Effects of oral contraceptives on carbohydrate and lipid metabolisms in a healthy population: The Telecom Study

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In a cross-sectional study that aimed to identify risk factors for diabetes, 1290 consecutive, healthy, nonpregnant women of child-bearing age were examined in a center for preventive medicine. An in-depth interview about menses, use of oral contraceptives, and menopause was performed. Plasma glucose at fasting and 2 hours after a 75 gm glucose load, glycated hemoglobin A_{1c}, fasting plasma insulin, total plasma cholesterol, and triglycerides were measured. Compared with nonusers taking no progestogens, oral contraceptive users (n = 431;33.4%) were younger ($p < 0.001$) and leaner ($p < 0.001$). After adjustment for age and body mass index, oral contraceptive users had higher 2-hour plasma glucose ($p < 0.001$), higher fasting plasma insulin ($p < 0.01$), and higher triglycerides levels ($p < 0.01$). Fasting plasma glucose, glycated hemoglobin A_{1c}, and total cholesterol did not significantly differ between the two groups. In relation to dosage and types of steroid components, few differences have been found between high-dose and low-dose oral contraceptives or according to the estrogen-progestogen balance of the preparations. Use of oral contraceptives appears to induce an increase of insulin-resistance markers, which have recently been cited as risk factors for ischemic vascular diseases. These markers should be carefully monitored in oral contraceptive users. (Am J Obstet Gynecol 1990;163:382-7.)

Key words: Oral contraceptives, high-dose/low-dose oral contraceptives, estrogen/progestogen balance, insulin resistance

Oral contraceptives are the most popular reversible method of contraception in the United States[1] and probably in all developed countries. Their low rate of failure, ranked second behind sterilization,[2] low cost, and acceptability will probably help keep consumption of oral contraceptives very high in the next decade worldwide. Thus there is a need to evaluate very carefully their side effects. Despite criticisms, which are mainly addressed at the observational nature of study designs used to investigate the relationship between oral contraceptives and cardiovascular diseases,[3] it is currently admitted that most of the epidemiologic surveys have indicated a link between oral contraceptive use and adverse cardiovascular events.[4-8] Oral contraceptives seem to generate these effects through deleterious changes in the coagulation process and in carbohydrate and lipid metabolisms.[9, 10] To reduce cardiovascular risk, a large-scale move toward preparations containing low doses of estrogens was initiated in the early 1970s, followed a few years later by efforts to minimize the dose of progestogens.[11, 12] Consequences of these changes in oral contraceptives prescription habits on carbohydrate and lipid metabolisms have been poorly evaluated as the ideal design—a prospective, comparative, randomized study of each new oral contraceptive[9] is difficult to realize because of obvious ethical and practical reasons. Moreover, the few surveys designed to address this issue have often been conducted on small samples and have led to contradictory conclusions.[13-21] Therefore this article assesses the influence of oral contraceptives on metabolic parameters in a large, healthy, female population and makes a comparison between oral contraceptive users and nonusers, and among users, according to estrogen dosage and estrogen/progestogen balance of the preparations.

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Subjects and methods

From April 1985 to October 1987, 1290 consecutive, healthy women of child-bearing age, who voluntarily attended a center for preventive medicine, were examined in a cross-sectional study. Women who were pregnant, who had a self-reported history of diabetes, who were treated by progestogens alone, or who had hemoglobinopathies, were excluded. The subjects were "France-Telecom" employees working in the Paris area who are offered a medical check-up, free of charge,

Table I. Description of the population

Characteristics	*No hormonal treatment (n = 859)*	*OC (n = 431)*	*p value*
Ethnic origin (%)			
White	85.9	88.7	
Black	13.4	10.8	NS
Asian	0.7	0.5	
Age (yr)	38.5 ± 0.3	29.5 ± 0.3	<0.001
Smokers (%)	23.7	34.2	0.72*
Family history of diabetes (%)	14.6	8.4	0.11*
Body mass index (kg/m²)	23.0 ± 0.1	21.5 ± 0.1	<0.001
Systolic blood pressure (mm Hg)†	118.4 ± 0.4	120.1 ± 0.7	<0.05
Diastolic blood pressure (mm Hg)†	68.3 ± 0.4	70.2 ± 0.6	0.01
GGT (U/L)†‡	9.5 (9.1-9.8)	11.2 (10.6-11.8)	<0.001
SHBG (nmol/L)†‡	36.5 (34.7-38.4)	56.7 (52.3-61.4)	<0.001

Results show percentage or mean ± SEM as appropriate.

GGT, γ-Glutamyltransferase; *SHBG*, sex hormone–binding globulin.

**p* Value calculated after adjustment for age.

†Values adjusted for age and body mass index (calculated for age = 35 years and body mass index = 22.5 kg/m²).

‡Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

every 5 years for those under 40 years and every 2 years for those over 40 years.

A self-questionnaire, which was filled out at home, inquired about gynecologic and obstetric history, present oral contraceptive use with the brand name if any, regularity of menstrual cycle, and the first day of the last period. During the consultation, a secretary reviewed carefully all these data with the client and gave her a letter to be returned when her next menses began; 80% responded and indicated the date of the following menses.

Height, weight, and blood pressure were recorded at physical examination. The Quetelet index [weight(kg)/height(m)²] was used as a measure of body mass index. Fasting plasma glucose, plasma insulin (22), total cholesterol, triglycerides, and glycated hemoglobin A_{1c}[23] were measured and plasma glucose was also measured 2 hours after a 75 gm glucose load (2-hour plasma glucose).

Table I describes the study population and compares each nonmetabolic parameter between oral contraceptive users and nonusers. The sample consisted of around 87% whites and 12% blacks, mainly natives from the West Indies. Oral contraceptive users were significantly younger and leaner (Table I). After adjustment for age and body mass index, systolic and diastolic blood pressures were significantly higher in oral contraceptive users who also had significantly higher level of γ-glutamyltransferase and sex hormone–binding globulin (Table I).

Regarding metabolic parameters, comparisons have been made between oral contraceptive users and nonusers in a first step. Among users, subdivisions were then made according to dosage and types of steroid components. Thus by crossing estrogen content (high-dose/low-dose) with hormonal balance (estrogen/progestogen dominance), four subgroups of oral contraceptives have been identified (Table II), in which dosage of ethinyl estradiol, progestogen content, and number of users have been indicated for each oral contraceptive.

This classification of oral contraceptives led us to perform four comparisons in a second step: between high-dose and low-dose oral contraceptive users inside each hormone-dominance group and between estrogen-dominant and progestogen-dominant oral contraceptive users inside each estrogen-dose group. Statistical analysis used programs accessible through SAS[24] on a VAX 8530. The χ^2 tests and analysis of variance have been performed after logarithmic transformation when needed. When a significant difference has been observed for age or/and body mass index, comparisons for metabolic parameters have been adjusted for age or/and body mass index. For quantitative variables, the values reported are mean ± SEM or the mean followed by the 95% confidence interval for the mean when logarithmic transformation has been needed.

Results

Compared with the 859 oral contraceptive nonusers, the 431 oral contraceptive users were not significantly different for hemoglobin A_{1c}, fasting plasma glucose, and total cholesterol concentrations (Table III), but they had significantly higher 2-hour plasma glucose, higher fasting plasma insulin, and higher triglyceride levels as shown in Table III.

Within both the estrogen-dominant (Table IV) and the progestogen-dominant (Table V) oral contraceptive users, no significant difference has been observed according to the estrogen dose of oral contraceptives.

Table II. Oral contraceptives used

	Brand name	*Progestogen content (mg)*		*n*
High dose (50 γ ethinyl estradiol)				
Estrogen dominance	Diane	Cyproterone acetate	2	20
	Ovanon	Lynestrenol	1.8*	7
	Physiostat	Lynestrenol	0.7*	1
	Milli-Anovlar	Norethisterone acetate	1	1
	Progylut	Norethisterone acetate	1*	1
Progestogen dominance	Stediril	DL. Norgestrel	0.5	45
	Planor	Norgestrienone	2	6
	Gynophase	Norethisterone acetate	1.5*	5
	Gynovlane	Norethisterone acetate	2	5
	Anovlar	Norethisterone acetate	4	1
Low dose (<40 γ ethinyl estradiol)				
Estrogen dominance	Varnoline	Desogestrel	0.15	34
	Triella	Norethisterone	0.75*	28
	Trinordiol	Levonorgestrel	0.09*	8
	Ovamezzo	Lynestrenol	0.75	2
	Normapause	Norethisterone	0.25*	1
Progestogen dominance	Adepal	Levonorgestrel	0.18*	166
	Minidril	Levonorgestrel	0.15	52
	Miniphase	Norethisterone acetate	1.5*	37
	Trentovlane	Norethisterone acetate	1	6
	Ortho-Novum	Norethisterone	1	4

*Mean progestogen content per tablet for sequential and phasic oral contraceptives.

Table III. Carbohydrate and lipid metabolisms according to use of oral contraceptives

Parameter	*No hormonal treatment (n = 859)*	*Oral contraceptives (n = 431)*	*p value*
Hemoglobin A_{1c} (% total hemoglobin)	4.95 ± 0.02	4.89 ± 0.03	0.17
Fasting plasma glucose (mg/dl)	86.7 ± 0.3	85.9 ± 0.4	0.11
2 hr plasma glucose (mg/dl)	99 ± 1	108 ± 1	<0.001
Fasting plasma insulin (μU/ml)*	6.7 (6.5-6.9)	7.3 (7.0-7.6)	<0.01
Total plasma cholesterol (mg/dl)	214 ± 1	212 ± 2	0.52
Plasma triglycerides (mg/dl)*	59 (57-61)	74 (71-77)	<0.01

All values (mean ± SEM) are adjusted for age and body mass index (calculated for age = 35 years and body mass index = 22.5 kg/m^2).

*Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

Table IV. Influence of estrogen dose in estrogen-dominant oral contraceptive users

Parameter	*Low dose (n = 73)*	*High dose (n = 30)*	*p value*
Age (yr)	28.6 ± 0.7	31.0 ± 0.9	0.05
Body mass index (kg/m^2)	22.1 ± 0.3	21.9 ± 0.5	0.70
Hemoglobin A_{1c} (% total hemoglobin)*	4.77 ± 0.06	4.71 ± 0.10	0.64
Fasting plasma glucose (mg/dl)*	84.3 ± 0.7	82.6 ± 1.1	0.20
2 hr plasma glucose (mg/dl)*	103 ± 3	98 ± 5	0.44
Fasting plasma insulin (μU/ml)*†	7.7 (7.0-8.4)	7.5 (6.5-8.6)	0.72
Total plasma cholesterol (mg/dl)*	209 ± 4	206 ± 6	0.70
Plasma triglycerides (mg/dl)*†	78 (72-86)	77 (68-88)	0.83

*Value adjusted for age (calculated for age = 29.3 years).

†Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

Among high-dose users, the estrogen-progestogen balance did not influence metabolic parameters (Table VI). On the contrary, when low-dose oral contraceptive users were considered, significant differences were found according to the estrogen-progestogen balance of the preparations (Table VII): users of progestogen-dominant, low-dose oral contraceptives were leaner ($p = 0.02$); after adjustment for body mass index, they had a marginally significant higher hemoglobin A_{1c} level (4.90% ± 0.03% vs 4.77% ± 0.07%; $p = 0.06$), with slighlty higher but nonsignificantly different plasma glucose values; their triglyceride level was significantly lower (71 mg/dl with 95% confidence interval = 68 to 74 mg/dl vs 78 mg/dl with 95% confidence

Table V. Influence of estrogen dose in progestogen-dominant oral contraceptive users

Parameter	*Low dose (n = 265)*	*High dose (n = 62)*	*p value*
Age (yr)	29.3 ± 0.4	30.5 ± 0.8	0.18
Body mass index (kg/m^2)	21.4 ± 0.1	21.4 ± 0.3	0.86
Hemoglobin A_{1c} (% total hemoglobin)	4.90 ± 0.03	4.82 ± 0.07	0.34
Fasting plasma glucose (mg/dl)	83.9 ± 0.4	83.4 ± 0.7	0.60
2 hr plasma glucose (mg/dl)	104 ± 1	109 ± 4	0.19
Fasting plasma insulin (μU/ml)*	7.3 (7.0-7.6)	6.8 (6.3-7.3)	0.12
Total plasma cholesterol (mg/dl)	208 ± 2	210 ± 4	0.61
Plasma triglycerides (mg/dl)*	71 (68-74)	71 (65-78)	0.89

*Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

Table VI. Influence of estrogen-progestogen balance in high-dose oral contraceptive users

Parameter	*Estrogen dominant (n = 30)*	*Progestogen dominant (n = 62)*	*p value*
Age (yr)	31.0 ± 0.9	30.5 ± 0.8	0.68
Body mass index (kg/m^2)	21.9 ± 0.5	21.4 ± 0.3	0.40
Hemoglobin A_{1c} (% total hemoglobin)	4.75 ± 0.09	4.82 ± 0.07	0.48
Fasting plasma glucose (mg/dl)	83.7 ± 1.3	83.4 ± 0.7	0.82
2 hr plasma glucose (mg/dl)	99 ± 5	109 ± 4	0.10
Fasting plasma insulin (μU/ml)*	7.4 (6.6-8.3)	6.8 (6.3-7.3)	0.19
Total plasma cholesterol (mg/dl)	207 ± 5	210 ± 4	0.66
Plasma triglycerides (mg/dl)*	77 (68-88)	71 (65-78)	0.31

*Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

interval = 72 to 85 mg/dl; $p = 0.03$) and the fasting plasma insulin slighlty but nonsignificantly decreased. No difference was observed for total cholesterol (Table VII).

Table VII. Influence of estrogen-progestogen balance in low dose oral contraceptive users

Parameter	*Estrogen dominant (n = 73)*	*Progestogen dominant (n = 265)*	*p value*
Age (yr)	28.6 ± 0.7	29.3 ± 0.4	0.40
Body mass index (kg/m^2)	22.1 ± 0.3	21.4 ± 0.1	0.02
Hemoglobin A_{1c} (% total hemoglobin)*	4.77 ± 0.07	4.90 ± 0.03	0.06
Fasting plasma glucose (mg/dl)*	83.6 ± 0.8	84.1 ± 0.4	0.43
2 hr plasma glucose (mg/dl)*	102 ± 3	104 ± 1	0.46
Fasting plasma insulin (μU/ml)*†	7.6 (7.1-8.3)	7.3 (7.0-7.6)	0.52
Total plasma cholesterol (mg/dl)*	208 ± 2	209 ± 4	0.99
Plasma triglycerides (mg/dl)*†	78 (72-85)	71 (68-74)	0.03

*Values adjusted for body mass index (calculated for body mass index = 21.8 kg/m^2).

†Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

Comment

Because recruitment was occupation based and consisted of volunteers, the sample of the study cannot be considered as representative of the French female population of child-bearing age: compared with a representative French sample of the same age,[25] a higher percentage of oral contraceptive users was found in our group (33.4% vs 28%; $p < 0.001$). This discrepancy can be explained by a difference in socioeconomic class, which was probably higher in our sample because subjects worked in a high-tech organization in the Paris area. It could also be from the lag time between the two surveys: oral contraceptive use probably increased in France between 1978 and 1985. Nevertheless, this lack of representativeness has probably no or little effect on the relationship observed between oral contraceptive use and metabolic abnormalities observed in our study. It is more important to emphasize the observational nature of this study: in daily medical practice, contraceptive method is not randomly allocated, but the most appropriate tool of contraception is proposed to each individual according to a set of characteristics—age, weight, personal gynecologic and obstetric history, family history of metabolic diseases, blood pressure, plasma glucose, and cholesterol values. This statement can explain a large part of the differences observed in age and probably also in body mass index between oral contraceptive users and nonusers. Adjustments for age and for body mass index were made to reduce discrepancies between the two groups.

Elevated values of 2-hour plasma glucose, fasting plasma insulin, and triglycerides we have observed in oral contraceptive users confirm previous published data.[9, 10, 15, 26, 27] Even if the cause of the increased incidence of both venous and arterial cardiovascular diseases in users of oral contraceptives appears to be thrombosis and not atherogenesis,[10] prospective studies have underlined the role of early markers of insulin resistance[28] as cardiovascular risk factors.[29, 30] Thus these markers should be carefully monitored in oral contraceptive users, at least for long-term use. On the contrary, no difference has been observed between oral contraceptive users and nonusers concerning fasting plasma glucose and hemoglobin A_{1c}—a cumulative es-

timate of the mean blood glucose concentration over the preceding 2 to 3 months,[31] more closely linked to fasting plasma glucose than to 2-hour plasma glucose.[32] It indicates the minimal or absent influence of oral contraceptives on basal glucose metabolism as previously reported.[27] As to total cholesterol, which did not differ according to oral contraceptive use, few conclusions can be drawn because cholesterol subfractions have not been measured.

The change in oral contraceptive prescriptions to low-dose preparations is probably reflected by the younger age of oral contraceptive users. The aim to reduce the metabolic disturbances of oral contraceptives appears not to have been reached according to our data. Once again, the observational nature of this study can explain such a result because a selection bias could interfer. A lack of power could also be considered an explanation. We must also be reminded that the relative safety of low-dose oral contraceptives with regard to cardiovascular reactions[11] has been argued at least concerning mortality from thromboembolic disease and frequency of arterial complications.[33] Thus the metabolic (and may be also the hemostatic) benefit of the reduction of estrogen content could indeed be not as important as expected.

The metabolic influence of the estrogen/progestogen balance appears negligible within the high-dose oral contraceptive group. Among low-dose oral contraceptive users, carbohydrate metabolism does not significantly differ according to the hormone balance, as previously reported.[21] The difference in plasma triglycerides, which are significantly lower in the progestogen-dominant group, must be considered cautiously, because many comparisons have been performed between all subgroups and the one significant difference ($p = 0.03$) could have been found only by chance. Such a decrease in triglycerides level with higher doses of progestogens seems contradictory to usual findings.[9]

This cross-sectional study underlines the metabolic alterations in oral contraceptive use, namely, an increase in insulin-resistance markers, which seems predictive of permanent diabetes[34] and could be involved in the atherogenic process.[29, 30] Monitoring of these indexes should be systematically performed on oral contraceptive users, mainly on women at risk for diabetes (history of gestational diabetes, family history of diabetes, or obesity) and treated with oral contraceptives for a long period. The composition of oral contraceptives appears to have little influence on carbohydrate and lipid metabolisms.

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