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Original Articles

Effect of Low Dose Oral Contraceptive Pill on Glycemic and Lipidemic status in Women with Normal and Low BMI

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Abstract:

Objective (s): *Aim of the study was to explore the effect of the most widely used low dose OCP (Shukhi) on glycemic and lipidemic factors of under weight (Low BMI) Bangladeshi women.*

Materials and Methods: *This case control study was conducted at the Department of Cell and Molecular Biology, Research Division, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic disorders (BIRDEM) and Family Planning Center of Dhaka Medical College Hospital during the period of Jan 2011 to Dec 2011. A total number of 40 women were included in this study having age range between 25-45 years. Twenty nine (29) were with normal BMI (>18.5) and 11 were with low BMI (<18.5) consuming Shukhi for six months to five years. The control group (n=29) constituted of women with normal BMI and the case group (n=11) constituted the women with low BMI (BMI<18.5). Both groups use low dose OCP (30µg ethinyl estradiol and 150 µg levonorgestrel for 6-60 months. Glycemic status was assessed by measuring blood glucose fasting and 2 hrs after 75g glucose, insulinemic status by measuring C-peptide and lipidemic status by measuring TG, T Chol, HDL, LDL.*

Results:*There was no significant differences between two groups in fasting blood glucose and two hours after 75g glucose. A significantly high C-peptide (p=0.043) level was found in low BMI users, but a significantly negative correlation was found between fasting blood glucose and BMI in underweight OCP users (r=622, p=0.041). A better insulin sensitivity was found in low BMI as compared to normal BMI. Significantly lower total cholesterol (p=0.018) and LDL cholesterol (p=0.017) levels were found in low BMI OCP users than those of normal BMI OCP users. However, no significant correlation existed between any lipids.*

Conclusion: *This study suggested that OCP don't affect the glycemic, insulinemic (insulin secretory and sensitivity) and lipidemic status of underweight subjects.*

Keywords: *Low dose OCP, Glycemic and Lipidemic status, normal and low BMI women.*

Introduction:

OCP (combined) is one of the effective methods of contraception and is well accepted by women of various socioeconomic conditions. Millions of women use these drugs. So questions regarding the safety of these agents are important. A number of side effects were encountered by the users. These included nausea, vomiting, dizziness, metabolic disorders such

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as hypertention, diabetes and thromboembolic menifestations in the form of pulmonary embolism, leg vein thrombosis, coronary thrombosis and thus the estrogen component of the OCP was initially implicated[1,2] in the pill-induced thromboembolic side effects. But later it was shown that the progestin component[3,4] too played a vital role in enhancing cardiovascular side effects. The introduction of low dose OCP with 30µg oestrogens was a step in the right direction but further reduction resulted in breakthrough bleeding[5].

Many studies have shown the extent of the potential alterations of carbohydrate metabolism caused by both combination and progesterone only OCP. Estrogens alone do not worsen diabetes and may even improve hyperglycemia in noninsulin dependent diabetes[6]. Administration of synthetic estrogen even in high doses, does not consistently affect glucose tolerance or insulin response to a glucose load in healthy young women[7]. This effect has been attributed to a direct action of estrogens on the liver and A and B cell of pancreatic islets resulting in an overall decreased portal secretion of insulin and glucagon with an increased insulin glucagon ratio[8]. Synthetic progestogens, administered alone even in small amounts and by an oral rout shown impaired glucose tolerance in spite of hyperinsulinemia. This has been well demonstrated in a series of studies in women receiving for 12 or more months low doses of either a 17-acetoxy progesterone derived progestogen (mestranol acetate 0.5 mg/day) or one of the 19 nortestosterone derived progestogens norethisterone (.035mg/day), ethanodiol diacetate (0.25mg/day) or norgestrel (0.075mg/day)[9,10]. With respect to carbohydrate metabolism, a better appreciation of insulin resistance is necessary. Determination of C-peptide level may help to quantify more accurately the metabolic burden imposed by OCPs, even in low doses.

However, such low dose was possible primarily because highly effective and more specific progestogen such as levonorgestrel, desogestrel, gestadene, norgestimate etc were developed and introduced. The development of levonorgestrel and third generation progestogens were potentially responsible for reducing severe cardiovascular side effects[11]

It was suggested that the increase in serum lipid might be due to an increased hepatic synthesis of triacylglycerol [12,13]. Oral contraceptives were found to elevate serum insulin level[14]. This elevated serum insulin stimulated increased synthesis of triacylglycerol by liver[13]. This might be the most important mechanism of increased endogenous triacylglycerol production[14]. It was reported that oral contraceptives cause elevation of plasma free fatty acids[15].

Synthetic progestins were found to decrease high density lipoprotein (HDL) and increase low density lipoprotein (LDL) by decreasing apoprotein-A and APO-B concentration respectively[16]. Synthetic progestogen antagonized the estrogen induced rise in triacylglycerol and very low density lipoproteins (VLDL)[17]. Women using exogenous sex hormone preparations had higher levels of triacylglycerol, total cholesterol, VLDL and HDL than non-users[18]. It was demonstrated that a significant increase in serum triacylglycerol and cholesterol occur in women taking OCPs. The effects of LDL-C and HDL-C levels were found to depend on the type of progestin used. Norgestrel with maximum androgenic potency caused elevation of LDL-C and fall in HDL-C[19].

A large number of Bangladeshi women of various socioeconomic status are using low dose OCP. There are different types of combined low dose OCP used by the Bangladeshi women eg: Shukhi, Femicon, Nordette-28 and Marvelon. All these OCPs contain 30µg of ethinyl estradiol, but their progestogen component varies.

Shukhi is mostly used by the women of low socio-economic status, because the family planning program of the government of Bangladesh has made it available to them free of cost. Studies[20.21]shows that newer combined low dose OCPs cause less upset in metabolic and coagulation parameters as it contains 30µg of ethinyl estradiol (EE). But these need to be confirmed in Bangladeshi population with low BMI as it is well known that diet and life style can affect pill induced changes in hepatic protein synthesis. Safety of OCP has not been studied in low BMI undernourished Bangladeshi women. Due to protein deficiencies in these low BMI groups there may be different biological response in these women resulting in different risk profile. Purpose of the study was to explore the effect of low dose OCP on glycemic and lipidemic status of Bangladeshi women with low BMI in comparison to normal BMI.

Materials and Methods:

This case control study was conducted at the Department of Cell and Molecular Biology, Research Division, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic disorders (BIRDEM) and Family Planning Center of Dhaka Medical College Hospital (DMCH) during the period of Jan 2011 to Dec 2011. Data was collected from the patients of the Family Planning Centre of DMCH. Forty (40) women were included in this study having age range between 25-45 years. Twenty nine (29) were with normal BMI (>18.5) and 11 were with low BMI (<18.5) consuming Shukhi for six months to five years. Normotensive women with no co-existing medical disorders were the target population. Women with hypertension, diabetes, H/O smoking and alcoholism and too obese patients (BMI >30) were excluded.

After taking consent of the patient blood samples were collected and plasma/serum were stored at -7^{0}C for biochemical analysis. The Glycemic status was assessed by measuring blood glucose, fasting and 2hrs after 75g glucose, insulinemic status by measuring C-peptide and Lipidemic status by measuring tryglyceride, total cholesterol, high density lipoprotein and low density lipoprotein.

Laboratory methods: Serum glucose estimation was done by glucose oxidase method; Serum C-peptide by Chemiluminescence technique; insulin sensitivity and insulin secretory capacity by HOMA method; serum triglycerides and total cholesterol by enzymatic colorimetric method; HDL by CHOD-PAP method; LDL calculated by Friedwald formula.

All analyses were done by using SPSS. Results were expressed as median and range. The statistical comparison between the groups were done by Mann-Whitney test. Difference between BMI and other parameters were analysed by Pearson's correlation coefficient test. P value <0.05 was taken as level of significance.

Results:

Characteristics of different groups of the study subject shown in Table I. There is no significant difference in characteristics of the patient.

Table-I

Characteristics of the patients

Groups	Normal BMI (n=29)		Low BMI (n=11)	
	Median	Range	Median	Range
Age (years)	28.00	25-45	26.00	25-32
BMI (kg/m2)	23.06	19.40-30.08	18.44	15.04-18.50
Duration (months)	24.00	7-60	12.00	6-24

BMI=Body Mass Index
Duration= Duration of OCP use

Table-II

Glycemic and insulinemic statusof the study subjects

Groups	Normal BMI (n=29)		Low BMI (n=11)		Significance
	Median	Range	Median	Range	
F Glucose (mmol/L)	4.1	2.50-5.25	3.7	2.5-5.25	0.309
2 hr glucose (mmol/L)	6.25	4.20-8.00	5.5	4.10-8.60	0.202
C pep(ng/ml)	1.30	0.89-4.8	1.1	0.55-4.60	0.043

F glucose= Fasting glucose,
2 hr_glucose= 2hour after 75 gm glucose intake,
C C pep=C peptide

Table-III

B cell function and insulin sensitivity of the study subjects by HOMA method

Groups	Normal BMI (n=29)		Low BMI (n=11)		Significance
	Median	Range	Median	Range	
HOMA B (%)	339.40	177.50-924.20	229.00	106.50-944.40	0.774
HOMA S (%)	34.40	10.20-56.60	47.30	10.70-100.60	0.047

HOMA B= B cell function,
HOMA S= insulin sensitivity.

Table-IV

Lipid profile of different groupsof the study subjects

Groups	Normal BMI (n=29)		Low BMI (n=11)		Significance
	Median	Range	Median	Range	
TG (mg/dl)	98	46-280	72	53-144	0.067
T.chol (mg/dl)	180	119-269	127	109-231	0.018
HDL.chol (mg/dl)	35	26-53	34	27-45	0.749
LDL.chol (mg/dl)	124	76-197	73	49-180	0.017

TG= Triglyceride,
T.chol-Total cholesterol,
HDL=High Density Lipoprotein,
LDL=Low Density Lipoprotein.

Table-V

Pearson correlation coefficient between BMI and glycemic and insulinemic status

Group	Normal BMI (n=29)		Low BMI (n=11)	
Fasting glucose	r	.389	r	-.622
	p	.037	p	.041
2 hr glucose	r	.326	r	-.57
	p	.085	p	.067
C-pep	r	.109	r	-.136
	p	.574	p	.689
HOMA B	r	-.245	r	.195
	p	.200	p	.566
HOMA S	r	-.196	r	.088
	p	.308	p	.798

r= pearson correlation coefficient,
p= significant value for 'r'

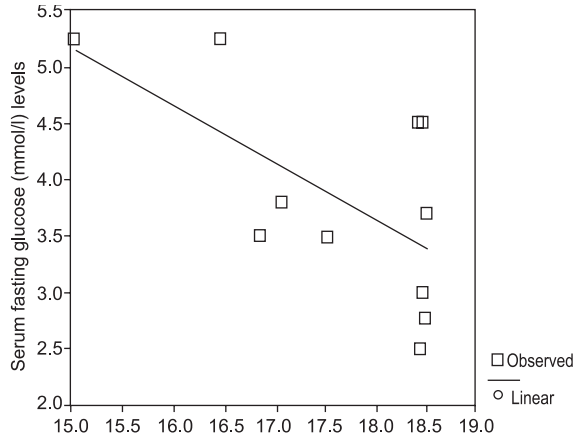

Fig.-1: *Pearson correlatin coefficient between serum fasting glucose and low BMI OCP users.*

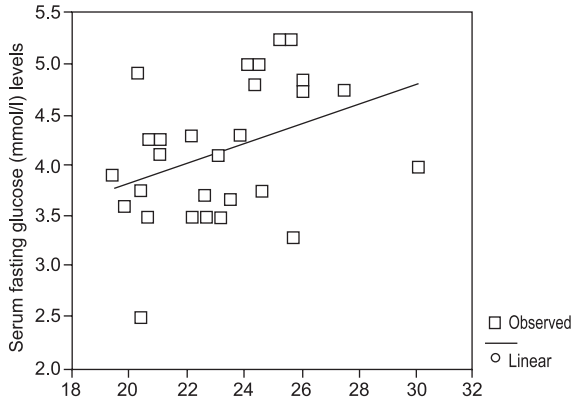

Fig.-2: *Pearson correlation coefficient between serum fawstring glucose and normal BMI.*

Table-VI

Pearson correlation coefficient between BMI and lipid profile

Group	Normal BMI (n=29)		Low BMI (n=11)	
TG	r	-.033	r	.254
	p	.866	p	.450
Chol.	r	-.120	r	.513
	p	.536	p	.106
HDL chol .	r	-.241	r	-.339
	p	.207	p	.308
LDL chol.	r	-.062	r	.489
	p	.751	p	.127

Pearson correlation coefficient did not show any significant correlation among lipid profile with BMI.

There is no statistically significant difference in the fasting blood glucose (p=0.309) and post prandial blood glucose level (p=0.202) in the two groups. Statistically significant difference was found in the serum C-peptide levels between these two groups of OCP users (p=0.043), but their blood levels were within the reference range (1.1-5 ng/ml). Their values were at the lowest end of the range (Table-II).

Table III shows B cell function and insulin sensitivity of the study subjects by HOMA method. A statistically significant insulin sensitivity was noted between two groups of pill users (p=0.047). Better insulin sensitivity was found in Low BMI pill users (47.30%).

There is overall decrease in triglyceride, total cholesterol, HDL and LDL cholesterol level, among the low BMI women using OCP than that of Normal BMI Group (Table IV).

In Pearson correlation coefficient between BMI and glycemic and insulinemic status a significant negative correlation was found among fasting blood glucose and Low BMI population (r= -622, p=0.041) (Table V)

Discussion:

Since the first report indicating a possible adverse effect of OCP use on carbohydrate metabolism[22], many studies have investigated the extent of the potential alteration caused by different steroid types and doses in both combination and progesterone only OCP. The studies with carbohydrate metabolism with contraceptive steroids suggests that synthetic estrogen namely, mestranol and ethinyl estradiol

produce few adverse effect [7].The reports also demonstrate different potencies with norethindrone having the least effect[9] and norgestrel greatest effect[23]. The effect of carbohydrate metabolism of the combination preparation containing the intermediate dose of levonorgestrel 150 ìg/day are controversial. Ahren et al[24] did not observe any adverse effect with this OCP, containing 150 ìg levonorgestrel. In this study women used low dose combination OCP, containing 150 µg levonorgestrel. No statistically significant change on blood glucose was noted in this with normal and low BMI women of Shukhi (30 µg EE + 150 µg levonorgestrel) users. Fasting blood glucose and 2 hrs glucose levels in this study does not differ from OCP non-user, non-diabetic Bangladeshi control subjects of other study.[25]Fasting C-peptide level in the present study also does not differ from OCP non-user control as shown by Hoque M[26]. The above Data suggest that the low dose OCP have no influence on glycemic status of the present study. B cell function and insulin sensitivity of the study subjects by HOMA method have shown no significant change in B cell function (p=0.774) but a significant difference in insulin sensitivity (p=0.047) was noted. As low BMI subjects secrete relatively less insulin but they are more insulin sensitive, this is how low BMI subjects are maintaining glycemic status. But a negative correlation exists between fasting blood glucose and low BMI (r= -622, p =0.041). Further extensive in-depth study is needed.

It is known that estrogen both endogenous and exogenous, increase the level of HDL cholesterol, so estrogen alone should be protective against the development of atherosclerosis. Some progestins have a substantially different effects, decreasing the HDL cholesterol and increasing the LDL cholesterol and therefore moving in the direction of an increased risk of atherosclerosis[27]. Low dose pill users, in our study, showed no significant change in serum total cholesterol, HDL cholesterol and LDL cholesterol. The result is similar to that of Wynn[28], who used the same low dose pill (30 µg EE+150 µg levonorgestrel) as used in this study[29]. Significant low total cholesterol (p=0.033) and LDL cholesterol (p=0.629) were found in low BMI pill users. Data from OCP non-users control of other study showed that serum lipid profile of this study subjects are nearly similar to them[26,30]. Blood lipids though altered were within normal limits both users with normal BMI and low BMI.

No apparent cardiovascular risk factor was indicated in this study. The absence of raised lipid profile and normal carbohydrate metabolism in the present study using combined OCP might probably be due to following reasons:

- All the study population are using low dose OCP containing 30 µg of EE and 150 µg levonorgestrel.
- Age of the study subjects in both groups were between 25-45 years.
- Other precipitating factors of hyperglycemia and hyperlipidemia were obesity, puerperium, hypertension, diabetes mellitus etc were excluded during screening of the subjects.
- Dietary habit of Bangladeshi women are different from western countries. Our women are mainly dependent on high fibre containing diet. These fibres probably make them less susceptible to hyperglycemia and hyperlipidemia.
- Studies among Asian women showed significantly low incidence of high lipid profile changes among OCP users as compared to western women. Therefore, the racial factor among the Bangladeshi women using OCP can not be ruled out.

Limitation of this study is small number of low BMI subjects. Initially it was thought that number of low BMI women of child bearing age using OCP will be widely prevalent. During data collection it was found that low BMI women in this age group are not so common as compared to normal BMI. Cause may be gaining of weight and less linear height in this nutritional group. Reasons for gaining of weight of these women might be child bearing, increasing age or OCP itself. On the other hand, average height of Bangladeshi women are low in comparison to nutritionally privileged women possibly this is how the normal range of BMI is maintained in women with low socioeconomic background and also the BMI parameter in developing country is different from that of developed country.

Conclusion:

From the statistical analysis of the results obtained in present study and their comparison data suggested the following:

Low dose OCP do not seem to affect the glycemic status, insulinemic status, insulin secretory and sensitivity status of low BMI Subjects. As in the case of non-pill users reduced weight seem to protect a woman from atherogenic lipids. The reported risks of hyperglycemia and hyperlipidemia in pill users seem to be dependent on obesity, in the lower weight playing

a protective role. Less number of low BMI subject is a limitation of this study. Yet this small study gave an impression that low dose OCP has no impact on glycemic and insulinemic status of underweight women. A large in-depth control study is needed to draw the conclusion.

References:

1. Royal College of General Practioners. Oral Contraceptives and health. An interim report for the oral contraception study of the Royal college of general practitioners. New York, Pitman Publishing Co. 1974; 98.
2. Prasad RNV, Ratnam SS. The cardiovascular and thromboembolic risks of oral contraception-A review. Sing J. Obstel Gynecol 1980;11:1, 7-19.
3. Ratnam SS, Prasad RNV. Oral contraceptives In: Practice of Fertility control (Chaudhuri,SK, Ed) Current Book Publishers, Calcutta 1983; 103.
4. Ulysse JG. Metabolic effects of Oral contraceptives. Am. J. Obstel Gynecol pt II suppl, 1987; 157:4, 1029-1014.
5. Ratnam SS, Prasad RNV. Recent developments in steroidal contraception. Sing J. Obstel Gynecol. 1980; 11:7-13.
6. Kalkhoff RK. Effect of oral contraceptive on carbohydrate metabolism. J. Steroid Biochem. 1975; 6: 945-956.
7. Spellacy WN, Buhi WC, Birk SA. The effect of estrogens on carbohydrate metabolism: glucose, insulin and growth hormones studies on one hundred seventy one women ingesting Premarin, mestranol and ethinyl estradiol for six months. Am. J. Obstel and Gynecol. 1972; 114: 378-390.
8. Mandour T, Kissebah AH, Wynn V. Mechanism of estrogen and progesteron effect on lipid and carbohydrade metabolism. Alteration in the insulin: glucagon molar ratio and hepatic enzyme activity. Eur. J. Clin. Invest. 1977;7: 181-187.
9. Spellacy WN, Buhi WC, Birk SA. Effect of norethindrone on carbohydrate and lipid metabolism. Obstel.Gynecol. 1975; 46: 560-563.
10. Spellacy WN, Buhi WC, Birk SA. carbohydrate and lipid metabolic studies before and after one year of treatment with ethynodiol diacetate in normal women. Fertil steril.1976; 27:900-904/
11. Skouby SO, Peterson KR and Jespersen J. The influence of new dose oral contraceptive on metabolic variables. Adv. Contra. 1991; 7(suppl.2) 77-88.
12. Wynn V. Doar IWH, Mills GL, Strokes T. Fasting serum triglyceride, cholesterol and lipoprotein levels during oral contraceptive therapy. The Lancet 1969;2:756-760.
13. Hazzard WR, Spiger MJ, Bagdade JD, Bierman EI. Studies on the mechanism of increased plasma triglyceride levels induced by oral contraceptive. N. Eng. J. Med. 1969; 280:471-474
14. Sachs BA, Wolfman L, Herzig-N. Plasma and lipoprotein alterations during oral contraceptive administration. Obstel. Gynecol.1969; 34: 530-535.
15. Wynn V, Doar JWH, Mills GL. Some effects of oral contraceptives on serum lipid and lipoprotein levels. The Lancet, 1966; 2: 720.
16. Bradley DD, Wingerd J, Petitte DB, Kraus RM, Ramcharans S. Serum high density lipoprotein cholesterol in women, using oral contraceptives, estrogens and progestines. N. Eng. J. Med. 1978; 299: 17-20.
17. Yaspard UJ. Metabolic effects of oral contraceptives. Am. J. Obstel. Gynecol. 1987; 159; 1029.
18. Heiss G, Tanier I, davis CE, Tyroler HA, Rifkind BM, Schonfeld G. Lipoprotein cholesterol distribution in selected North American Populations. The lipid research clinics program prevalence study. Circulation, 1980; 61: 302.
19. Lipson A. Stoy DB, La Rosa J, Muesing RA, Cleary PA, Miller VT. Progestines and oral contraceptive induced lipoprotein changes; a prospective study. Contraception, 1986; 34: 121-134.
20. Samsioe G. Comparative effects of Oral contraceptive combinations 0.15 mg desogestrel + 0.03 mg ethinyl oestradiol and 0.15 mg levonorgestrel + 0.03 mg ethinyl oestradiol on lipid and lipoprotein metabolism in healthy female volunteers. Contraception 1982; 25(5): 487-503.
21. Lanchnit- Fixon. Triphasic pill “neutral”effects on lipid profile. XI world congress on fertility and sterility Newsletter. Schering AG. Publishers 1983; 4.

22. Waine H, Freedew EH, Caplan HI, Cole T. Metabolic effect of Enovid in rheumatoid patients (abstract). Arthritis Rheum, 1963; 6: 796.

23. Spellacy WN, Carbohydrate metabolism during treatment with estrogen, progestogen and low dose oral contraceptives. Am. J. Obstel. Gynecol.1982;6:732-734.

24. Ahren J. Victor A, Lethelt H, Johansson EDB. Comparison of the metabolic effects of two hormonal contraceptive methods: an oral formulation and a cervical vaginal ring. Contraception, 1981; 24: 415-427.

25. Khan LA, Alam AMS, Ali L, Goswami, Hassan Z, Sattar S, Banik NG, Khan AKZ. Serum and urinary magnesium in young diabetic subject in Bangladesh. Am. J. Cli. Nutr. 1999; 69: 70-73.

26. Hoque M. Pathogenesis of platelet aggregation, hyperfibinogenemia and increased VWF factor in diabetes mellitus, MD thesis, BIRDEM Academy, Dhaka University, July 1999.

27. Kay CR. Progestogens and arterial disease: Evidence from Royal College of General Practioners Study. J. Obstel. Gynecol. 1982; 142: 762-765.

28. Prasad RNV, Kohs & Ratham SS. Effect of three types of combined OCPs on blood coagulation, fibrinolysis and platelet function. Contraception. 1989; 29 (4): 369-383.

29. Wynm V. Niththyananthan R. The effect of progestin in combined oral contraceptives on serum lipids with special references to HDL. Am. J. Obstel Gynecol. 1982; 142: 766-772.

30. Dr. Fouzia. Role of autoimmunity in the pathogenesis of young onset diabetes in Bangladesh. MD thesis, BIRDEM Academy, Dhaka University, July 2000.