Clinical and Metabolic Study of a New Monophasic Formulation Containing Ethinylestradiol and Gestodene

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Abstract : *Clinical and metabolic parameters were studied in healthy Thai women who took a new monophasic oral contraceptive formulation containing 30 mcg ethinylestradiol and 75 mcg gestoden (Δ -15-levonorgestrel) over 12 cycles.*

One hundred and seven patients were included in the clinical evaluation which covered a total of 913 woman-cycles. No accidental pregnancy occurred. Cycle control was excellent and body weight and blood pressure were not affected during one year of pill use. Continuation rate after 12 months was 70.9 per cent.

Of the 107 patients evaluated, 15 were included in the metabolic investigation which consisted of serial determinations of plasma glucose and insulin during periodic oral glucose tolerance testing (OGTT), serum cholesterol and lipoproteins and coagulation and fibrinolytic factors. Determinations were done at baseline, cycle 3, 6 and 12. There were small changes in plasma insulin and blood glucose levels during the OGTT. The minimal changes in lipid metabolism included a rise in triglyceride concentration and a decrease in LDL, HDL and total cholesterol. APTT, PT and Factor VII remained unchanged throughout the cycles but the AT III levels significantly decreased. (Thai J Obstet Gynaecol 1989 ; 1 : 81-9.)

Key words : clinical and metabolic study, monophasic formulation, ethinylestradiol, gestodene

Since combined estrogen-progestogen oral contraceptives (OCs) became available in the 1960s, an estimated 60 million women are currently using this method of contraception which to date, still represent the most effective reversible means of contraception.

The present formulations of combined OC pills differ from the earlier preparations in two respects: a lower dose of ethinylestradiol and the use of more appropriate progestogens. The

gonan class of progestogens has become the standard component through the years. Gestoden (Δ -15-levonorgestrel) is a new progestogen from the gonan class. Multicenter clinical and metabolic studies involving more than 19,000 woman-cycles of use with an OC formulation containing 75 mcg gestoden combined with 30 mcg ethinylestradiol showed high contraceptive efficacy, good cycle control and good patient acceptability[1-2].

This present study aims to evaluate the clinical and metabolic effects of this monophasic gestoden-ethinylestradiol combination in Thai women.

Patients and Methods

Healthy Thai women aged between 18 and 40 years old consulting at the Family Planning Clinic of the Department of Obstetrics and Gynaecology, Chulalongkorn University Hospital were considered eligible for inclusion in the study. Eligible patients were appraised of the objectives of the study and those consenting to take part in the study underwent complete history taking and physical examination including cytological evaluation. All patients without any of the exclusion criteria stipulated in the trial protocol were instructed to take the OC formulation which came as a standard calendar pack of 21 tablets containing 75 mcg gestoden and 30 mcg ethinylestradiol per tablet. A tablet was taken everyday starting on the first day of the menstrual cycle followed by a 7-day tablet-free interval. The patients took the pill for 12 cycles and were asked to come back for evaluation at cycle 3, 6, 9 and 12. Standard case report forms were used to record baseline parameters and subsequent findings through the treatment cycles. Clinical and gynaecologic parameters that were observed include incidence of accidental pregnancy, changes in blood pressure and body weight, cycle control (i.e., cycle length, amount and duration of bleeding, and incidence of breakthrough bleeding and spotting) and subjective and objective complaints.

Fifteen patients participating in the clinical evaluation were further evaluated as regards changes in laboratory parameters pertinent to carbohydrate and lipid metabolism as well as coagulation and fibrinolytic factors. The patients fasted at least 12 hours prior to venepuncture. Plasma insulin and glucose levels were measured before and after a glucose load of 75 g and then after 30 min, 1 hour, 1 1/2 hours, 2 hours and 3 hours. Plasma glucose was measured by the oxidase-peroxidase method. Plasma insulin was determined by radioimmunoassay.

Cholesterol and triglyceride determinations were carried out with the CHOD-PAP enzymatic test. Lipid fractions were separated by ultracentrifugation and apolipoprotein levels were determined using immunochemical assays. Blood coagulation and fibrinolytic factors were determined using standard commercial kits.

Data were analyzed using the statistical package for the social sciences (SPSS) utilizing paired *t* - test and other parametric tests, as appropriate, to test

statistical significance of the changes through the treatment cycles.

Results

Clinical parameters

One hundred and seven healthy Thai women were included in the clinical study. The patients went through 12 treatment cycles for a total of 913 woman-cycles of observation. The baseline paremeters are shown in Table 1.

Despite errors of tablet-taking in 2 per cent of cycles, no accidental pregnancies occurred.

Cycle length progressively shortened throughout the treatment cycles and duration of bleeding likewise reflected shorter duration of cycles, Table 2.

Plasma lipid and apolipoprotein fractions were evaluated as follows :

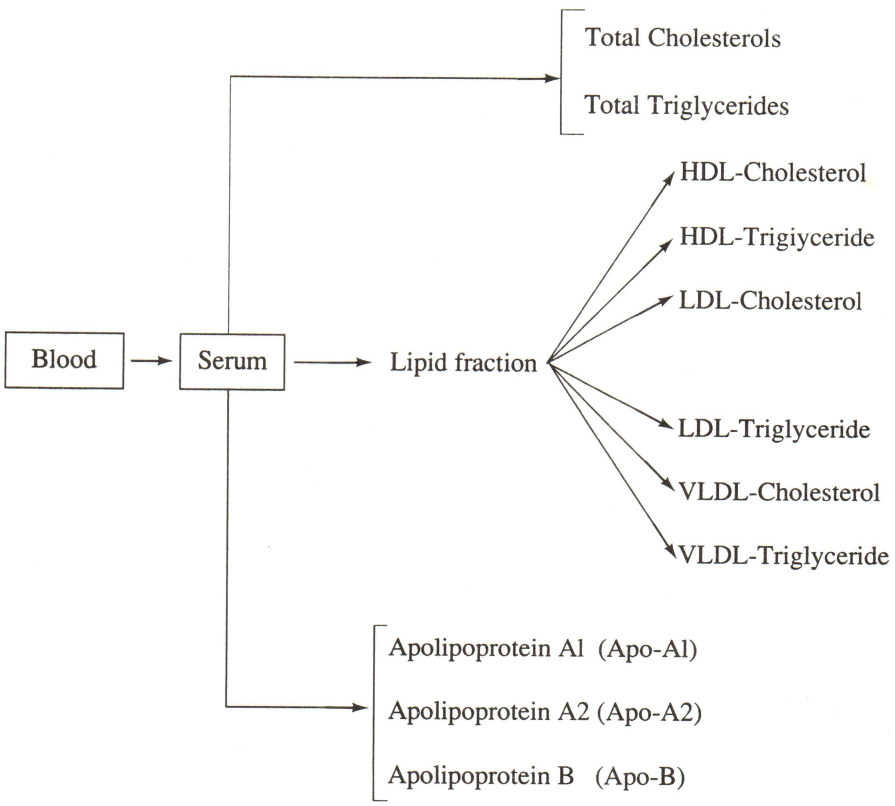

Table 1 Clinical data of the volunteers

Mean age (yrs)	25.2 (19-35)
Wight (kg)	50.5 (38-63)
Height (cm)	153 (142-164)
Quatelet index	22.9
Parity	0 - 2

Table 2 Changes in the clinical parameters throughout the cycles (mean values and % change from baseline)

	Mean cycle length (days)	Mean duration of bleeding (days)	Mean body weight(kg)
Pretreatment	30.5	4.2	50.5
Cycle 3	26.3	3.8	49.5
Cycle 6	28.4	3.9	49.7
Cycle 9	28.3	3.8	49.2
Cycle 12	28.3	3.8	50.2

Mean body weight showed minimal changes throughout the treatment cycles and these were all within < 1 kg weight fluctuations, Table 2.

Changes in blood pressure throughout the treatment cycles are reflected in Table 3. There were no clinically significant changes in both the systolic and diastolic pressures, with an overall mean percentage change from baseline equal only to 5 and 1 per cent respectively.

Table 3 Blood pressure changes (mean and % change from baseline)

	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Pretreatment	111.9	66.5
Cycle 3	106.3 *(-5.0%)*	68.1 *(+2.4%)*
Cycle 6	106.0 *(-5.0%)*	68.1 *(+2.4%)*
Cycle 9	104.2 *(-6.9%)*	64.8 *(-2.6%)*
Cycle 12	107.4 *(-4.1%)*	67.7 *(+1.8%)*
Overall mean change	*-5.25%*	*+1.0%*

Minimal side effects were noted during the study. Of the 50 patients who dropped out by the end of the study period, only 8 (16 per cent) were due to medical reasons or unwanted effects; 25 (50 per cent) were lost to follow-up and 17 (34 per cent) were due to personal reasons not related to the treatment or medication. Figure 1 shows the life table analysis throughout the treatment cycles. Continuation rate after 12 months was 70.9 per cent.

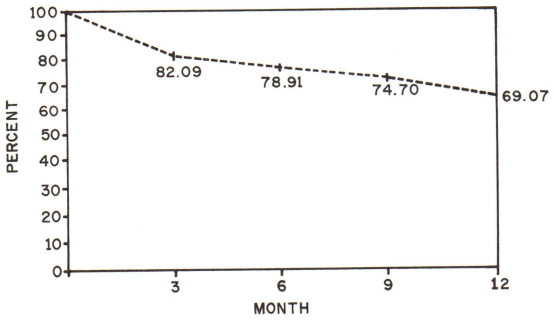

Fig. 1 Life table analysis

Metablic parameters

Fifteen volunteers underwent serial serum determinations of blood glucose and insulin during periodic oral glucose tolerance testing; cholesterol and lipoproteins; and coagulation and fibrinolytic factors.

Table 4 shows the results of the oral glucose tolerance tests done at baseline, cycle 3, cycle 6 and cycle 12.

Table 4 Blood glucose (mg/dl) and insulin levels (μu/ml) during the OGTT

	0 Min.	30 Min.	60 Min.	90 Min.	120 Min.	180 Min.
Baseline						
glucose	83.77	128.08	125.46	112.46	111.08	94.54
insulin	13.38	68.10	67.26	61.16	68.09	39.73
Cycle 3						
glucose	81.92	136.54	139.69	+ 132.00*	123.54	+ 103.46*
insulin	14.45	78.05	75.03	+ 85.14*	85.07	53.88
Cycle 6						
glucose	86.58	131.25	136.25	+ 133.67*	+ 130.08*	104.58
insulin	13.68	60.12	62.13	69.84	84.32	60.19
Cycle 12						
glucose	81.30	136.15	144.77	+ 138.54*	127.85	+ 101.54*
insulin	13.60	82.65	85.49	+ 86.57*	+ 105.05	64.36*

*statistically significant difference form baseline, $p < 0.05$

Compared with baseline there was statistically significant elevation of blood glucose levels at the 90th minute for cycle 3, 6, and 12. There were corresponding increases in plasma insulin which was significant for cycle 3 and cycle 12. Overall the area under the glucose concentration-time curve during the periodic OGTT (AUC) remained within the normal range.

Table 5 shows the cholesterol and lipoprotein determinations throughout the treatment cycles. Total cholesterol showed a consistent reduction throughout the cycles as well as HDL-C and LDL-C. Cholesterol VLDL showed a slight increase together with the triglycerides and its subfractions.

Table 5 Cholesterol and lipoprotein levels before treatment and at the end of the study

	Pretreatment levels (Mean)	Cycle 12 (Mean and % change from baseline)
Chol. VLDL*	.63	.65 (+ 3.2%)
Chol. LDL*	2.66	2.48 (-6.8%)
Chol. HDL*	1.53	1.43 (-6.5%)
Total chol.*	5.13	4.64 (-9.5%)
Trigly. VLDL*	.52	.60 (+15%)
Trigly. LDL*	.26	.35 (+ 34.6%)
Trigly. HDL*	.20	.28 (+ 40%)
Total trigly.*	1.14	1.51 (+ 32.5%)
HDL-C/Apo AI	.43	.37 (- 13.9%)
Apo B/Apo AI	.65	.52 (+ 20%)
Apo AI (mg/dl)	138.20	156.30 (+ 13.1%)
Apo AII (mg/dl)	26.80	34.20 (+ 27.6%)
Apo B (mg/dl)	86.50	78.90 (-8.8%)

*mmol/L

Table 6 Coagulation and fibrinolytic factors

	Pretreatment	Cycle			Overall
	(Mean)	3	6	12	Mean % change
		(Mean and % change)			
APTT (sec)	39.2	38.2 *(-2.5%)*	38.5 *(-1.7%)*	39 *(-0.5%)*	*(-1.6%)*
PT (sec)	11.9	11.8 *(-0.8%)*	11.6 *(-2.5%)*	11.7 *(-1.6%)*	*(-1.6%)*
TT (sec)	11.4	11.0 *(-3.5%)*	11.7 *(+6.1%)*	12.0 *(+5.3%)*	*(+2.6%)*
AT III (IU/ml)	49.1	29.6 *(-39.7%)*	32.4 *(-34.0%)*	20.9 *(-57.4%)*	*(-43.7%)*
Factor VII (%)	116.7	118.0 *(+1.1%)*	123.6 *(+5.9%)*	123.8 *(+6.1%)*	*(+4.4%)*

Table 6 shows the values of the coagulation and fibrinolytic factors. There were no significant changes in the values of APT/PT and Factor VII. Thrombin time was slightly increased at cycles 6, and this only reflects a mean increase of 2.6 per cent from baseline. Antithrombin III showed a significant decrease throughout treatment cycles.

Discussion

The long-term efficacy, acceptability and safety of any drug may only be established through epidemiological cohort studies. However, short of undertaking these extended, long-running investigations, a well-conducted clinical and metabolic assessment of changes occurring among a group of patients within a limited period of observation may suffice to evaluate new and promising drugs, especially when results from different centers turn out to be consistent and reproducible.

Gestoden, the newest progestogen from the levonorgestrel class, appears to possess favorable properties which allow halving of the progestogen content in a fixed combination pill when compared with the otherwise lowest-dose pills today[3]. Previous studies have demonstrated the OC formulation's minimal effects on the body's metabolic functions, combined with high contraceptive efficacy and acceptability. One British study has concluded that this gestoden-ethinylestradiol combination OC pill appears to be an ideal alternative to currently used OCs[1].

The results of the clinical parameters evaluated in this study are consistent with previous reports. Despite errors of tablet-taking in 2 per cent of the cycles, no pregnancy occurred and cycle control was excellent. Mean sys-

tolic pressure decreased throughout the cycles, with an overall mean percentage decrease of about 5 per cent after 6 cycles. This observation has been a consistent finding in similar gestoden studies and may not be what is expected, since earlier clinical experience with older, higher-dose OC formulations showed minimal but significant rise in BP among OC users and which reverted to normal after cessation of pill taking[4]. The mechanism apparently involves estrogenic stimulation of the renin-angiotensin-aldosterone mechanism (via increased hepatic synthesis of the renin substrate). Under physiologic conditions, the natural progesterone which possesses an aldosterone-antagonistic effect at the receptor level restores this imbalance caused by estrogens[5]. Gestoden is, as yet, the only progestogen shown to possess about 60 per cent of the aldosterone-antagonistic effect of the natural progesterone[6]. None of the synthetic progestogens used in OCs hitherto, possess this feature of gestoden. Previous clinical trials with gestoden-containing formulations have actually demonstrated normalization of previously elevated blood pressure in some women after taking this pill[7]. However, more evidence is needed to further confirm the clinical relevance of the unique pharmacological profile, especially in the low dose used in the pill.

Body weight remained unchanged; changes were within a kilogram which is well-within the normal physiologic weight variability of ± 2 kg.

The good tolerance and acceptability contributed to a very low drop-out rate of only 16 per cent after 12 cycles, due to medical reasons.

The mechanisms by which the hormones in OCs affect blood sugar levels are not exactly known. However, it has been demonstrated that plasma cortisol levels are increased in women taking OCs and this apparently causes the liver to release glucose into the blood stream, while at the same time inhibiting the utilization of glucose in the cells[8]. With OCs containing 50 mcg of estrogen and having high progestogen content, an overall risk of developing an abnormal OGTT was estimated to be 44 per cent among women with previous gestational diabetes[9, 10]. However, with a low-dose triphasic OC, Skouby and co-workers[11] found that none of their patients with previous gestational diabetes developed any worsening of the OGTT.

In this study, there was overall good tolerance to the glucose challenge as reflected in the area under the glucose concentration-time curve (AUC) remaining within normal limits. The small but statistically significant rises in plasma insulin are similar to the results obtained by Skouby and co-workers[11] among non-diabetics on low-dose OCs. The significance of this slight increase in plasma insulin during the OGTT is blunted by the unchanged areas under the curves. Interestingly, the values of plasma insulin before, during and after the OGTT, were all within acceptable limits throughout the cycle (normal value : up to 150 u/ml during OGTT).

The effect of contraceptive steroid on plasma cholesterol and lipoproteins

has been the topic of debates for years. Estrogens and estrogen-dominant pills increase serum hormone binding globulin (SHBG) and HDL-C, the latter presumed to be beneficial as regards the development of atherosclerotic disease. However, there are no data to show that lowering or raising HDL-C with OCs promotes or retards atherosclerosis or premature atherosclerotic disease[12]. Further, whatever appears to profoundly increase HDL-C, likewise may cause other metabolic effects, notably an imbalance in the coagulation and fibrinolytic factors[13, 14].

In this study, there were minimal although statistically significant changes in lipid metabolism, a rise in total triglycerides and a decrease in LDL, HDL and total cholesterol. These changes reflect that this OC formulation under study is not estrogen-dominant. An estrogen-dominant pill will show a profound increase in HDL-C and a more profound effect on coagulation and fibrinolytic factors. There were no significant changes in coagulation Factor VII. There was, however, a significant decrease in anti-thrombin III, a finding not consistent with previous studies. In the other reports, a net increase or only a slight nonsignificant decrease in the level of AT III was demonstrated[11, 16]. AT III works to antagonize the conversion of prothrombin to thrombin. If the AT III decrease was indeed significant, there should have been significant changes in the thrombin time (TT). In this study, there were no significant changes in the TT, as well as the thromboplastin time (PT) and the activated partial thromboplastin time (APTT). There is, therefore, reason to believe that this gestoden formulation has no adverse effects on coagulation and fibrinolytic system as previously reported[15-16].

Methodologically, however, a clinical investigation such as this present study has its limitations. As in similar studies, the drop-out rate was difficult to control. Although most of the drop-outs were not due to medical reasons, the number of evaluable and comparable patients progressively dwindled through the treatment cycles. Other limitations of the study include the limited number of patients, the limited observation time, and other extraneous variables like standardization of laboratory tests used, diet and psychosocial activities of the patients, and others.

Despite all these limitations, however, this gestoden-containing OC formulation proved its high contraceptive reliability, patient acceptability and minimal metabolic effects. Throughout the treatment cycles, the levels of the various laboratory parameters, despite the apparent fluctuations, all remained well-within the acceptable normal range.

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