



Effect of Duration of Use of COCs (Combination of ethinylestradiol (0.03mg) and norgestrel (0.3mg)) on serum Lipid Profiles, Fasting Blood Sugar, Blood Pressure and BMI in Child Bearing Age Women

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ABSTRACT

Background: Combined Oral Contraceptives Pills (COCs) are effective and widely used method for contraception. There is a positive relationship between COCs and lipid and carbohydrate metabolism in previous studies. We have seen the effect of duration of COCs (0.3mg norgestrel and 0.03mg ethinyl estradiol) used in tertiary care hospitals of Peshawar Khyber Pukhtunkhwa Pakistan on the lipid and carbohydrate metabolism in women taking combined oral contraceptives.

Study Design: This cross sectional analytical study included 100 participants women of child bearing age 14-49yrs using COCs divided in three groups according to the duration of use group A at least 6 month COCs users, group B were 1 year COCs users, group C more than 1 year COCs users. Serum Total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), fasting blood sugar (FBS) were determined by using standard colorimetric techniques BMI and BP were also measured in all subjects. Their levels were found gradually increasing from 6 months to those who are using it for 1 year and more than 1 year.

Results: To estimate the effect of duration of use of combined oral contraceptives on the levels of different biochemical parameters, the results showed significant elevation of cholesterol (p-0.0003), HDL-C (p-0.0229), LDL-C (p-0.0271), VLDL-C (p-0.0004), Triglycerides (p-0.0006) levels in the group of more than 1 year users females when compared with 6 months users.

Conclusion: The levels of cholesterol, HDL, LDL, VLDL and Triglyceride levels were found to be increased with the duration of use in the women of child bearing age of Khyber Pukhtunkhwa.

INTRODUCTION

The combined oral contraceptives are common and widely accepted method used for contraception.[1] In Pakistan it is used since its introduction in international market and the most common combined oral contraceptive is the combination of ethinylestradiol (0.03mg) and norgestrel (0.3mg) .[2,3]

The contraceptive prevalence in the urban Pakistan is 5.5% more than twice (9.8% vs. 3.9%) that of rural prevalence. [4]The combined oral contraceptive pills changes the serum lipoprotein profile, HDL increase and decrease in LDL due to estrogens (a desirable effect), [5,6]whereas these beneficial effects of estrogen are negated by progestin.[7] Therefore, the preparations having dominant estrogen is best for individuals with elevated serum cholesterol. The estrogen regulate in the fat tissue lipolysis, lipogenesis and adipogenesis. [8, 9, 10]The dose and type of progestin also affect the lipids blood levels. [11, 12]

Many experimental studies have indicated that the use of combined oral contraceptives altered lipid metabolism by increasing the levels of triglyceride, LDL-cholesterol, and VLDL-cholesterol with the duration of use. [13]Serum TG, HDL-C and VLDL levels were significantly higher and LDL-C levels found lower in users of combined oral contraceptives. [14] The combined oral contraceptive has positive effect on carbohydrate metabolism by changing their fasting levels. [15, 16] and was also reported high risk of diabetes among the premenopausal

women who were recently on oral contraceptives as well as were using oral contraceptive for more than 1 year. [17]The previous studies shows no positive influence on body weigh with the long-term use of combined oral contraceptives. [18]

The systolic and diastolic B.P was also an important factor in women taking combined oral contraceptive pills because the gradual increase in systolic and diastolic B.P was seen in combined oral contraceptives users with age [19, 20].

The cardiovascular effects of long term use of hormonal contraception have continued to generate interest from scientists, unfortunately, most of the studies have focused mainly on the evaluation of changes in serum lipids and not much has been reported on long term use effects of combined oral contraceptives. This present study seeks to determine the effect of duration of combined oral contraceptives use on lipids and carbohydrates metabolism and also on BMI and BP in Peshawar Khyber Pakhtunkhwa province of Pakistan.

MATERIALS AND METHODS

Study design

A cross sectional/analytical study was conducted after ethical approval from ethical board of institutional research ethical board (IREB) Postgraduate Medical Institute (PGMI) Hayat Abad Medical Complex Peshawar.

Hundred women using combined oral contraceptives for at least 6 months onwards. This

study was conducted in the Family Planning Department of tertiary referral health care facilities of Peshawar, viz. Khyber Teaching Hospital, PGMI Hayatabad Medical Complex Peshawar and PGMI Lady reading Hospital Khyber pukhtonkhwa Province (KPK) Pakistan. The analytical work was done in Pakistan Medical Research Council (PMRC) Research Centre, Khyber Medical College, Peshawar and Institute of Basic Medical Sciences Khyber Medical University.

Study groups The participants were randomly selected without a personal and family history of hypertension, diabetes mellitus, renal/cardiovascular diseases, stroke, familial tendency of obesity and smoking and screened for changes in lipid and carbohydrate metabolism by taking fasting blood samples.

The combined oral contraceptives user's women were grouped in six month users group A, one year users group B and more than one year users group C, to compare their biochemical and other parameters.

Our study population was women of reproductive age group taking hormonal contraceptives for at least six months from the family planning departments of tertiary care hospitals of Peshawar (KPK) within a defined period coming to Family Planning Department of tertiary referral health care facilities without a history of hypertension, diabetes mellitus, renal/cardiovascular diseases, stroke, familial tendency of obesity and smoking were randomly selected and screened for changes in lipid and carbohydrate metabolism by taking fasting blood samples. Women taking any medication, which is affecting lipid metabolism or blood glucose or any medication that may interact with combined oral contraceptives and women with family history of diabetes and hypertension were excluded from the study.

After explaining aims and objectives, informed consent was taken from each subject for participation in this study. The height, weight, BMI and two readings of blood pressure were recorded and take the mean of the blood pressure. The data was processed on computer software package SPSS version 16. The numerical and categorical data was presented as mean. The Student's t test was applied to evaluate mean differences in serum lipid concentrations between COCs users and control subjects. Significance among the means of groups was expressed in term of P-value. 95% Confidence Interval (CI) , $P < 0.05$ was considered as significant, $P < 0.01$ was considered as more significant, $P < 0.001$ was considered as Highly significant and $P < 0.0001$ as very highly significant.

RESULTS

We compared the levels of different biochemical Parameters and BMI, systolic and diastolic B.P in women with different duration of combined oral contraceptive users. The **table-1** summarized these values and showed gradual increase of Cholesterol, LDL, VLDL, Triglyceride, and Fasting blood sugar with increase in duration of combined oral contraceptive use. Their levels are gradually increasing from 6months to those who are using it for more than 1year.The Cholesterol level was 170.73mg/dL in 6 months users and the women who used it more than 1 year was 204.561mg/dL, LDL from 90.69 mg/dL to 109.04mg/dL, VLDL from 36.08mg/dL to 46.61mg/dL, Triglyceride from 180.00mg/dL to 232.92mg/dL and FBS 114.0mg/dL to 122.78mg/dL, the mean BMI kg/m² in 6months users was25.64 and in 1 year users was 27.74 Kg/m² and in group of more than 1 year was 28.36kg/m². The BMI, systolic and diastolic B.P also showed gradual increase.

Table-1 Effect of duration of use of Oral contraceptives on different Parameters

Parameters	6 months Oral cont users (n=23) Mean ± SEM	1 yr Oral cont users (n=36) Mean ± SEM	> 1yr Oral cont users(n=41) Mean ± SEM
T- Cholesterol mg/dL	170.73 ± 6.08	174.27 ± 4.85	204.56 ± 4.46
HDL-C mg/dL	43.95 ± 1.63	44.50 ± 1.28	48.90 ± 1.29
LDL-C mg/dL	90.69 ± 5.88	90.63 ± 4.63	109.04 ± 5.13
VLDL-C mg/dL	36.08 ± 1.32	39.13 ± 0.43	46.61 ± 1.99
Triglycerides mg/dL	180.00 ± 6.58	195.63 ± 2.14	232.92 ± 9.96
FBS mg/dL	114.00 ± 2.48	115.97 ± 9.19	122.78 ± 7.39
BMI Kg/m ²	25.64 ± 0.86	27.74 ± 0.48	28.36 ± 0.59
Systolic B.P mmHg	128.04 ± 2.94	133.88 ± 2.10	135.73 ± 3.32
diastolic B.P mmHg	80.87 ± 2.36	84.16 ± 1.52	87.68 ± 2.05

In table-2 the different parameters with duration of use of combined oral contraceptives was compared and t-test applied and P value found. VLDL, Triglycerides showed significantly high value of 0.012 and 0.010 respectively.

Table-2 Comparison of different parameters with 6months users and 1year users of combined oral contraceptives

Parameters	6 months COCs users (n= 23) Mean ± SEM	1 yr COCs users (n=36) Mean ± SEM	t-test p value
T- Cholesterol mg/dL	170.73 ± 6.08	174.27 ± 4.85	0.6511
HDL-C mg/dL	43.95 ± 1.63	44.50 ± 1.28	0.7938
LDL-C mg/dL	90.69 ± 5.88	90.63 ± 4.63	0.9939
VLDL-C mg/dL	36.08 ± 1.32	39.13 ± 0.43	0.0127
Triglycerides mg/dL	180.00 ± 6.58	195.63 ± 2.14	0.0102
FBS mg/dL	114.00 ± 2.48	115.97 ± 9.19	0.8668

The table- 3 shows comparison of different parameter in women taking combined oral contraceptives for 1 year and women who take it from more than 1 year user. A high significant increase in T-Cholesterol, VLDL-C and Triglyceride were noted in combined oral contraceptive users of > 1year duration. The change in FBS was not significant.

Table-3 Comparison of different parameters of 1year users with more than 1year users of combined oral contraceptives

Parameters	1 yr COCs users (n=36) Mean ± SEM	> 1yr COCs users (n=41) Mean ± SEM	t-test p value
T- Cholesterol mg/dL	174.27 ± 4.85	204.56 ± 4.46	0.000168
HDL-C mg/dL	44.50 ± 1.28	48.90 ± 1.29	0.018710
LDL-C mg/dL	90.63 ± 4.63	109.04 ± 5.13	0.0102
VLDL-C mg/dL	39.13 ± 0.43	46.61 ± 1.99	0.000921
Triglycerides mg/dL	195.63 ± 2.14	232.92 ± 9.96	0.000948
FBS mg/dL	115.97 ± 9.19	122.78 ± 7.39	0.5058

In **table-4** similarly the women taking Oral contraceptives for 6months and those women who used it for more than 1 year were compared, t-test applied and P value found. The results are summarized with very high significant of $P < 0.00029$ in case of Cholesterol levels. VLDL and Triglyceride also show high significance of $p < 0.004$ and 0.006 , HDL and LDL show significant levels of $p < 0.0229$ and 0.0271 respectively. No significant change was noted for FBS.

Table-4 Comparison of different parameters of 6months users with more than 1year users of combined Oral contraceptives

Parameters	6 months COCs users (n=23) Mean \pm SEM	> 1yr COCs users(n=41) Mean \pm SEM	t-test p value
T- Cholesterol mg/dL	170.73 \pm 6.08	204.56 \pm 4.46	0.00029
HDL-C mg/dL	43.95 \pm 1.63	48.90 \pm 1.29	0.0229
LDL-C mg/dL	90.69 \pm 5.88	109.04 \pm 5.13	0.0271
VLDL-C mg/dL	36.08 \pm 1.32	46.61 \pm 1.99	0.0004
Triglycerides mg/dL	180.00 \pm 6.58	232.92 \pm 9.96	0.0006
FBS mg/dL	114.00 \pm 2.48	122.78 \pm 7.39	0.3893

Table-5 shows changes in BMI with increase in the duration of combined oral contraceptive use (25%) of combined oral contraceptive users were the women who used combined oral contraceptives for more than 1 year and their BMI was ≥ 27 kg/m².

Table-5 Effect of duration of use of Oral contraceptives on BMI

BMI Kg/m ²	6months users		1 year users		More than 1 year users	
	(n)	%	(n)	%	(n)	%
<22.99	6	6	1	1	3	3
23 – 24.99	6	6	6	6	7	7
25 – 26.99	5	5	7	7	6	6
>27	6	6	22	22	25	25

DISCUSSION

About 100 million women worldwide use combined oral contraceptives and in the United States 11.6 million women or 19% of the adult female population used it which demonstrated its efficacy and safety since their introduction. [26]

The contraceptive prevalence in the urban Pakistan is 5.5% more than twice (9.8% vs. 3.9%) that of rural prevalence. [4] However, epidemiologically an increased risk of cardiovascular diseases remains a cause for concern in the combined oral contraceptives users. Several factors associated with cardiovascular diseases risk in women taking combined oral contraceptives, including the ethinylestradiol dose [27] and type of progestogens used [27,28].

Combined oral contraceptives are divided on the bases of its doses of estrogen and type of progestin content and according to the sequence of their development into different generation by decreasing the doses of hormones and improving their side effects. [29]

Reductions in the dose of ethinylestradiol ($< 50 \mu\text{g}$) have resulted in a decreased incidence of cardiovascular diseases [27, 28]. Even very low doses of ethinylestradiol (i.e., $10 \mu\text{g}$) have been shown to adversely affect haemostatic parameters [27].

The change in the composition and dosage in different generation of combined oral contraceptives and the careful selection for use by women lower the risk of cardiovascular diseases. The World Health Organization (WHO) “study of cardiovascular diseases and steroid hormone contraception conducted in developing and developed countries” revealed a higher overall risk of Ischemic stroke among combined oral contraceptives users in developing countries than those in developed countries of Europe. These differences were attributed to the type of combined oral contraceptives used and the frequency with which users reported that their blood pressure and other parameters had been checked prior to or during combined oral contraceptives use. [30]

This randomized analytical study was done to see the effects of duration of use of second generation monophasic combined oral contraceptives which are commonly used in Pakistan on the carbohydrate and lipid metabolism, blood pressure and BMI. We have divided the oral contraceptive users in three groups according to the duration of the use of these hormones 6 months Oral contraceptive users (n=23), 1 yr Oral contraceptive users (n=36) and > 1yr Oral contraceptive users (n=41). The clear influence was noted on the fasting biochemical parameters of lipid profile and blood sugar levels, blood pressure and basal metabolic index.

When we compared the fasting lipids levels between 6months combined oral contraceptives users and 1 year combined oral contraceptives users, the significant high levels of VLDL and Triglycerides was noted. In previous study they observed significant increased levels of triglyceride, LDL-cholesterol, and VLDL-cholesterol with the duration of oral contraceptive use. [13]

We also compared these different parameters in women taking oral contraceptives for 1 year and women who take it from more than 1 year. A high significant increase in T-Cholesterol, VLDL-C and Triglyceride were noted in combined oral contraceptive users of > 1year duration. Similar results were shown by the studies conducted by [24, 25]. Different observation was reported by other investigators they observed that serum triglyceride, LDL and VLDL cholesterol did not showed significant variations with duration of use of combined oral contraceptives.[31].

The fasting blood sugar in our study groups shows no significant change. A dose-response relationship was revealed between the duration of combined oral contraceptives use and the risk of diabetes among premenopausal Chinese women [17].

The mean fasting glucose level was not changed at 6 cycles from baseline in the study conducted by [21]. This is similar to previous studies [22, 23].

In "Nurses' Health Study" a small increased risk of diabetes was found among past combined oral contraceptives users, and significant increased risk of diabetes was observed among recent and long-term OC users [32]

The mean systolic and diastolic BP were found increasing in our study with the duration of use of the combined oral contraceptives and was recorded as 128.043 ± 2.944 mmHg, 133.889 ± 2.100 mmHg, 135.732 ± 3.325 mmHg in 6 months, 1 year and more than 1 year users groups.

The Mean BMI Kg/m² in 6 months, 1 year and more than 1 year users groups were recorded as 25.646 ± 0.868 Kg/m², 27.741 ± 0.484 Kg/m² and 28.367 ± 0.592 Kg/m². It was noted that (25%) of combined oral contraceptive users were the women who used combined oral contraceptives for more than 1 year and their BMI was ≥ 27 kg/m².

A study conducted on third generation combined oral contraceptives using women in their child bearing age. The results of that study do not indicate a long-term influence of combined oral contraceptives on weight gain but it was the age of the combined oral contraceptive users reported a weight increase in excess of 10 kg during period from 19 to 44 years of age [18]. Another study reported that there was no evidence of weight gain of the combined contraceptive users [19, 33]

The high level of lipid and sugar raised systolic and diastolic blood pressure and BMI has high risk of cardiovascular diseases (CVD). Our study revealed these risk factors in combined oral contraceptive users of Khyber Pakhtunkhwa province of Pakistan and the association between these risk factors with the duration of combined oral contraceptive use. Similar results were shown by previous study [34].

The resulting difference in our study as compared to other international studies may be due to the combined oral contraceptive which is the second generation and also due to the social and the cultural attitude and racial differences between different countries. The importance and strength of our study lies in the fact that it is the first study which analyses the effect of duration of use of combined oral contraceptive on lipids and carbohydrate metabolism, BMI and BP in Peshawar Pakistan.

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