

A COMPARATIVE ANALYSIS OF THREE METHODS OF CONTRACEPTION: EFFECTS ON BLOOD GLUCOSE AND SERUM LIPID PROFILES

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Background: Hormonal contraceptives are one of the major means of family planning, yet their use is not without side effects. In this study, we have tried to assess some of the metabolic effects of three hormonal contraceptives commonly used by young females.

Patients and Methods: Three hundred young, healthy, nonsmoking and normotensive women of childbearing age who were seeking contraceptive advice were randomly allocated to one of the three groups receiving ethinyl estradiol and norgestrel (group 1), medroxyprogesterone acetate (group 2), and levonorgestrel capsules (group 3). Levels of fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), were measured prior to the initiation of therapy and after termination of the study (6 months).

Results: There was no significant difference between the three groups as far as the mean age, height and weight were concerned. FBG increased in all three groups, but the difference in the rate of increase was not statistically significant ($P=0.29$). Total cholesterol, TG and LDL-C increased, while HDL-C level decreased in groups 1 and 2. These changes were, however, more profound in the group 2 cases. In those receiving levonorgestrel, all lipid parameters decreased. The amount of change for the total cholesterol and triglyceride was quite significant ($P<0.001$), while the reduction in HDL-C was not significantly different from the other two groups by pairwise comparisons (Tukey-HSD procedure). The LDL-C/HDL-C ratio was found to be significantly increased in groups 1 and 2, but it remained almost unchanged in the group 3 cases ($P<0.001$).

Conclusion: Because of these favorable biochemical findings, we believe that levonorgestrel should be the contraceptive drug of choice for women of childbearing age who are seeking a safe method of contraception. *Ann Saudi Med 1999;19(1):8-11.*

Key Words: Ethinyl estradiol, norgestrel, medroxyprogesterone acetate, levonorgestrel, glucose metabolism, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol.

Hormonal contraceptives continue to be one of the most effective reversible means of family planning. Although they were first marketed in 1957, it was not until the early 1960s that attention was drawn to their adverse metabolic effects.¹

Glucose intolerance was one of the first reported metabolic derangements associated with the use of oral contraceptives (OC).² In the Walnut Creek Contraceptive Drug Study, its prevalence was 2% in OC users, compared to 1% prevalence in non-users. High-dose OC can have significant adverse effects on lipids too, and as in cases of glucose metabolism, is related to the androgenic potency of progestin and its dose.³

The effect of medroxyprogesterone acetate on plasma lipids has been inconsistent. In general, however, it is associated with a modest reduction in total cholesterol (TC) and triglyceride (TG), slight reduction in high-density lipoprotein cholesterol (HDL-C) and slight increase in low-density lipoprotein cholesterol (LDL-C) levels. Mild glucose intolerance may also be seen in medroxyprogesterone users.⁴ Glucose tolerance tests show a small elevation of blood glucose as well.

TABLE 1. Age, height and weight of the three groups of subjects.

	Group 1 Mean±SD	Group 2 Mean±SD	Group 3 Mean±SD
Age (years)	25.5±5.1	25.8±5.3	25.3±5.4
Height (cm)	157.7±7.1	158±7.0	158.2±7.2
Weight (kg)	54.5±8.6	54.5±8.0	55.1±7.0

P-value was not significant. Group 1 received contraceptive pills, group 2 medroxyprogesterone and group 3 levonorgestrel.

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TABLE 2. The mean levels of fasting blood glucose (FBG), total cholesterol, triglyceride and their percent change after six months of therapy.

	Group 1		Group 2		Group 3		P-value
	Mean±SD	% Change	Mean±SD	% Change	Mean±SD	% Change	
FBG (mmol/L)							
Baseline	3.84±0.5	22.3 (+)	3.7±6.68	29.2 (+)	3.9±0.7	22.4 (+)	0.29
After six months	4.7±1.0		4.77±0.92		4.8±0.8		
Cholesterol (mmol/L)							
Baseline	3.90±0.8	7.3 (+)	3.6±0.77	15.8 (+)	4.2±0.8	9.5 (-)	<0.001
After six months	4.20±0.98		4.2±0.88		3.77±0.72		
Triglyceride (mmol/L)							
Baseline	1.05±0.39	19.2 (+)	0.96±0.38	17.6 (+)	1.06±0.33	20.7 (-)	<0.001
After six months	1.25±0.96		1.13±0.59		0.84±0.43		

+ = increased; - = decreased.

Since subdermal implants that provide sustained release of progestins do not cause peaks in progestin levels or use estrogens, they are without some of the side effects associated with the use of OCs or injectable contraceptives.

As the use of available hormone-containing contraceptives is by no means without side effects,⁵⁻⁶ it seemed reasonable to assess some of the metabolic effects of three of the ones which are commonly used by women of childbearing age.

Patients and Methods

Of 340 apparently healthy women of childbearing age, 300 were selected for the present study. These women were nonsmoking volunteers not on any therapy, and having no known history of cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, hepatic or renal dysfunction, thyroid disease or thromboembolic complications, and who were willing to accept one of the three modalities of contraception. All subjects gave an informed consent to participate, and the study was approved by the local ethics committee. The study period was six months.

All participants underwent a thorough medical interview and physical examination. Demographic data was collected and a baseline fasting blood glucose and lipid profile, including TC, TG, LDL-C and HDL-C, was taken. Forty subjects with a history of menstrual irregularities, gastrointestinal symptoms, including occasional nausea or vomiting, mildly elevated FBG and abnormalities in baseline lipid profile were excluded from the study. The remaining 300 cases were then randomly divided into three groups. The subjects in group 1 received oral contraceptive pills containing ethinyl estradiol (30 µg) and norgestrel (150 µg). The pills were started each month on the 5th day of the menstrual cycle, and were continued until day 21. Group 2 initially received medroxyprogesterone acetate (150 mg) intramuscularly, and at three-month intervals thereafter. Six levonorgestrel capsules (each containing 36 mg of crystalized levonorgestrel) were implanted under local anesthesia in the upper arms of subjects in group 3. All cases had

regular clinical follow-up every three months and as needed until the termination of the six-month study period, at which time the fasting blood glucose and the same lipid profile were repeated.

Methods of Analysis

The data were analyzed using the SPSS (statistical package for the social science) computer program. Analysis of variance (ANOVA) and pair-wise comparisons by Tukey-HSD procedure were used as required. The relative difference (RD) (% change) was calculated using the following formula:

$$RD = \% \text{ change} = \frac{\bar{X}_{6 \text{ months}} - \bar{X}_{\text{baseline}}}{\bar{X}_{\text{baseline}}} \times 100, \text{ and the}$$

absolute difference ($X_{6 \text{ months}} - X_{\text{baseline}}$) was compared, using the ANOVA method. A *P*-value of <0.05 was considered statistically significant.

Results

There were no significant differences in the age, height or weight of the three groups of subjects (Table 1). The baseline FBG and lipid profile of the three groups compared with the values of the same parameters and their percentage change after six months of follow-up are shown in Table 2. The blood glucose was increased in all groups, but the absolute change was almost similar (*P*=0.29). Total cholesterol and TG both increased in groups 1 and 2, but they significantly decreased (*P*<0.001) in those with implantable levonorgestrel, who had about 10% and 20% reduction in the serum TG and TG concentrations, respectively (Table 2).

The HDL-C level decreased in all three groups, but the least reduction occurred in the cases receiving oral contraceptive pills (*P*<0.05). While the LDL-C concentration increased in groups 1 and 2, it decreased considerably in the group 3 cases (*P*<0.001). The increase in the mean LDL/HDL ratios was 14.1, 49.7, and 0.4, for groups 1, 2 and 3, respectively. These differences were statistically significant (*P*<0.001) in all three treatment groups (Table 3).

TABLE 3. The mean values of the lipoproteins and their percent change after six months of therapy.

	Group 1		Group 2		Group 3		P-value
	Mean±SD	% Change	Mean±SD	% Change	Mean±SD	% Change	
LDL-C (mmol/L)							
Baseline	2.43±0.73	10.1 (+)	2.09±0.66	31.1 (+)	2.6±0.76	7.0 (-)	<0.001
After six months	2.67±0.85		2.74±0.76		2.4±0.72		
HDL-C (mmol/L)							
Baseline	1.11±0.22	0.2 (-)	1.2±0.24	11.6 (-)	1.16±0.21	5.6 (-)	<0.05
After six months	1.10±0.30		1.07±0.22		1.09±0.20		
LDL-C/HDL-C							
Baseline	0.06±0.02	14.1 (+)	0.05±0.02	49.7 (+)	0.06±0.02	0.4 (+)	<0.001
After six months	0.07±0.03		0.07±0.02		0.06±0.03		

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; +=increased; -=decreased.

Discussion

The use of oral contraceptive pills may be associated with the development of a reversible insulin resistance and subsequent impairment of glucose tolerance.⁷ This altered carbohydrate metabolism is believed to be mainly due to the effects of progesterone.^{8,9} The rise in FBG levels was also seen in our three groups. The difference in the amount of change, however, was not statistically significant among these groups. An increase in the levels of serum TC, TG, and LDL-C, associated with a concomitant decrease in the level of HDL-C, was seen in our patients receiving OCs and injectable medroxyprogesterone acetate. These changes, however, were more profound in the latter group (significant at 0.05 level by pairwise comparisons). Similar effects have been observed for injectable contraceptives by other investigators.^{8,10} The variable effects of oral contraceptive pills on plasma lipids and blood glucose levels depend on their relative estrogen and progestin content, as well as their specific progestin component.^{11,12} Although varying degrees of elevation of plasma lipids have been reported with the use of the older combination OCs,¹¹ the newly developed monophasic and triphasic ethinyl estradiol/norgestimate preparations have consistently shown a favorable impact on these metabolic parameters, especially the HDL level and LDL/HDL ratios.¹³⁻¹⁵ A recent meta-analysis has actually shown a potential cardiovascular benefit with the prolonged use of 150 µg desogestrel and 30 µg ethinyl estradiol as a contraceptive drug.¹⁶ The level of HDL-C was significantly decreased ($P<0.05$), and that of LDL-C increased appreciably ($P<0.001$) in patients receiving medroxyprogesterone acetate. Although conflicting results on the effect of this agent on plasma lipids have been reported,^{11,17,18} observations from a recent multicenter trial⁴ indicate an overall elevation of plasma LDL-C and a reduction of HDL-C levels. The findings in the latter study are in agreement with the results of this study. Since a low HDL-C level and a high LDL-C level are independent risk factors for the development of atherosclerosis and cardiovascular disease, one might hesitate advocating long-term use of the injectable medroxyprogesterone

acetate. Of interest was the observation that all serum lipid parameters declined following the implantation of levonorgestrel. This included a decline in the LDL-C level. The LDL-C/HDL-C ratio, however, did not change significantly in this group of patients. Singh et al.,¹⁹ who followed up women using levonorgestrel for two years, reported a decrease in values of serum TC, TG and LDL-C levels, with no statistically significant change in the HDL-C/LDL-C ratio. Roy et al.,²⁰ however, found no change in the lipid profiles of cases using levonorgestrel over a two-year period. Darney et al.²¹ reviewed the effects of levonorgestrel on selected lipoprotein levels, as reported in six different studies. All lipid parameters were found to have decreased or remained unchanged, except for the HDL-C, which was found to have increased in two out of the six reported series.

Since effective contraception can be achieved by the use of implantable levonorgestrel at a very low clinical probability of inducing cardiovascular hazards,²² we believe it would be desirable to advocate this mode of contraception for women of childbearing age who are seeking a safe method of contraception. However, long-term controlled studies are needed before we can come to a definitive conclusion regarding the changes in the FBG, TC, TG and the lipoprotein levels associated with the use of contraceptive drugs, especially the new oral and implantable contraceptive formulations.

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