± 7.4	97.5 ± 8.0
	6	77.1 ± 8.3*	102.6 ± 6.9*
	12	71.0 ± 6.1* * +	112.1 ± 10.1**

* Statistically significant difference between treatment groups ($p<0.05$)

** Statistically significant difference between treatment groups ($p<0.01$)

\+ Statistically significant difference compared to baseline ($p<0.01$)

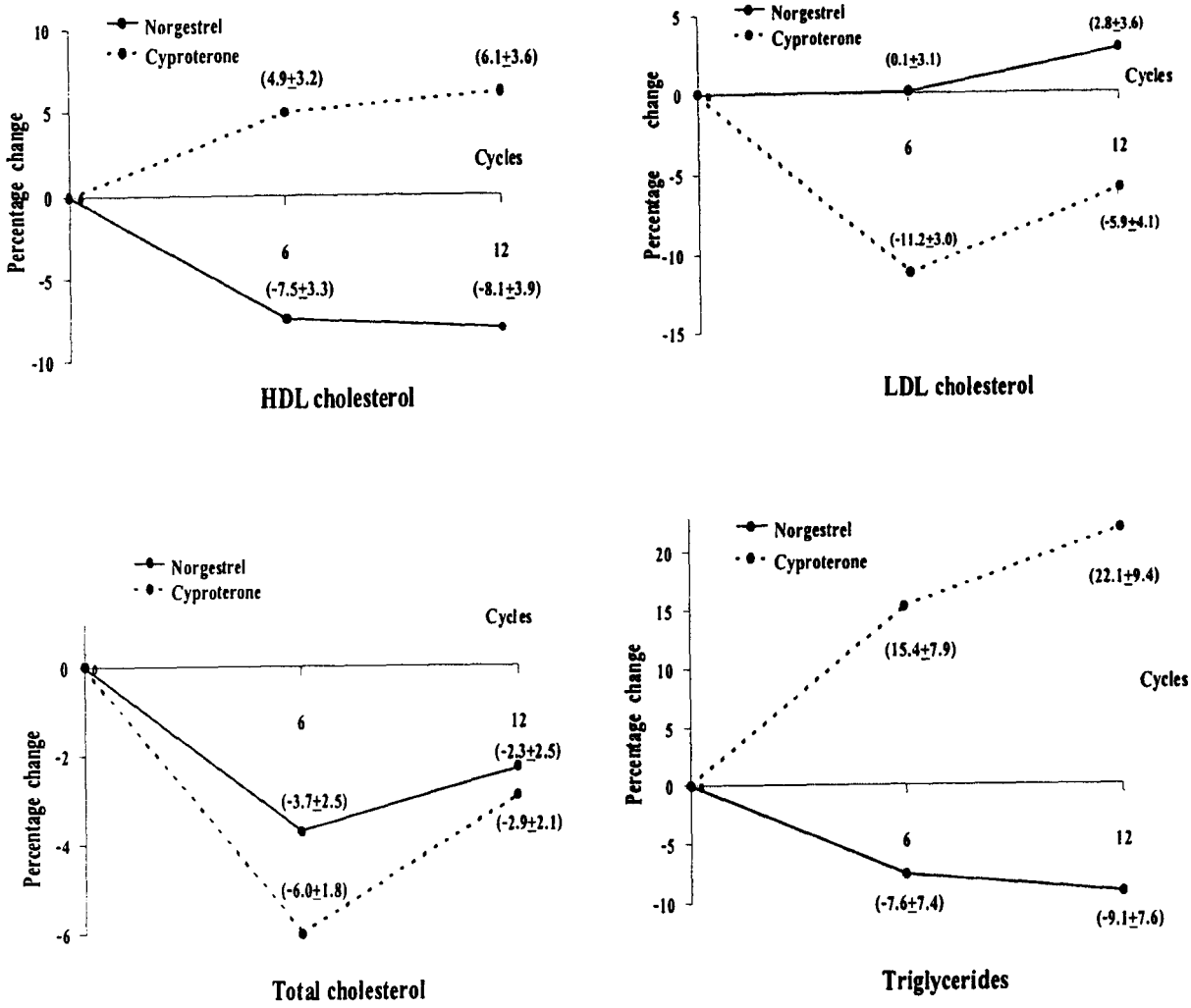

Fig. 1. Mean percentage change of lipid profile from baseline.

cholesterol falls or remains unchanged[4]. The levels of LDL cholesterol already start to gradually increase 2 years before menopause while a gradual decrease in HDL cholesterol occurs[2]. This provides evidence that perimenopausal women are also at an increased risk for coronary heart disease.

This study showed that norgestrel combined with estradiol could reduce HDL cholesterol levels, whereas cyproterone acetate combined with estradiol did not significantly alter the HDL cholesterol levels from the baseline values. It seemed that the expected estrogen-induced rise of HDL cholesterol was eliminated by addition of any type of progestogens in this study. Upon comparison between groups, the HDL cholesterol levels were significantly lower in the norgestrel group than in the cyproterone group. Thus, the addition of progestogen had different effects on HDL cholesterol and these might depend on the androgenic property of each progestogen.

Table 3. Adverse events during follow-up.

Adverse event	Cycle			
	3	6	9	12
Nausea				
Norgestrel	1 (3.3)	3 (10.0)	2 (6.7)	1 (3.3)
Cyproterone	2 (6.3)	4 (12.9)	1 (3.2)	0
Headache				
Norgestrel	5 (16.7)	4 (13.3)	6 (20.0)	3 (10.0)
Cyproterone	6 (18.8)	5 (16.1)	5 (16.1)	2 (6.5)
Weight gain				
Norgestrel	5 (16.7)	6 (20.0)	4 (13.3)	6 (20.0)
Cyproterone	5 (15.6)	5 (16.1)	6 (19.4)	4 (12.9)
Breast pain				
Norgestrel	15 (50.0)	20 (66.7)	12 (40.0)	10 (33.3)
Cyproterone	18 (56.3)	20 (64.5)	15 (48.4)	11 (35.5)
Abnormal uterine bleeding*				
Norgestrel	5 (16.7)	3 (10.0)	3 (10.0)	2 (6.7)
Cyproterone	5 (15.6)	4 (12.9)	3 (9.7)	2 (6.5)
Acne				
Norgestrel	2 (6.7)	1 (3.3)	0	0
Cyproterone	0	0	0	0

Data are presented as number of patients (%)
N = 32 in each group at the beginning of the study
N = 30 in the norgestrel group at 3, 6, 9 and 12 cycles
N = 32, 31, 31 and 31 in the cyproterone group at 3, 6, 9 and 12 cycles respectively
* Nonperiodic bleeding, irregular bleeding, midcycle spotting

It has been reported that unopposed estrogen decreases LDL cholesterol levels[6]. Recent studies indicated that the addition of progestogen did not interfere with this effect[7,19]. According to our study, LDL cholesterol levels at the end of the study were unchanged compared with the initial values in both groups. The difference in our results from those of other studies might be due to the differences of the population we studied or to unknown mechanisms underlying progestogen action on LDL cholesterol metabolism.

Regarding total cholesterol, it would appear from this study that both these regimens were found to have no effect on total cholesterol levels at the end of the study.

Oral estrogen, increases triglyceride levels, but such increases were not seen with commonly used doses (2 mg) of estradiol[20]. The result from this study showed that androgenic property of norgestrel tended to lower triglyceride levels, this being an effect which should be considered favorable with respect to coronary heart disease.

All adverse events found in this study caused only minor consequences. We found no significant difference in all other adverse events between both groups except acne, which had been found only in women of the norgestrel group. The androgenic action of norgestrel may be responsible for this effect.

In conclusion, this study demonstrated that the change in HDL cholesterol in both groups was dependent on the type of progestogen. The more androgenic the property, the less favorable the effect on HDL cholesterol. Both hormonal regimens did not appear to influence LDL cholesterol and total cholesterol. Regarding triglycerides, the effect of norgestrel on this lipid might be considered more favorable than that of cyproterone acetate. The small sample size and short duration of this study

prohibited broad generalizations. Larger studies using different progestogens at various doses will be required to define a postmenopausal regimen that is protective of lipid profile.

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การศึกษาผลของฮอร์โมนทดแทนรวมที่มีโปรเจสโตเจนชนิดนอร์เจสเตร็ลเปรียบเทียบกับซัยโปรเตอโรน อะซีเตทต่อระดับไขมันและไลโปโปรตีนในเลือด

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เพื่อเปรียบเทียบผลของฮอร์โมนทดแทนรวมที่มีโปรเจสโตเจนต่างชนิดกันต่อระดับไขมันและไลโปโปรตีนในเลือดในสตรีวัยใกล้หมดระดูและวัยหมดระดูระยะต้น (1-5 ปี) ได้แบ่งสตรีวัยดังกล่าวที่มีอายุระหว่าง 40 ถึง 55 ปี เป็น 2 กลุ่ม โดยการสุ่ม สตรีทั้ง 2 กลุ่มได้รับฮอร์โมน 12 รอบ ๆ ละ 28 วัน ฮอร์โมนที่ใช้ในการศึกษาคือ Estradiol valerate 2 มิลลิกรัมต่อวันเป็นเวลา 21 วัน ร่วมกับโปรเจสโตเจนชนิดใดชนิดหนึ่งคือ กลุ่มที่หนึ่งได้รับ Norgestrel 0.5 มิลลิกรัมต่อวัน กลุ่มที่สองได้รับ Cyproterone acetate 1 มิลลิกรัมต่อวัน ในวันที่ 12 ถึง 21 และหยุดฮอร์โมนเป็นเวลา 7 วันในแต่ละรอบ สตรีที่เข้าร่วมการศึกษาได้รับการเจาะเลือดเพื่อตรวจหาระดับไขมันและไลโปโปรตีนก่อนได้รับฮอร์โมนและในรอบที่ 6 และ 12 ผลการศึกษาพบว่ามีสตรีจำนวน 61 ราย แบ่งเป็นกลุ่มที่หนึ่ง 30 ราย และกลุ่มที่สอง 31 ราย พบว่าระดับ HDL cholesterol ลดลงอย่างมีนัยสำคัญทางสถิติในกลุ่มที่หนึ่ง ($p<0.01$) และมีระดับต่ำกว่ากลุ่มที่สองอย่างมีนัยสำคัญทางสถิติ ($p<0.05$) ระดับของ LDL cholesterol และ Total cholesterol ของทั้ง 2 กลุ่มไม่มีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติ สำหรับระดับ Triglycerides พบว่าในกลุ่มที่หนึ่งมีระดับลดลงอย่างมีนัยสำคัญทางสถิติ ($p<0.01$) แต่ไม่พบมีการเปลี่ยนแปลงในกลุ่มที่สอง นอกจากนี้ยังพบว่าระดับ Triglycerids ในกลุ่มที่หนึ่งมีค่าต่ำกว่ากลุ่มที่สองอย่างมีนัยสำคัญทางสถิติ ($p<0.01$) กล่าวโดยสรุปการวิจัยนี้พบว่าฮอร์โมนทดแทนรวมที่มีโปรเจสโตเจนชนิด Norgestrel ทำให้ระดับ HDL cholesterol และ Triglycerides ลดลงอย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบกับชนิด Cyproterone acetate

คำสำคัญ : ฮอร์โมนทดแทน, ระดับไขมันในเลือด

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