Clinical and Metabolic Study of Triphasic Contraceptive Pill (Triquilar)®

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Abstract: *One hundred and forty healthy women were recruited for clinical and metabolic study. Each woman was instructed to take a triphasic pill at bed time. Forty-two percent of the volunteers completed 24 cycles for a total of 1847 cycles. The cycle control was quite satisfactory and no accidental pregnancy occurred. Changes in blood pressure and body weight were insignificant during the trial. Three cases showed an abnormal glucose tolerance test at six and nine months after taking pill. Fasting state serum transaminase, and bilirubin showed no sinificant changes of mean values, but significant decreases in alkaline phosphatase were observed at 3,6 and 12 months after taking the OC. Lipid metabolism, serum cholesterol, triglycerides and its fractions remained unchanged during treatment period. (Thai J Obstet Gynaecol 1989;1:31-38)*

Key words: clinical and metabolic study, triphasic contraceptive pill

Clinical trials of combined oral contraceptive pills have shown that they are effective and that they regulate the menstrual cycle with respect to intermenstrual bleeding, cycle length, duration and intensity of withdrawal bleeding. Levonorgestrel (LNg), a synthetic biologically active progestin, has been combined with ethinyl estradiol (EE) in three different dose ratios as a triphasic pill (Triquilar)®. The contraceptive effectiveness of this preparation has been shown to be high in previous studies.[1,2] Suppression of ovulation with the low-dose contraceptive is similar to that of high-dose fixed ratio preparations. A study of a small number of subjects in a recent report indicated that this compound has minimal influence on the metabolism of lipids and carbohydrates.[3] Changes in plasma concentrations of lipoproteins such as increased total cholesterol or LDL cholesterol, increased triglycerides of VLDL and reduced HDL cholesterol are

major risk factors for ischemic cardiovascular diseases. It has been shown that testosterone-derived progestogens reduce HDL levels in women.[4,5] A previous study demonstrated the positive correlation between mean changes in HDL or triglyceride levels, and the mean changes in sex hormone binding globulin concentration or the ethinylestradiol/levonorgestrel ratio illustrate that changes in HDL and triglycerides during OC treatment are influenced by the total estrogenicity of the drug used.[6] In short term use, results indicated there was no statistically significant difference between the mean values at baseline and during treatment of any lipids[3].

The relationship of oral contraceptive agents and the glucose tolerance test have been examined by many investigators with conflicting results being reported. Wynn and Doar[7] and others[8], using a variety of oral contraceptive agents over varying time, observed no difference in the fasting glucose levels in normal women associated with the use of oral contraceptive agents. Deterioration of glucose tolerance has, however, been reported by orthers[9,10,11].

Admittedly, many differences can be explained by the type of contraceptive agent used, the duration of its administration, the methods used and the characteristics of the patient group under study. Race and diet may influence the results. Most studies have been done in developed countries. We felt it worthwhile to evaluate this triphasic combination of LNg and EE in Thai women with special attention to effectiveness, cyclic menstrual beeding and metabolic changes.

Materials and Methods

One hundred and forty Thai women desiring oral contraception volunteered for this trial. The subjects had regular menstrual cycles before enrollment. They were healthy and under 35 years of age. No woman has used oral contraceptives or injectable hormonal contraceptives for at least six months prior to the study. A history was taken and a physical examination was performed before the subjects entered the study and every 6 months for its duration. The volunteers were seen at the Family Planning Clinic, Department of Obstetrics and Gynaecology, Chulalongkorn Hospital, every third cycle. Each subject was encouraged to record abnormal bleeding and any side effects that may have occurred in a diary card. The clinical characteristics of the volunteers are shown in Table 1.

Table 1 Clincal details of subjects participating in the study. Values are means ± SD, figures in parentheses are ranges

Age (years)	25.2	±	3.7
	(20	-	34)
Weight/Height^2	21.38	±	2.51
(Quetelet's index)	(18.9	-	23.9)
Blood pressure-systolic	103.1	±	15.6
diastolic	65.8	±	8.2
Cycle length (days)	29.7	±	2.6
	(25	-	38)
Menses (days)	4.6	±	1.1
	(3	-	7)

Metabolic studies were carried out in 20 subjects to evaluate the effect of the pill on carbohydrate and lipid metabolism. Blood samples were collected before and at 3,6,12, and 24 months of

pill intake. The subjects were asked to fast at least 12 hours before collecting blood. For the glucose tolerance test (OGTT), a 250 ml solution containing 50 g of glucose was given to each woman to drink within five minutes. Repeated venous blood samples were drawn at 0,30,60,90,120 and 180 minutes. Plasma glucose was determined by the glucose oxidase-perioxidase method which was previously described by Trinder[12]. The total area under the curve was calculated according to Wynn et al[7]. Fasting blood samples were allowed to clot and serum was separated. The lipid fractions in serum were separated by ultracentrifugation in a saline-density gradient modified from the previously described method.[13] The cholesterol content in each fraction was determined by means of commercially available kits (CHOD-PAP Boehringer-Mannheim, A.G.Mannheim, West Germany), while the triglyceride content was measured by the "Fully enzymatic (UV) test", using Boehringer-Mannheim reagents.

Liver enzymes, SGOT, SGPT, alkaline phosphatase and bilirubin were measured by the use of a LKB 8600 reaction rate analyzer. Reagents for determining liver enzymes were obtained from Boehringer-Mannheim. Statistical analysis of the results were performed by using student's *t-test* for paired or unpaired data, or the two-way analysis of variance as appropriate.

Results

Clinical Data

Of the 140 women who started the trial, the continuation rate at three month intervals is shown in Fig. 1 .49% completed twelve cycles and 24% completed 34 cycles for a total of 1847 cycles. No accidental pregnancy occurred during the study period. Possibly drug-related medical reasons accounted for withdrawal from the trial of 7.8% of the subjects. Table 2 presents the number of subjects who withdrew for medical reasons, personal reasons and of drop outs by cycle interval.

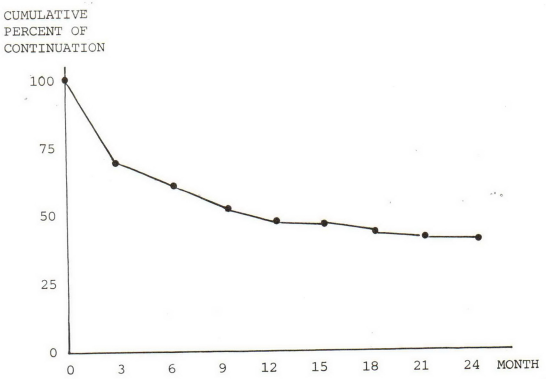

Fig. 1 Continuation rate at 3-month intervals. (1847 cycles)

Table 2 Reasons for discontinuation of trial

Reasons	Months of use								
	3	6	9	12	15	18	21	24	Total
Bleeding/spotting	-	-	-	-	1	-	-	-	1
Malaria infestation	3	-	-	-	-	-	-	-	3
Abnomal OGTT	1	2	-	-	-	-	-	-	
Weakness/weight loss	2	-	-	-	-	-	-	-	2
Nausea-vomiting	3	-	1	1	-	-	-	-	5
Plan pregnancy	-	-	-	2	2	1	-	-	5
Change method	2	1	1	1	-	-	-	-	5
Move away	6	2	-	1	-	-	3	-	12
Loss follow-up	23	6	2	2	-	2	1	-	37
Indigestion	1	-	-	-	-	-	-	-	1
Incorrect taking pill	7	-	1	-	-	-	-	-	8
Personal	4	-	-	-	-	1	-	-	5
Total	52	11	5	7	4	4	7	-	
Continuation	140	88	77	72	65	62	58	53	

Metabolic Data

Three cases showed an abnormal area under the curve (over 800) at six and nine months (Fig. 2). They were asked to stop taking the OC and a repeat glucose tolerance test was performed six months later. The glucose tolerance test results had returned to the normal range after cessation of the OC.

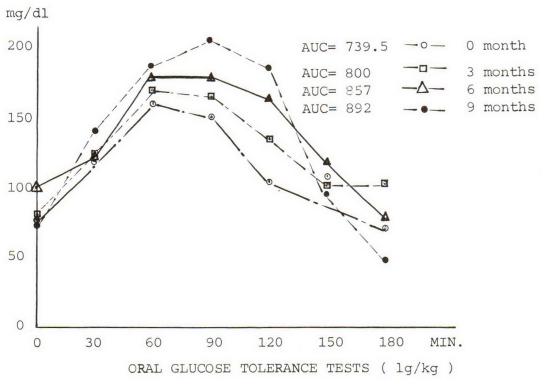

Fig. 2 Plasma glucose during oral glucose tolerance tests performed before and after treatment, An abnormal area under curve (AUC) over 800, demonstrated at 6 and 9 months.

The mean plasma values of glucose before and after OC therapy did not differ significantly in the fasting state. There were statistically significant changes of plasma glucose at 60,90,120,150 and 180 minutes after ingestion of gluclose (Table 3).

Fasting state serum transaminase (SGOT, SGPT), alkaline phosphatase and bilirubin were assessed in 18 subjects. There were no significant changes of mean values of transaminase and bilirubin in serum, but a significant decrease in alkaline phosphatase was observed at 3,6 and 12 months after taking the OC (Table 4).

Table 3 Plasma glucose levels (mean ± SD) and area under curve (AUC) at different time intervals after ingesting glucose (N=20). Figures in parenthesis denote range values. Asterisk denotes significant different levels.

	Changes in oral glucose tolerance test Times (min)							
Months	0	30	60	90	120	150	180	AUC
0	80.8 ± 8.3 (60-99)	117.1 ± 20.3 (86-153)	114.6± 36.5 (70-196)	92.3± 26.0 (52-160)	89.4 ± 14.0 (70-121)	81.8 ± 15.4 (50-113)	76.9 ± 13.4 (54-99)	574.0 ± 91.9 (421-728)
			**	***	****	***	*	****
3	80.2 ± 8.7 (70-108)	127.2 ± 18.8 (100-170)	136.8 ± 33.5 (77-204)	117.9 ± 33.8 (71-195)	109.8 ± 19.7 (87-151)	98.8 ±16.5 (71-133)	86.9 ±15.1 (55-107)	674.1 ±110.3 (495-889)
			*	****	***	****	*	****
6	80.1 ± 6.7 (65-92)	125.6 ± 20.4 (83-166)	135.0 ± 26.6 (88-176)	121.7 ± 29.6 (84-182)	110.0 ± 22.9 (74-161)	97.8 ± 16.7 (70-127)	88.2 ± 20.9 (57-136)	673.8 ± 98.7 (512.5-846.5)
		***	***	***	***	****		
12	81.7 ± 8.6 (69-97)	122.1 ± 17.5 (95-148)	134.1 ± 26.9 (85-201)	119.1 ± 28.3 (76-177)	130.2 ±13.2 (77-128)	93.8 ± 14.5 (63-120)	80.3 ± 14.7 (58-108)	653.3 ± 76.7 (498.5-788.5)
		***	***	****	***	*		****
24	83.5 ± 5.9 (75-92)	138.0 ± 15.6 (113-159)	153.5 ± 26.2 (114-207)	134.4 ± 31.1 (81-197)	114.7 ± 9.9 (99-123)	105.0 ± 14.7 (83-133)	89.5 ± 22.6 (57-140)	726.8 ± 79.9 (618.5-849.5)

* P < 0.05 ** P < 0.01 *** P < 0.005 **** P < 0.001

Table 4 Serum levels of bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic phosphoacetic transaminase (SGPT) in 20 subjects, all values are mean ± SD. Figures in parentheses are range values. Asterisk indicated significant changes at different levels

Changes in liver function tests (n=20)

	Treatment period (months)				
	0	3	6	12	24
SGOT (U/L)	9.11± 3.3 (5.0-16.2)	8.4 ± 3.3 (1.4-16.4)	9.0 ± 2.6 (5.7-13.9)	8.2 ± 1.9 (4.7-12.2)	8.4 ± 2.3 (6.2-11.8)
SGPT (U/L)	5.0 ±2.4 (1.8-10.5)	4.2 ± 2.5 (2.1-11.2)	4.5 ± 2.3 (1.9-9.3)	4.3 ± 1.2 (2.3-5.6)	3.4 ± 0.7 (2.6 - 4.5)
ALK (U/L)	21.1 ± 7.2 (12.1-39.2)	15.7± 4.2 (10.0-26.0)	16.3 ± 4.8 (10.4-24.6)	15.8 ± 4.9 (9.7-23.5)	17.5 ± 5.3 (13.4-26.8)
BILIRUBIN (MG/DL)	0.5 ± 0.2 (0.2-1.2)	0.4 ± 0.2 (0.2-0.9)	0.5 ± 0.2 (0.2-0.8)	0.4 ± 0.1 (0.2-0.8)	0.4 ± 0.1 (0.3-0.6)
	** P < 0.01		**** P < 0.001		

Table 5 Serum lipid (VLDL-cholesterol, LDL-cholesterol, HDL-cholesterol and total cholesterol) of 18 subjects, all values are mean ± SD and the concentration are in mmol/L

	Treatment period (months)				
	0	3	6	12	24
VLDL-C	0.32 ± 0.15	0.29 ± 0.12	0.34 ± 0.13	0.30 ± 0.13	0.31± 0.12
LDL-C	2.31 ± 0.69	2.21 ± 0.54	2.37 ± 0.62	2.49 ± 0.70	2.37± 0.58
HDL-C	1.12 ± 0.18	1.09 ± 0.21	1.09 ± 0.14	1.09 ± 0.25	1.22± 0.23
T-C	4.37 ± 1.03	4.22 ± 0.75	4.20 ± 0.57	4.25 ± 0.80	4.13± 0.56

Table 6 Serum triglycerides (VLDL-triglyceride, LDL-triglyceride, HDL-triglyceride and total triglyceride) in 18 subjects. All values are means ± SD and the concentrations are in mmol/L

	Treatment period (months)				
	0	3	6	12	24
VLDL	0.46 ± 0.24 (0.18-1.11)	0.43 ± 0.19 (0.19-1.00)	0.46 ± 0.18 (0.18-0.96)	0.44 ± 0.18 (0.04 - 0.81)	0.41 ± 0.17 (0.19-0.77)
LDL	0.27 ± 0.08 (0.16-0.53)	0.26 ± 0.09 (0.13-0.56)	0.28 ± 0.11 (0.14-0.57)	0.28 ±0.09 (0.14-0.51)	0.27 ± 0.08 (0.16-0.45)
HDL	0.20 ± 0.05 (0.12-0.29)	0.19 ± 0.05 (0.10-0.31)	0.02 ± 0.07 (0.09-0.39)	0.20 ± 0.06 (0.91-0.32)	0.21 ± 0.08 (0.07-0.36)
T-TRIGLY-CERIDE	1.09 ± 0.36 (0.59-1.83)	1.04 ± 0.31 (0.57-1.83)	1.08 ± 0.38 (0.50-1.85)	1.11 ± 0.30 (0.55-1.72)	1.18 ± 1.03 (0.50-1.68)

Lipid metabolism, serum cholesterol, triglycerides and its fractions remained unchanged during treatment (Tables 5 and 6).

Discussion

The introduction of a triphasic approach of oral contraception represents a

noteworthy contribution in contraceptive technology. The reduction in synthetic progestogen per cycle is accomplished by taking advantage of the well defined hormonal events during the normal menstrual cycle. The triphasic mode of administration gave promising results in cycle control and the present study showed stable menstrual cycles. There was a signficant reduction in cycle length and an increased menstrual flow during the first three months of use. The duration of bleeding was, however, significantly decreased after ten months of use. These findings may reflect the direct effect of synthetic steroid on the endometrium. Breakthrough bleeding and spotting during the trial of Triquilar® were reported in 1.2-10% of cycles[2,3]. Side effects of intermenstrual spotting led to discontinuation in one case. Cycle control was quite satisfactory.

Changes in blood pressure and body weight were insignificant during the trial. Side effects were difficult to interpret. Nausea, vomiting, dizziness and headache were most frequently reported in the first three cycles, abating subsequently. The continuation among patients in this study was low (about 50% at 12 months) when compared to earlier report[2]. One of the major problems for patient's discontinuation in the trial was loss to follow-up. This is difficult to interpret and we were not able to determine the reasons for drop out in most patients.

Triphasic preparations of ethinyl estradiol and levonorgestrel, with a progestogen content of less than that in any of the monophasic products, have been associated with a minimal effect on carbohydrate metabolism. The progestogen-estrogen ratio of combined oral contraceptive seems to be the major factor influencing metabolism[11,12]. Previous studies have shown that levonorgestrel will cause hyperinsulinemia in doses of 150 µg or more[14,15,16]. This effect occurs without necessarily altering glucose tolerance. The present study revealed that after three months of use there was significant increase in plasma glucose at 60,90,120 and 150 minutes. At 180 minutes after ingestion of glucose, however, the plasma glucose returned to a normal range. There were three cases that exhibited an abnormal glucose tolerance test, and they were asked to stop the OC. Three months later the glucose tolerance test result had become normal (Fig 3). It has been shown that progesterone is metabolised in the splanchnic bed (65%) and brain (35%)[17]. It is possible that the fasting blood glucose level may be altered by a central effect of progestogen on the brain[18]. The mechanism behind the influence on glucose metabolism by contraceptive steroid compounds is not fully known. There is evidence that pro-

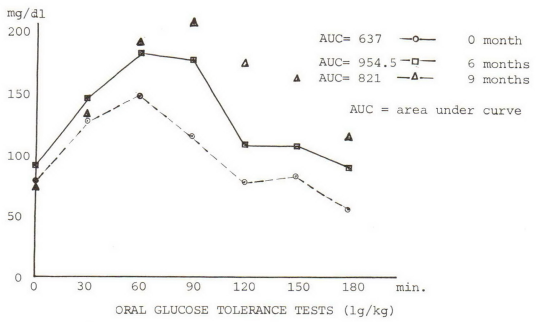

Fig. 3 Illustration of an abnormal area under the curve at 6 months after taking OC. Plasma glucose level (AUC) returned to normal range after stopping OC 9-month curve

gestogens alone or combined with estrogens induce a decrease in tissue sensitivity to insulin[14,19]. Moreover, the increased plasma cortisol levels found in women treated with oral contraceptives, may impair glucose tolerance as the result of an increase in hepatic glucose production and an inhibition of glucose uptake in peripheral cells[20].

The association between lipoprotein levels and coronary heart disease is well known[21]. In general, HDL-cholesterol levels are increased by estrogens and decreased by progestogens. There have been reports that triphasic compounds raise plasma triglycerides to a greater extent than low-dose monophasic ethinylestradiol/levonorgestrel combinations[12]. Recent studies have demonstrated that triglycerides remained unchanged in women with previous gestational diabetes[22,23]. Our present study confirmed previous findings in Thai women. Serum triglycerides remained unchanged after 24 months of OC use. It is of interest to note that serum lipids and triglycerides were thus unaffected by hormonal intake. This ocurred despite elevated glucose levels in some patients. Unchanged high density lipoprotein, low-density lipoprotein and very-low density lipoprotein cholesterol levels together with unchanged serum triglycerides levels during OC use appear to be favorable findings.[24]

A previous study has shown that liver enzymes and alkaline phosphatase levels were affected by estrogens and progestogens. They increased by higher progestogen and decreased with high estrogen[25]. If a decrease in the alkaline phohatase level indicates a decrease in cholestasis, this might be a further benefit of ethinyl estradiol/levonorgestrel triphasic agent. The present study showed a statiscally significant reduction of alkaline phosphatase levels. The transaminase remained the same.

We conclude that Triquilar® in a short term study has a low incidence of side effects, affords good cycle control and is effective. This low-dose triphasic pill may cause transient deterioration in gluclose metabolism but has no effect on lipid and lipoprotein levels. Changes in liver enzyme levels were minimal. To sum-up, the present study confirms that a triphasic principle and dosage of this preparation, affords good cycle control and is effective.

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