ORIGINAL INVESTIGATION

Oral Contraceptive Use and Hormone Replacement Therapy Are Associated With Microalbuminuria

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Background: Controversy exists regarding the adverse and beneficial effects of oral contraceptive use and hormone replacement therapy. Microalbuminuria is associated with increased risk of renal and cardiovascular disease.

Objective: To examine the association between oral contraceptive use or hormone replacement therapy and microalbuminuria.

Methods: We performed a case-control study of the baseline data and historical pharmacy data of 4301 female subjects of the Prevention of Renal and Vascular End Stage Disease study cohort, aged 28 to 75 years, excluding women who were pregnant or had type 1 diabetes mellitus. The main outcome measure was microalbuminuria, defined as a urinary albumin excretion of 30 to 300 mg per 24 hours (recorded as the mean of two 24-hour urine collections).

Results: After adjusting for age, hypertension, diabetes, obesity, hyperlipidemia, and smoking, the odds ratio (OR) for having microalbuminuria was 1.90 (95% confidence interval [CI], 1.23-2.93) for premenopausal oral contraceptive users and 2.05 (95% CI, 1.12-3.77) for postmenopausal hormone replacement therapy users. The point estimate increased in a dose-dependent fashion, albeit insignificantly, according to the estrogen content of the oral contraceptives (<30 µg ethinyl estradiol: OR, 1.11; 95% CI, 0.14-8.56; 30 to <50 µg: OR, 1.83; 95% CI, 1.17-2.87; and 50 µg: OR, 2.72; 95% CI, 0.81-9.08). The OR was greater in oral contraceptives with a second-generation (OR, 2.04; 95% CI, 1.28-3.25) vs a third-generation progestin (OR, 1.39; 95% CI, 0.63-3.06). The OR increased with the duration of hormone replacement therapy (≤5 years, OR, 1.28; 95% CI, 0.37-4.50; >5 years, OR, 2.56; 95% CI, 1.32-4.97).

Conclusion: Regular and long-term oral contraceptive use and hormone replacement therapy are associated with an increased risk for microalbuminuria and cardiovascular disease.

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HORMONE therapy, defined as treatment with estrogens, progestin, or a combination of them, is widely used among women of all ages. Premenopausal oral contraceptive use and postmenopausal hormone replacement therapy are associated with a risk for cardiovascular diseases. This is the most frequently reported adverse effect of hormonal oral contraceptives[1-3] but is affected by the presence of known risk factors, such as smoking, hypertension, and diabetes.[4-6] Moreover, the incidence of this adverse effect may also be related to the estrogen and progestin content of the oral contraceptive.[1-3,7] Observational data[8-11] show a beneficial effect of hormone replacement therapy on cardiovascular risk factors and mortality rates. Randomized clinical trials, however, do not support this beneficial role of hormone replacement therapy. The first randomized controlled trial of the effect of hormone replacement therapy on cardiovascular disease (Heart and Estrogen/progestin Replacement Study)[12] showed that this therapy does not reduce the overall incidence of coronary heart disease in postmenopausal users with established coronary disease. Recently, the results of the Estrogen Replacement and Atherosclerosis study[13,14] confirmed these findings.

Microalbuminuria is a marker for early vascular endothelial damage,[15] and studies[16-19] show that microalbuminuria is associated with an increased cardiovascular risk in subjects with and without diabetes. We therefore questioned whether premenopausal and postmenopausal use of hormonal preparations heightened the risk for microalbuminuria, hypothesizing that measurement of microalbuminuria might discriminate between women

SUBJECTS AND METHODS

STUDY POPULATION AND DESIGN

We used the data of the Prevention of Renal and Vascular End Stage Disease cohort, consisting of 8592 subjects, aged 28 to 75 years, from Groningen, the Netherlands. This group was investigated for the presence of increased urinary albumin excretion.[20] From this study cohort, only women were included (n=4301).

The participants completed a questionnaire, from which information was gathered on menopausal status, duration of oral contraceptive use and hormone replacement therapy, tobacco use, and whether they were medically treated for hypertension, hyperlipidemia, or diabetes.

Body weight was measured to the nearest 0.5 kg, using a balance scale (seca Vogel & Halke GmbH & Co, Hamburg, Germany) after removal of shoes and heavy clothing. Height was measured to the nearest 0.5 cm using a statiometer measuring board with right angle. Body mass index was calculated as weight in kilograms divided by the square of height in meters. In the supine position, blood pressure in the right arm was measured at 2 visits, every minute for 10 minutes using an automatic blood pressure monitoring device (Dinamap XL 9300; Johnson & Johnson, Arlington, Tex). Systolic and diastolic blood pressure was calculated as the mean of the last 2 measurements at both visits. At the second visit, fasting blood samples were drawn for direct measurement of glucose and cholesterol levels. The subjects also provided two 24-hour urine collections at the second visit.

Plasma glucose, serum cholesterol, and serum and urinary creatinine levels were recorded based on findings of an automated dry chemistry analyzer system (Kodak Ectachem; Eastman Kodak, Rochester, NY). Creatinine clearance was defined as the mean of 2 creatinine clearances, based on 24-hour urinary creatinine excretion, divided by plasma creatinine. Urinary albumin concentration was determined by nephelometry (Dade Behring Diagnostics, Marburg, Germany), with a threshold of 2.3 mg/L and intra- and interassay coefficients of variation of less than 4.3% and 4.4%, respectively. Leukocyte and erythrocyte counts of the urine were determined based on urine stick findings. Subjects were excluded from analysis in cases of erythrocyturia greater than 50 per microliter or leukocyturia greater than 75 per microliter, or leucocyturia of 75 or more per microliter and erythrocyturia greater than 5 per microliter.

DEFINITIONS

If subjects reported last menstruating more than 1 year previously or if using hormone replacement therapy for postmenopausal conditions, they were classified as postmenopausal, otherwise they were considered premenopausal. Microalbuminuria was defined as a urinary albumin excretion of 30 to 300 mg per 24 hours, measured as the mean of two 24-hour urine collections. A urinary albumin excretion greater than 300 mg per 24 hours was defined as macroalbuminuria. Hypertension was defined as systolic blood pressure of 160 mm Hg or greater, diastolic blood pressure of 95 mm Hg or greater, or use of antihypertensive drugs. Diabetes was defined as having a fasting glucose level of 140.5 mg/dL or greater (≥7.8 mmol/L), a nonfasting glucose level of 200 mg/dL or greater (≥11.1 mmol/L), or use of antidiabetic medication. We also analyzed our data using current definitions of hypertension (blood pressure, ≥140/90 mm Hg) and diabetes (fasting glucose, ≥126.1 mg/dL [≥7.0 mmol/L]), resulting in similar findings. A body mass index of 30 or higher was classified as obesity. Hyperlipidemia was defined as a serum cholesterol level of 308.9 mg/dL or greater (≥8.0 mmol/L), or 193.1 mg/dL or greater (≥5.0 mmol/L) if the person had suffered a myocardial infarction, or use of lipid-lowering medication. Subjects were classified as smokers if they reported current smoking or had stopped smoking less than 1 year previously; otherwise, they were classified as nonsmokers.

PHARMACY RECORDS

Pharmacy records were collected at community pharmacies. Because Dutch patients usually register at a single community pharmacy, use of pharmacy records provides an almost complete listing of a subject's prescribed drugs.[21] The pharmacy data contain, among others, the name of the drug, number of units dispensed, prescribed daily dose, date the drugs were obtained, and Anatomical Therapeutical Chemical classification code of the drug. It was determined whether subjects had been dispensed oral contraceptives or hormone replacement therapy during the year preceding the baseline investigation with the urine collections. A subject was considered using a drug if she had at least one prescription for the drug during this year.

Oral contraceptives were defined as preparations containing ethinyl estradiol and a progestin. They were classified according to their ethinyl estradiol content in micrograms, as 50, sub-50 (30 to <50), or sub-30 tablets. Progestins were classified as second generation (levonorgestrel, lynestrenol, and norethindrone) or third generation (desogestrel, gestodene, and norgestimate). Hormone replacement therapy was defined as oral preparations containing conjugated estrogens or estradiol valerate, or transdermal preparations containing estradiol. Hormone replacement therapy was subdivided into therapies with or without additional progestin. Vaginal preparations, defined as creams or vaginal tablets containing estriol or dienestrol, were not considered hormone replacement therapy.

STATISTICAL ANALYSIS

Analyses were performed using commercially available statistical software (SPSS version 9.0; SPSS Inc, Chicago, Ill). Continuous data are reported as mean±SD. Differences between continuous variables were tested using *t* tests. Differences in proportions were assessed by χ^2 and Fisher exact tests. Logistic regression analysis was performed to determine the association between oral contraceptive use or hormone replacement therapy and microalbuminuria, using a regression model with variables that included age; presence of hypertension, obesity, diabetes, or hyperlipidemia; and smoking status. Odds ratios (ORs) and corresponding 95% confidence intervals were calculated as approximations of relative risk. $P<.05$ was considered statistically significant; all *P* values were 2-tailed.

Table 1. Subject Characteristics According to Menopausal Status and Presence of Microalbuminuria*

	Premenopausal Microalbuminuria		Postmenopausal Microalbuminuria	
	No	Yes	No	Yes
No. of subjects	1673	114	1330	188
Age, y, mean (SD)	39.6 (6.6)	40.6 (6.6)	58.1 (9.1)	60.4 (9.0)†
Oral contraceptive users	26.7	36.8‡	5.1	7.4
Hormone replacement therapy users	0	0	7.7	8.6
Hypertension	5.0	13.4†	25.7	45.6†
Diabetes mellitus	0.5	1.8	3.8	11.7†
Obesity	10.6	23.7†	21.1	33.2†
Hyperlipidemia	1.5	2.7	10.9	20.5†
Smoking	40.7	40.4	33.7	36.9
Creatinine clearance, mL/min,§ mean (SD)	100.0 (21.4)	104.5 (23.4)‡	87.3 (20.9)	91.0 (27.8)

*Data are given as percentages unless otherwise indicated. Premenopausal and postmenopausal women were analyzed separately. *P* values are comparison of women with and without microalbuminuria.
†$P<.005$.
‡$P<.05$.
§To convert creatinine clearance from milliliters per minute to milliliters per second, multiply milliliters per minute by 0.0167.

Table 2. Subject Characteristics According to Menopausal Status and Use of Oral Contraceptives (OC) or Hormone Replacement Therapy (HRT)*

	Premenopausal Hormone Use		Postmenopausal Hormone Use†		
	No	OC	No	OC	HRT
No. of subjects	1298	489	1245	78	120
Age, y, mean (SD)	40.8 (6.5)	36.7 (5.7)‡	59.8 (8.6)	45.4 (7.3)‡	52.8 (6.1)‡
Microalbuminuria	5.5	8.6§	11.6	16.7	14.2
Hypertension	5.5	5.6	29.6	14.7§	22.9
Diabetes mellitus	0.8	0.0	5.2	3.9	0.0§
Obesity	11.8	10.5	23.8	19.2	17.5
Hyperlipidemia	1.5	1.7	13.4	1.5§	6.3§
Smoking	40.2	41.9	32.8	44.9§	44.2§
Creatinine clearance, mL/min,‖ mean (SD)	99.3 (21.5)	103.0 (21.8)‡	86.7 (22.1)	96.3 (24.0)‡	94.0 (21.2)‡

*Data are given as percentages unless otherwise indicated. Premenopausal and postmenopausal women were analyzed separately. *P* values are comparison of hormone users vs nonusers.
†Women using vaginal preparations or preparations containing progestin only are not shown because of small numbers.
‡$P<.005$.
§$P<.05$.
‖To convert creatinine clearance to milliliters per second, see last footnote in Table 1.

who are and who are not at risk for cardiovascular events. To that end, we studied the association of oral contraceptive use and hormone replacement therapy with microalbuminuria in the female subjects of the Prevention of Renal and Vascular End Stage Disease population, an ongoing study on the effect of microalbuminuria in the general population.

RESULTS

Subjects were excluded if they had erythrocyturia or leucocyturia (n=360) or macroalbuminuria (n=39), if they could not be classified as premenopausal or postmenopausal (n=205), or if pharmacy data could not be obtained (n=392), leaving 3305 subjects for analysis.

The characteristics of women with microalbuminuria, according to their menopausal status, are shown in **Table 1**. In women who were premenopausal, oral contraceptive use was significantly more prevalent in those with microalbuminuria compared with those without. Microalbuminuria in the premenopausal group was also associated with hypertension, obesity, and higher creatinine clearance. In women who were postmenopausal, there was a tendency toward more hormone use in the group with microalbuminuria compared with those without. Also in the postmenopausal group, those with microalbuminuria were older and had a higher prevalence of hypertension, diabetes, obesity, and hyperlipidemia compared with those without microalbuminuria.

Table 2 shows the characteristics of subjects, according to menopausal status and oral contraceptive use or hormone replacement therapy. Premenopausal oral contraceptive users were significantly younger and had a higher prevalence of microalbuminuria compared with nonusers, although the cardiovascular risk factors did not differ between the groups. In women who were postmenopausal, oral contraceptive and hormone replacement therapy users were significantly younger than nonusers. Interestingly, users of oral contraceptives ($P = .18$)

Table 3. Crude and Adjusted Odds Ratios (ORs) for Microalbuminuria*

	OR Crude	OR Adjusted†	OR Adjusted‡
Premenopausal, oral contraceptive use vs nonuse	1.60 (1.08-2.38)	1.87 (1.23-2.84)	1.90 (1.23-2.93)
Postmenopausal, hormone replacement therapy use vs nonuse	1.26 (0.73-2.17)	1.83 (1.03-3.25)	2.05 (1.12-3.77)

*Data are given as OR (95% confidence interval).
†Adjusted for age.
‡Adjusted for age, hypertension, diabetes, obesity, hyperlipidemia, and smoking.

and hormone replacement therapy (P = .40) scored better on most risk factors associated with microalbuminuria (Table 1), but still had a higher, though nonsignificant, prevalence of microalbuminuria than nonusers. Creatinine clearance was also higher in women using oral contraceptives or hormone replacement therapy compared with nonusers.

Table 3 gives the crude ORs for having microalbuminuria, ORs adjusted for age alone, and ORs adjusted for age, hypertension, diabetes, obesity, hyperlipidemia, and smoking. Adjustment for age alone and for all factors increased the ORs for microalbuminuria in premenopausal oral contraceptive users and in postmenopausal hormone replacement therapy users. Oral contraceptive use and hormone replacement therapy were independently associated with microalbuminuria. Of the adjustment factors, age demonstrated the largest effect.

In the premenopausal group using hormone therapy, we calculated ORs for different estrogen dosages, progestin types, and durations of use (**Table 4**). There was a tendency toward an association between microalbuminuria risk and estrogen content in oral contraceptives. Furthermore, women using oral contraceptives containing second-generation progestins had a higher risk than users of third-generation progestins. However, neither the estrogen (P=.25) nor the progestin (P=.36) difference was statistically significant. The results were similar for women using oral contraceptives longer than 5 years vs 5 years or less. To determine whether the increased albumin excretion was related to creatinine clearance, we added this variable to the regression model. The association of oral contraceptive use with microalbuminuria, however, did not change after addition of this factor (OR, 1.88; 95% confidence interval, 1.22-2.90).

In the postmenopausal group, users of hormone replacement therapy and oral contraceptives showed an increased OR for having microalbuminuria. Findings were similar in users of hormone replacement therapy with and without addition of progestins. Women using hormone replacement therapy for more than 5 years had a higher risk of having microalbuminuria compared with those using this therapy for 5 years or less. Use of estrogens or progestins in general was also associated with microalbuminuria (OR, 2.36; confidence interval, 1.53-3.65). The association of hormone replacement therapy with microalbuminuria was not related to higher creatinine clearance; addition of this variable to the regression model hardly changed the association (OR, 1.99; confidence interval, 1.08-3.67).

Table 4. Adjusted Odds Ratios (ORs) for Microalbuminuria (MA) According to Different Hormonal Preparations*

	No. of Users		
	No MA	MA	OR (95% CI)
Premenopausal			
OC	447	42	1.90 (1.23-2.93)
Estrogen strength, μg			
<30	19	1	1.11 (0.14-8.56)
30 to <50	408	37	1.83 (1.17-2.87)
50	20	4	2.72 (0.81-9.08)
Progestin type			
Second generation	319	33	2.04 (1.28-3.25)
Third generation	118	8	1.39 (0.63-3.06)
Duration of OC use, y			
≤5	169	16	2.02 (1.10-3.71)
>5	245	24	1.82 (1.09-3.07)
Postmenopausal			
HRT	103	17	2.05 (1.12-3.77)
Without progestin	39	8	2.13 (0.89-5.08)
With progestin	64	9	1.98 (0.91-4.30)
OC	65	13	2.75 (1.24-6.09)
Duration of HRT use, y			
≤5	32	3	1.28 (0.37-4.50)
>5	65	14	2.56 (1.32-4.97)

*OC indicates oral contraceptive; CI, confidence interval; and HRT, hormone replacement therapy. All ORs are calculated vs nonhormone users and are adjusted for age, hypertension, diabetes, obesity, hyperlipidemia, and smoking.

COMMENT

This study gives the first epidemiological evidence that the risk for having microalbuminuria is increased in women using oral contraceptives before and after menopause, and in women using hormone replacement therapy after menopause. Because microalbuminuria is an early marker for increased risk of cardiovascular disease,[17-19] users of estrogen preparations may have an increased risk for cardiovascular morbidity and mortality. The association between oral contraceptive use or hormone replacement therapy and microalbuminuria is dependent on several factors: (1) the age of the subject and, for hormone replacement therapy, the number of years of use; (2) the type of progestin in an oral contraceptive, but not the addition of a progestin to hormone replacement therapy; and (3) the estrogen content in the oral contraceptive used.

Our findings regarding the association between oral contraceptive use and microalbuminuria are in agreement with those of Ribstein et al,[22] who found that a group of 57 oral contraceptive users had a higher prevalence of microalbuminuria compared with a group of 57

matched nonusers. They also showed this difference to be independent of blood pressure readings. The finding of an increased risk of microalbuminuria among users of hormone replacement therapy raises further questions about the cardiovascular benefits of oral contraceptive use and hormone replacement therapy.[13,14] Based on observational studies,[8-11] hormone replacement therapy was reported to be protective against cardiovascular events. However, the first randomized clinical trial[12] failed to show a beneficial effect of estrogens against secondary cardiovascular events in postmenopausal users. Furthermore, recent investigations in healthy women who are postmenopausal have shown that hormone replacement therapy is associated with an impaired procoagulant-anticoagulant balance[23] and a rise in C-reactive protein,[24] another marker that is predictive of cardiovascular events in healthy men and women.[25]

Our observation that duration of hormone replacement therapy longer than 5 years increases the risk for microalbuminuria is important, because most observational data are representative of 5 years or less. Differences in duration of hormone replacement therapy may thus bias the results. The association between estrogen preparations and microalbuminuria in women, regardless of menopausal status, remained after adjustment for age, hypertension, diabetes, obesity, hyperlipidemia, and smoking, factors considered to be associated with microalbuminuria. It has been suggested that microalbuminuria reflects generalized vascular endothelial dysfunction.[15] However, based on our data, it is not possible to conclude whether there is a direct effect on the vascular endothelium, or whether it is secondary to unknown effects of oral contraceptive use or hormone replacement therapy on vascular endothelial function and structure.[23] An alternative explanation is that estrogens induce glomerular hyperfiltration, which via a greater tubular load of albumin, and perhaps in combination with an altered tubular albumin handling, could lead to an elevated albumin excretion. Our data demonstrated that oral contraceptive use and hormone replacement therapy are associated with an elevated creatinine clearance. This is in agreement with the data of Ribstein et al.[22] It has recently been shown that, as in persons with diabetes, glomerular filtration rate (measured as creatinine clearance and using the Cockcroft and Gault formula) is elevated in subjects without diabetes with microalbuminuria, but more so in subjects with high-normal urinary albumin excretion (15-30 mg/24 h).[20] However, in our study, adjustment for creatinine clearance did not change the observed association between oral contraceptive use or hormone replacement therapy and microalbuminuria, making this a less likely explanation.

Our study has several shortcomings. First, it is a cross-sectional analysis and therefore does not allow us to draw conclusions on a cause and effect relationship between oral contraceptive use or hormone replacement therapy and microalbuminuria. A long-term prospective follow-up of our cohort, with monitoring of pharmacy records, will show whether urinary albumin excretion increases with continued use of estrogen-containing preparations. Second, even though we studied 3305 women, of whom 762 used hormonal preparations, the number of women in the various subgroups, analyzed for effects of different therapies, was limited. These small numbers and the adjustment for several confounders prevented us from drawing definite conclusions about the effects in subgroups. Third, this study was limited to women 28 years and older, rendering our findings inconclusive regarding younger women. Younger women increasingly are using newer oral contraceptives, while most oral contraceptive users in this study used sub-50 oral contraceptive preparations. Therefore, a comparison between estrogen strengths is hard to make, and the present data do not allow us to recommend the use of sub-30 vs sub-50 oral contraceptives. Moreover, older women who are premenopausal are more likely to have used oral contraceptives longer, although our findings did not suggest that the duration of oral contraceptive use was significant.

Finally, our finding that second- but not third-generation oral contraceptives are associated with microalbuminuria is relevant in the debate whether second-generation progestins should be preferred, because of the greater risk for venous thromboembolism with the third-generation progestins. A lower risk for microalbuminuria, and possibly for atherosclerotic events, with the use of third-generation oral contraceptives[6] may outweigh the benefits of the second-generation ones.

In conclusion, oral contraceptive use either before or after menopause and hormone replacement therapy after menopause, are associated with microalbuminuria, a predictor of cardiovascular risk. These data shed new light on the potential effects of these treatments on cardiovascular morbidity and mortality.

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