Lipoprotein changes in women taking low-dose combined oral contraceptive pills: a cross-sectional study in Basra, Iraq

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تغيُّرات البروتين الشحمي في النساء اللاتي يتناولن جرعة منخفضة من أقراص التوليفات المانعة للحمل: دراسة مستعرضة في مدينة البصرة بالعراق

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الخلاصة: وقد قاس الباحثون مستويات الشحميَّات والبروتينات الشحمية في مئة امرأة يتناوَلْنَ جرعة مخفّضة من أقراص التوليفات المانعة للحمل، وفي مئة امرأة شاهدة، لا يتناولن هذه الأقراص، من مُرتادات مركز تنظيم الأسرة، ومركز رعاية الأمومة، ومستشفى الأطفال في مدينة البصرة في العراق. وقد جُمعت عينات الدم بعد 12-14 ساعة من الصيام، وقيست مستويات ثلاثي الغليسريد المصلي، والكوليسترول الكلي، وكوليسترول البروتين الشحمي الرفيع الكثافة HDL، وكوليسترول البروتين الشحمي الخفيض الكثافة LDL، وكوليسترول البروتين الشحمي الوضيع الكثافة VLDL. وكانت المستويات المصلية لثلاثي الغليسريد، وكوليسترول البروتين الشحمي الرفيع الكثافة، وكوليسترول البروتين الشحمي الوضيع الكثافة أعلى، ومستوى كوليسترول البروتين الشحمي الخفيض الكثافة أدنى بدرجة يُعتَدُّ بها إحصائياً بين من تناوَلْنَ تلك الأقراص مقارنةً بمن لم يتناوَلْنَها، ولكن لم تختلف مستويات الكوليسترول الكلي بين المجموعتين. وتزايَدَتْ مستويات ثلاثي الغليسريد المصلي، وكوليسترول البروتين الشحمي رفيع الكثافة، وكوليسترول البروتين الشحمي الوضيع الكثافة مع العمر ومدة تناول الأقراص، في حين تناقَصَتْ مستويات كوليسترول البروتين الشحمي الخفيض الكثافة؛ ولم تتغير مستويات الكوليسترول الكلي.

ABSTRACT We assessed lipid and lipoprotein levels in 100 women taking low-dose COCs and a control group of 100 non-users attending the family planning centre Basra Maternity and Child Hospital, Iraq. Venous blood was collected after 12–14 hours fasting, and serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein (VLDL) levels were measured. Serum TG, HDL-C and VLDL levels were significantly higher and LDL-C levels lower in users than non-users but TC levels did not differ between the 2 groups. TG, HDL-C and VLDL levels rose with age and duration of use while LDL-C levels decreased; TC levels did not change.

Modification des taux de lipoprotéines chez les femmes sous contraceptifs oraux associés faiblement dosés : une étude transversale réalisée à Bassora (Iraq)

RÉSUMÉ Nous avons évalué les taux des lipides et des lipoprotéines chez 100 femmes sous contraceptifs oraux associés faiblement dosés et chez 100 femmes témoins non utilisatrices consultant le centre de planification familiale du *Maternity and Child Hospital* [Hôpital de la mère et de l'enfant] de la ville de Bassora (Iraq). Un prélèvement de sang veineux a été effectué après 12 à 14 heures à jeun, et les taux des triglycérides sériques, de cholestérol total et de cholestérol des lipoprotéines de haute densité, basse densité et très basse densité ont été mesurés. Les taux des triglycérides sériques et de cholestérol des lipoprotéines de haute densité et de très basse densité étaient nettement plus élevés, et le taux de cholestérol des lipoprotéines de basse densité était plus faible chez les utilisatrices de contraceptifs que chez les autres femmes, alors que le taux de cholestérol total était similaire dans les deux groupes. Les taux des triglycérides sériques et de cholestérol des lipoprotéines de haute densité et de très basse densité augmentaient avec l'âge et la durée d'utilisation des contraceptifs, alors que le taux de cholestérol des lipoprotéines de basse densité diminuait, et que le cholestérol total restait stable.

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Introduction

Most modern preparation of combined oral contraceptive contain the estrogen (ethinyl estradiol) in a daily dose between 20–35 μg [1]. Pills containing higher dose of estrogen > 50 μg have been linked to an increased risk of both arterial and venous thrombosis [2]. Current combined oral contraceptive (COCs) contain progestogen, classed as a second or third generation and which are all derivatives from 19-nor testosterone [3].

Several researchers have reported the advantages [4], complications and side-effects of combined oral contraceptives [5]. The effects of combined oral contraceptives on plasma lipid and lipoproteins have also been studied. An increase in serum triglycerides (TG), which are mainly present in very low-density lipoprotein (VLDL), has been reported [6,7]. Another study reported that the serum cholesterol level was unchanged in women taking low-dose combined oral contraceptives; however the proportion of serum cholesterol carried by high-density lipoprotein (HDL) was decreased, while that carried by low-density lipoprotein (LDL) and VLDL was increased [8]. Yet another study reported that serum HDL-cholesterol (HDL-C) levels varied with the type and the dose of steroids, and the net effect of using combined oral contraceptives on HDL-C depended on its formulation [9]. Decreased plasma LDL-cholesterol (LDL-C) has also been reported [10].

There have been no studies conducted among women in Iraq on the effects of combined oral contraceptives (COCs) on plasma lipids and lipoproteins. Therefore, in this study we aimed: to evaluate the concentrations of TG, total cholesterol (TC), HDL-C, LDL-C and VLDL in women in Basra who were using a low dose of a combined oral contraceptive pill in relation to those not using these pills; and to clarify the relationship between lipid profile changes and the duration of using these contraceptives.

Methods

Study setting

A cross-sectional study was conducted in Basra Maternity and Child Hospital over a period of 7 months, from 1 October 2001 to 31 May 2002.

Study sample

The sample was drawn from women attending the family planning centre of the Basra Maternity Hospital.

User group: This included 100 women , who took combined oral contraceptive pills (30 μg ethinyl estradiol and 150 μg levonorgestrel). Their ages ranged from 15–45 years (women over 45 years were excluded) and the duration of using combined oral contraceptives ranged from 1–60 months. The pills that were used in the present study were Microgynon, containing 30 μg eithinyl estradiol and 150 μg levonorgestrel. These were the only pills available the centre at the time of the study.

Non-user group: This included 100 apparently healthy women not using these contraceptive pills.

All women agreed to participate and there were no drop-outs.

The women (users and non-users) were classified into 3 groups according to their age. The user group were also categorized into 5 groups according to their duration of using these pills.

From each woman, full information was obtained that included: name, age, occupation, well as the following question about not receiving medical treatment and had no diseases of diabetes mellitus, coronary heart disease, hypertension and chronic renal failure. Women with these conditions were excluded.

For each woman, 5 mL of venous blood were collected after 12–14 hours of fasting. Serum concentrations of TC, TG, HDL-C (after precipitation with sodium phosphotungstate–magnesium chloride) were determined enzymatically using kits from BioMérieux, France. All procedures were followed according to the instructions of the manufacturer. LDL-C and VLDL serum concentrations were calculated using Friedewald formulae [11]: LDL-C = TC–(HDL-C + TG/5) and VLDL = TG/5.

The above formulae are applicable when serum TG level is < 400mg/dL. Quality control sera from BioMérieux were included in each assay batch for all the above analytes. The inter-assay coefficient of variation was 4% for TC and TG and 6% for HDL-C.

Statistical analysis

Statistical analysis with each group of subjects was performed by analysis of variance (ANOVA), and the results are expressed as mean [standard deviation (SD)]. $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the characteristics of the 2 groups.

Table 2 shows the effect of age on plasma lipids and lipoproteins in the studied groups. Mean serum concentrations of TG, VLDL and HDL-C were significantly higher in the oral contraceptive user group compared with the non-user group ($P < 0.01$), while serum LDL-C level was significantly lower ($P < 0.01$). However, the concentration of total serum cholesterol was not significantly altered ($P > 0.05$). This was true for in age groups and overall.

For the 3 age groups of oral contraceptive users, there was a significant elevation of serum TG, VLDL and HDL-C levels with advancing age ($P < 0.01$). However, serum LDL-C level significantly decreased with age ($P < 0.01$), but there were no significant changes in the serum TC levels ($P > 0.05$). There were no significant relationships among non-users.

Table 1 Characteristics of the oral contraceptive users and nonusers

Variable	Oral contraceptives	
	Non-users (*n* = 100)	Users (*n* = 100)
Age (years)		
15–24	12	20
25–34	41	35
35–45	47	45
Mean age (SD)	33.2 (7.1)	32.5 (8.1)
Duration of contraception use (months)		
1–12	–	36
13–24	–	16
25–36	–	14
37–48	–	13
49–60	–	21
Mean (SD) duration	–	28.2 (21.6)
Mean (SD) no. of pregnancies	5.2 (1.9)	5.6 (2.1)
Mean (SD) blood pressure (mmHg)		
Systolic:	113.8 (52)	112.5 (6.8)
Diastolic	83.7 (5.1)	82.4 (4.7)
Mean (SD) weight (kg)	66.8 (9.2)	65.4 (7.3)

SD = standard deviation.

Table 3 shows the effect of duration of contraception use on plasma lipids and lipoproteins in the studied groups. Serum concentrations of TG, VLDL and HDL-C were significantly higher in users than non-users in all categories of duration of use, even in users of 1–12 months ($P < 0.01$), while serum LDL-C level were significantly lower. Serum total cholesterol level however was not significantly different ($P > 0.05$).

Table 4 shows the multivariate analysis of the correlation between age, duration and lipoprotein levels. There was a significant positive correlation between age and duration of contraception use and mean levels of TG, VLDL and HDL-C concentrations ($P < 0.01$) and a significant negative correlation with concentration of LDL-C ($P < 0.01$), while, the mean level of TC concentration did not correlate significantly with either age or duration ($P > 0.05$). In addition, LDL-C showed a significant positive correlation with TC ($P < 0.01$) and significant negative correlation with TG, VLDL and HDL-C ($P < 0.01$). On the other hand a significant positive correlations (P<0.01) was found among TG, VLDL and HDL-C in the user group.

Discussion

Our results showed serum TG, HDL-C and VLDL levels were significantly higher in all user groups compared with non-users but the LDL-C level was significantly lower. Furthermore, TG, HDL-C and VLDL levels increased with age and duration of contraceptive use, while LDL-C levels decreased. However, serum total cholesterol levels did not differ between the groups nor change with age or length of contraceptive use.

Our results for serum total cholesterol are consistent with some other

Table 2 Effect of age on lipoprotein level in users and nonusers oral contraceptive pills by age group

Age group (years)/ User status	No.	Total cholesterol	HDL-C	LDL-C	TGs	VLDL
		Mean (SD) mg/dL	Mean (SD) mg/dL	Mean (SD) mg/dL	Mean (SD) mg/dL	Mean (SD) mg/dL
15–24						
User	12	172 (31.9)	55 (9.3)^{**a,b}	97.4 (15.5)^{**a,b}	106 (11.2)^{**a,b}	21.4 (3.1)^{**a,b}
Non-user	20	176 (22.2)	46 (9.4)	113 (14.47)	89.5 (16.6)	18 (3.8)
25–34						
User	41	174 (23.3)	65 (10.5)^{**a,b}	83 (16.5)^{**a,b}	119 (13.5)^{**a,b}	24 (2.5)^{**a,b}
Non-user	35	183 (23.8)	48 (10.8)	118 (177)	97 (14.1)	19.5 (3.7)
35–45						
User	47	177 (20.5)	74 (10.9)^{**a,b}	67 (15.23)^{**a,b}	148.6 (12.3)^{**a,b}	29.9 (3.1)^{**a,b}
Non-user	45	186 (28.1)	46.3 (11)	122 (17)	103 (12.7)	20.8 (4.1)

$^{**}P < 0.01$
^{a}Significance between oral contraceptive users and control group.
^{b}Significance between the three age groups in oral contraceptive users.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TGs = triglyceride; VLDL = very low-density lipoprotein; SD = standard deviation.

Table 3 Effect of duration on lipid profiles in users and nonusers of contraceptive pills

Duration of use (months)	No.	Total cholesterol	HDL-C	LDL-C	TGs	VLDL
		Mean (SD) mg/dL	Mean (SD) mg/dL	Mean (SD) mg/dL	Mean (SD) mg/dL	Mean (SD) mg/dL
1–12	36	173 (28.7)	56 (8.9)**a,b	99.4 (13.84)**a,b	101 (15.1)**a,b	20 (3.12)**a,b
13–24	16	174 (27.6)	64 (9.6)**a,b	86.8 (16.43)**a,b	113 (14.2)**a,b	22.7 (2.68)**a,b
25–36	14	175 (22.4)	72.3 (5.6)**a,b	76 (15.35)**a,b	125.8 (13.1)**a,b	25.3 (2.8)**a,b
37–48	13	177 (29.1)	78.7 (6.7)**a,b	63 (17.21)**a,b	140 (13.3)**a,b	28 (2.5)**a,b
49–60	21	178.4 (27.2)	85.6 (5.9)**a,b	51 (13.92)**a,b	152 (11.2)**a,b	31 (3.4)**a,b
Nonusers	100	181 (25.7)	46.7 (10.3)	117 (18.9)	96 (16.1)	19 (3.8)

***P < 0.01.*
[a]Significance between oral contraceptive users and control group.
[b]Significance between duration groups in oral contraceptive users.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TGs = triglyceride; VLDL = very low-density lipoprotein; SD = standard deviation.

studies [12,13], whereas one study reported a significant increase in serum TC levels associated with the use of low-dose combined contraceptive pills [14]. A possible explanation of these different results could be the regulation of serum cholesterol, which is affected by its rate of synthesis or LDL receptor activity or its ability to be converted into bile acid [15]. Therefore, the use of low-dose combined oral contraceptives might have a negligible effect on cholesterol homeostasis. However, ate the same time cholesterol has a strong positive correlation with LDL-C.

The higher serum TG level in users and the increase in serum TG levels with increasing age and length of contraceptive use imply that low doses of estrogen increase serum TG, which is mainly present in VLDL. It has been suggested that the TG changes are due to the induction by estrogens of a hepatic microsomal enzyme that limits the rate of TG synthesis. These changes are usually no longer detectable a few months after stopping treatment [7]. The significant positive correlation between age and TG could be attributed to the long-term use of estrogen-containing contraceptive pills and this is supported by the strong positive correlation between duration of use and TG levels.

The increase in serum VLDL and HDL-C levels and decrease in LDL levels in the user group compared to non-users, and the changes with age and duration of use may be explained by the effect of estrogen on these lipoproteins. This elevates liver lipogenesis which causes increases in TG, VLDL and HDL-C levels [7] and also causes an increase in the synthesis of hepatic LDL-C receptors and a resulting increase in the removal of serum LDL-C and hence reduction in its levels [15]. The positive correlation of age with VLDL and HDL-C illustrated by prolonged consumption of estrogen is reinforced by the strong positive correlation of duration with VLDL and HDL-C.

On the other hand, the inverse correlation of LDL-C with both age and duration can be attributed to the effect of prolonged estrogen use. A recent study suggested that the estrogen-induced LDL-C lowering effect resulted from enhancement of LDL receptor activity [7]. It has also been reported that estrogen can reduce dietary cholesterol absorption by 6% to 10%, but this small

Table 4 Correlation between age, duration and lipid profile

Parameter	Age (years)	Duration (months)	Total cholesterol (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	TGs (mg/dL)L	VLDL (mg/dL)
	r	*r*	*r*	*r*	*r*	*r*	*r*
Age	1.000	0.92**	0.142	0.867**	–0.767**	0.887**	0.888**
Duration	0.92**	1.000	0.102	0.806**	–0.719**	0.736**	0.738**
Cholesterol	0.142	0.102	1.000	0.284	0.65**	0.195	0.187
HDL-C	0.867**	0.806**	0.284**	1.000	–0.610**	0.731**	0.729**
LDL-C	–0.767**	–0.719**	0.65**	–0.610**	1.000	–0.726**	–0.732**
TGs	0.887**	0.736**	0.195	0.731**	–0.726**	1.000	0.996**
VLDL	0.888**	0.738**	0.187	0.729**	–0.732**	0.996**	1.000

***Correlation is significant at P < 0.01 (2-tailed).*
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TGs = triglycerides; VLDL = very low-density lipoprotein.

decrease does not seem to contribute greatly to the LDL-C lowering effect of estrogen [16].

There are marked differences between countries in patterns of contraceptive use both in types and extent of use [17]. These differences reflect availability and accessibility as well as social and cultural attitudes towards fertility control, sexuality and roles of women in society [18]. What is important is that any contraceptive used should not adversely affect the health of the user. Our findings of a significant rise in TG, VLDL and HDL-C and significant decrease in LDL-C levels, with no significant alteration in the serum cholesterol level among women using low-dose combined oral contraceptive pills suggest that the use of these pills may decrease the risk of coronary heart and other heart diseases.

References

1. Glasier A. Contraception. In: Edmonds DK, ed. *Dewhurst's textbook of obstetrics and gynaecology for postgraduates*, 6th ed. London, Blackwell Science, 1999:374.
2. Guillebaud J. *Contraception: your questions answered*, 2nd ed. Edinburgh, Churchill Livingstone, 1993.
3. Burkman RT et al. Current perspectives on oral contraceptive use. *American Journal of Obstetrics and Gynecology*, 2001, 185(2 Suppl.):S4–12.
4. Hatcher RA et al. *The essentials of contraceptive technology*. Baltimore, Johns Hopkins School of Public Health, Population Information Program, 1997:1–28.
5. Moore JG. Contraception and sterilization. In: Hacker NF, Moore JG, eds. *Essentials of obstetrics and gynecology*, 2nd ed. Philadelphia, WB Saunders Company, 1992:453-467.
6. Fotherby K. Twelve years of clinical experience with an oral contraceptive containing 30 micrograms ethinyloestradiol and 150 micrograms desogestrel. *Contraception*, 1995, 51:3–12.
7. Warren MP. Metabolic effects of contraceptive steroids. *American Journal of the Medical Sciences*, 1973, 265:4–21.
8. Nash AL, Cornish EJ, Hain R. Metabolic effects of oral contraceptives containing 30 micrograms and 50 micrograms of oestrogen. *Medical Journal of Australia*, 1979, 2:277–281.
9. Straznicky NE et al. A study of the interactive effects of oral contraceptive use and dietary fat intake on blood pressure, cardiovascular reactivity and glucose tolerance in normotensive women. *Journal of Hypertension*, 1998, 16:357–368.
10. Akerlund M. Clinical experience of a combined oral contraceptive with very low dose ethinyl estradiol. *Acta Obstetricia et Gynecologica Scandinavica. Supplement*, 1997, 164:63–65.
11. Cong KJ, Wang TT, Liu GR. Lipid metabolism and pregnancy induced hypertension. *Zhonghua Fu Chan Ke Za Zhi*, 1994, 29(11):561–563, 697–698.
12. Kasule J et al. Evaluation of combined oral contraceptive pill in black Zimbabwean women. *Central African Journal of Medicine*, 1999, 37:403–409.
13. Esrobar-Morreal H, Lasuncien M, Sancho J. Treatment of hirsutism with ethinyl estradiol contraceptive pills. *Fertility and Sterility*, 2000, 74:816–819.
14. Chen JK et al. A pharmacodynamic and pharmacokinetic study of the Chinese No. 1 pill. *Contraception*, 1990, 42:439–453.
15. Burtis CA, Ashwood ER. *Teitz textbook of clinical chemistry*, 2nd ed. Philadelphia, WB Saunders Company, 1994:1002–1093.
16. Karjalainen A et al. Mechanisms regulating LDL metabolism in subjects on peroral and transdermal estrogen replacement therapy. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 2000, 20:1101–1106.
17. Mintzer M. Contraception. In: Sloane PD, Slatt LM, Baker RM, eds. *Essentials of family medicine*. Baltimore, Williams and Wilkins, 1988:175–176.
18. Leridon H. Fertility and contraception in 12 developed countries. *Family Planning Perspectives*, 1981, 13:93–102.