Renal Characteristics and Effect of Angiotensin Suppression in Oral Contraceptive Users

Jean Ribstein, Jean-Michel Halimi, Guilhem du Cailar, Albert Mimran

Abstract—The determinants of the increase in arterial blood pressure associated with the use of estrogen-progestogen oral contraceptives (OC) remain poorly known. The purpose of this study was to assess the renal characteristics and the role of the renin-angiotensin system in women with OC-associated hypertension. Urinary clearances of technetium-labeled diethylene triaminopentaacetic acid (glomerular filtration rate) and $^{131}$I-ortho iodohippurate (effective renal plasma flow) were estimated before and after acute administration of captopril in 38 women who became hypertensive while taking OC, 38 non-OC users with essential hypertension matched for age, body mass index, and level of blood pressure, and 38 normotensive women (19 with and 19 without OC). Plasma renin activity was higher in OC hypertensives when compared with those with essential hypertension, but captopril-induced changes in blood pressure and renal hemodynamics and function were similar in both groups. In addition, 24-hours urinary albumin excretion was increased in OC users when compared with nonusers with similar arterial blood pressure. In 13 hypertensive women followed up for 6 months after OC withdrawal, a decrease in plasma renin activity, blood pressure, and glomerular filtration rate but no significant change in urinary albumin excretion and captopril-induced changes in blood pressure and renal hemodynamics were observed. These results indicate that the use of OC is associated with an increased albuminuria and no evidence of a prominent role for the renin-angiotensin system in the maintenance of high blood pressure and renal hemodynamics when compared with non-OC users with essential hypertension. (Hypertension. 1999;33:90-95.)

Key Words: oral contraceptives • hypertension, essential • microalbuminuria • renal hemodynamics • angiotensin-converting enzyme inhibition

The use of oral contraceptive (OC) drugs is associated with an increased risk of stroke, myocardial infarction, and venous thromboembolism. OC use may also result, albeit rarely, in accelerated hypertension and biopsy-proven renal damage in the absence of primary renal disease. When compared with earlier studies, a decreased cardiovascular morbidity was recently observed in OC users, possibly because of a tendency to refrain from OC in smoking older women and the reduction in dosages of both estrogen and progestogen components to about one fifth to one sixth. The absolute cardiovascular risk associated with OC use is now rather low in women with no risk factors for cardiovascular disease. However, a recent worldwide survey indicated that among current OC users, a history of hypertension increased the risk of ischemic stroke by 11-fold in western Europeans and even more in subjects from developing countries.

A small elevation in blood pressure is observed in almost all women taking OC, reaching a level $>140$ to $90$ mm Hg in 5% of those taking combined products containing $>50$ μg estrogen. In a recent large prospective cohort study conducted in American nurses, a doubling in the adjusted relative risk for hypertension was documented in current users of low-dose OC. Although hypertension is a fairly common side effect of OC, it is not agreed on whether the risk of OC-associated hypertension increases with the duration of OC use. In addition, the mechanisms involved in the initiation and maintenance of high blood pressure in OC users are not well understood. A role for an altered renin-angiotensin system was suggested by the fact that estrogen administration stimulates the hepatic synthesis of angiotensinogen.

In this study, the clinical and renal characteristics of women in whom hypertension developed during OC administration were compared with those of non-OC-using women with essential hypertension as well as normotensive subjects with or without OC. The role of the renin-angiotensin system was assessed through the response of arterial pressure and renal hemodynamics to acute blockade of angiotensin-converting enzyme. After withdrawal of OCs, renal studies were repeated in a subset of hypertensive patients.

Methods

Patients

The study population consisted of 38 women, age 21 to 48 years, in whom hypertension developed during a period of contraception (69±10 months) with combined estrogen-progestogen drugs containing $35±2$ μg ethinylestradiol. This group was compared with a group of 38 non-OC users, matched for the level of arterial pressure,
30-minute urine collections were obtained by spontaneous voiding. Water diuresis and a 90-minute equilibration period, three 20- to 30-minute urine collections were obtained by spontaneous voiding. Patients with a known history of alcohol abuse (5 drinks per day) were excluded from the study. In all subjects, no clinical proteinuria (Albustix positive). No electrocardiographic or Doppler echocardiographic signs of valvular, primary myocardial, or coronary artery disease were observed. Also included were patients with a known history of alcohol abuse (>5 drinks per day) and patients with diabetes mellitus (defined as a fasting blood glucose >6.4 mmol/L). None of the women was obese, as defined by a body mass index (weight/height2) >27 kg/m2. The protocol was approved by the ethics committee of our institution, and all patients gave informed consent.

**Protocol**

Studies were performed between 8 AM and 1 PM. After an overnight fast, patients came to the ward with 2 consecutive 24-hour urine collections for the determination of creatinine, electrolytes, and clinical characteristics were similar in all groups, except for age and the incidence of a positive family history of hypertension, which were both higher in hypertensive than normotensive subjects. The duration of OC use was longer in hypertensive users when compared with normotensive users.

**Analytical Methods**

Clearances obtained during the precaptopril and postcaptopril periods were averaged and proportioned to 1.73 m2 of body surface area. Plasma renin activity (CEA Sorin kit), plasma aldosterone (Amer sham), urinary albumin (Pharmacia), and β2-microglobulin (Immuno tech) were estimated by radioimmunoassay techniques. Filtration fraction was calculated as GFR/ERPF and renal vascular resistance as MAP×(1-hematocrit)/ERPF, where MAP is mean arterial pressure.

**Statistical Analysis**

Data are presented as mean and SEM. Because values of UAE were not normally distributed, data were analyzed after logarithmic transformation. Statistical analysis was carried out with the use of ANOVA followed by Dunnett’s test and paired Student’s t test when appropriate. A P value of 0.05 was taken as the minimum level of significance.

**Results**

**Clinical Parameters**

As summarized in Tables 1 and 2, demographic parameters and clinical characteristics were similar in all groups, except for age and the incidence of a positive family history of hypertension, which were both higher in hypertensive than normotensive subjects. The duration of OC use was longer in hypertensive users when compared with normotensive users.
Although the body mass index was similar in all groups, the waist/hip ratio was higher in patients with OC-associated hypertension when compared with other groups. Serum triglyceride levels were higher in OC users than nonusers, whether hypertensive or normotensive. Levels of both total and HDL cholesterol as well as blood glucose and glycosylated hemoglobin were similar in all groups.

Arterial pressure was similar in the 2 hypertensive subgroups, whereas systolic but not diastolic pressure was higher in normotensive OC users when compared with nonusers. Levels of both total and HDL cholesterol as well as blood glucose and glycosylated hemoglobin were similar in all groups.

Baseline Renal Hemodynamics and Function

As summarized in Table 2, no difference in GFR or ERPF between hypertensive and normotensive populations could be detected. Filtration fraction was higher in both hypertensive groups when compared with normotensive groups, and no difference in filtration fraction attributable to OC was observed within these groups. Plasma renin activity was higher in OC users when compared with nonusers, whether hypertensive or normotensive. Plasma aldosterone was similar in all groups.

Effect of Acute Administration of Captopril

As depicted in Figure 2, acute administration of captopril resulted in similar effects on arterial blood pressure (decrease by 9 ± 1 vs 0 ± 1 mm Hg), ERPF (increase by 42 ± 12 vs 39 ± 11 mL/min per 1.73 m²), GFR (no change), plasma renin activity (increase by 1.9 ± 0.4 vs 1.9 ± 0.7 ng/mL per hour), or plasma aldosterone concentration (decrease by 9 ± 2 vs 6 ± 1 ng/dL) in the OC-associated hypertension and essential hypertension groups, respectively. Urinary sodium excretion tended to decrease in OC users and to increase in non-OC users, but the difference did not reach statistical significance.

Table 2. Blood Pressure and Renal Function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypertensive OC Users</th>
<th>Hypertensive OC Nonusers</th>
<th>Normotensive OC Users</th>
<th>Normotensive OC Nonusers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>161 ± 3</td>
<td>158 ± 2</td>
<td>119 ± 2*</td>
<td>112 ± 2†</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>100 ± 2</td>
<td>99 ± 1</td>
<td>72 ± 1*</td>
<td>68 ± 2†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>73 ± 1</td>
<td>67 ± 1†</td>
<td>69 ± 2</td>
<td>64 ± 2</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min per 1.73 m²</td>
<td>118 ± 4</td>
<td>110 ± 3</td>
<td>118 ± 6</td>
<td>119 ± 4</td>
</tr>
<tr>
<td>Effective renal plasma flow, mL/min per 1.73 m²</td>
<td>491 ± 20</td>
<td>460 ± 16</td>
<td>508 ± 16</td>
<td>530 ± 15</td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>0.151 ± 0.007</td>
<td>0.158 ± 0.006</td>
<td>0.103 ± 0.004*</td>
<td>0.093 ± 0.004†</td>
</tr>
<tr>
<td>Filtration fraction, %</td>
<td>24.6 ± 0.6</td>
<td>24.4 ± 0.5</td>
<td>22.3 ± 0.7*</td>
<td>22.5 ± 0.8*</td>
</tr>
<tr>
<td>Plasma renin activity, ng · mL⁻¹ · h⁻¹</td>
<td>2.96 ± 0.59</td>
<td>1.70 ± 0.22†</td>
<td>2.89 ± 0.65</td>
<td>1.71 ± 0.23†</td>
</tr>
<tr>
<td>Plasma aldosterone concentration, ng · dL⁻¹</td>
<td>18 ± 2</td>
<td>16 ± 1</td>
<td>14 ± 2</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 h</td>
<td>126 ± 9</td>
<td>125 ± 8</td>
<td>111 ± 10</td>
<td>141 ± 16</td>
</tr>
<tr>
<td>Urinary potassium, mmol/24 h</td>
<td>46 ± 3</td>
<td>53 ± 3</td>
<td>55 ± 7</td>
<td>53 ± 6</td>
</tr>
<tr>
<td>Urinary urea, mmol/24 h</td>
<td>300 ± 16</td>
<td>325 ± 16</td>
<td>352 ± 22</td>
<td>311 ± 19</td>
</tr>
<tr>
<td>Prevalence of microalbuminuria, %</td>
<td>26</td>
<td>13†</td>
<td>21</td>
<td>0†</td>
</tr>
</tbody>
</table>

*†P < 0.05 between hypertensive and normotensive subjects with and without OC and between OC users and nonusers with similar arterial blood pressure, respectively.

Figure 1. Daily UAE in hypertensive and normotensive subjects with (OC+) or without (OC−) estrogen-progestogen OC. *P < 0.05.

Figure 2. Percent change in mean arterial pressure (MAP) and renal function (effective renal plasma flow, ERPF; glomerular filtration rate, GFR; renal vascular resistance, RVR; filtration fraction, FF; urinary sodium excretion, UNaV) after acute administration of captopril in hypertensive OC users (OC+) and nonusers (OC−).
Influence of OC Withdrawal

In 13 hypertensive patients, arterial blood pressure decreased by 16±4/9±2 mm Hg within 6±1 months after OC withdrawal. No significant change in body weight, hematocrit, or urinary electrolyte excretion was observed (Table 3). GFR decreased by 12±4 mL/min per 1.73 m², whereas effective renal plasma flow remained unchanged, thus resulting in a significant fall in filtration fraction. UAE, which was elevated in 5 of 13 patients, did not decrease significantly during follow-up. A decrease in plasma renin activity was observed after OC withdrawal, whereas plasma aldosterone concentration remained unchanged.

The response to acute administration of captopril was assessed in 11 of 13 patients, both before and after OC withdrawal. As shown in Figure 3, arterial pressure decreased and ERPF increased to a similar extent on both occasions. In contrast, the captopril-induced change in sodium excretion was converted from a decrease (while receiving OC) to an increase after OC discontinuation.

Table 3. Clinical and Renal Changes 3 to 9 Months After Withdrawal of Oral Contraceptives in 13 Patients With OC-Associated Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Withdrawal</th>
<th>After Withdrawal</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>60±3</td>
<td>60±3</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>156±3</td>
<td>139±3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>98±3</td>
<td>88±3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±2</td>
<td>69±2</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>42.0±0.7</td>
<td>41.6±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min per 1.73 m²</td>
<td>115±7</td>
<td>103±5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Effective renal plasma flow, mL/min per 1.73 m²</td>
<td>448±34</td>
<td>445±26</td>
<td>NS</td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>0.163±0.011</td>
<td>0.145±0.011</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Filtration fraction, %</td>
<td>25.9±0.9</td>
<td>23.4±0.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 h</td>
<td>116±14</td>
<td>133±9</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary potassium, mmol/24 h</td>
<td>48±7</td>
<td>50±5</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary urea, mmol/24 h</td>
<td>334±35</td>
<td>337±29</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary albumin, mg/24 h</td>
<td>20±6</td>
<td>15±3</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary β₂-microglobulin, μg/24 h</td>
<td>153±33</td>
<td>138±28</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity, ng/mL per hour</td>
<td>3.2±0.8</td>
<td>1.7±0.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Plasma aldosterone concentration, ng/dL</td>
<td>20±2</td>
<td>16±2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Of note, after OC withdrawal, diastolic pressure was normalized (<90 mm Hg) in 5 and improved in 8 patients. No significant difference in baseline characteristics was observed between the 2 subgroups. Interestingly, captopril administration resulted in a similar fall in arterial pressure in both groups and a significant renal vasodilation only in the “normalized” group.

Discussion

This study failed to demonstrate a prominent role for the renin-angiotensin system in maintaining high blood pressure in women with OC-associated hypertension. Despite higher levels of plasma renin activity, the change in arterial pressure associated with acute angiotensin-converting enzyme blockade was similar to that observed in non–OC-using women with essential hypertension.

Involvement of the renin-angiotensin system in the pathogenesis of OC hypertension was initially suggested by the finding of increased plasma levels of renin and angiotensinogen in women receiving estrogen therapy.11,14,15 However, plasma levels of angiotensinogen were increased to the same extent in normotensive and hypertensive OC users, and plasma levels of angiotensin II were not consistently increased.6,16 It was also hypothesized that in women who became hypertensive while using OC, the increase in circulating angiotensin II resulting from higher substrate availability did not exert the expected inhibitory effect on renal production of renin.11,16,17

To date, only a few studies have attempted to assess the effects of blockade of the renin-angiotensin system in OC-associated hypertension. In a model of hypertension induced by a 26-week period of administration of mestranol and norethindrel, infusion of the competitive angiotensin II receptor antagonist saralasin was associated with a decrease in mean arterial pressure of 28 mm Hg in anesthetized, female rats, whereas no change occurred in controls.18 In a
further larger study from the same laboratory, saralasin failed to alter arterial pressure in similarly pretreated but conscious rats, despite the finding of a markedly elevated level of plasma renin substrate (but not renin activity or renin concentration). In women taking OC, the response of arterial pressure to saralasin was believed to predict the change in blood pressure observed after discontinuation of steroids. These findings were not confirmed in subsequent very small series. The observation that the captopril-induced fall in arterial pressure was similar in patients who became normotensive and those who did not after CO discontinuation indicates that the acute systemic response to blockade of the renin-angiotensin system is not predictive of the response to OC withdrawal.

In this study, no difference in baseline values of ERPF was observed between hypertensive OC users and nonusers, whereas renal vascular resistance was slightly higher in normotensive OC users when compared with control subjects. Previous studies suggested that acute or short-term administration of progesterone to normotensive subjects was associated with an increase in renal plasma flow and a blunting of the renal vascular responsiveness to angiotensin II, whereas estrogens had no effect. On the other hand, a 25% reduction in renal blood flow (as estimated from radioactive xenon disappearance curve) was observed in normotensive women receiving long-term OC. In addition, circulating levels of angiotensin II were inappropriately elevated with regard to sodium intake and correlated with renal blood flow, whereas renal vascular responsiveness to angiotensin II infused into the renal artery was reduced. It was suggested that angiotensin II may mediate an OC-associated reduction in renal blood flow through a mechanism other than altered sodium balance. In contrast, the present data did not document any difference in captopril-induced renal vasodilation between OC users and nonusers, whether normotensive or hypertensive.

In hypertensive OC users, urinary excretion of sodium tended to decrease in parallel with the captopril-induced fall in blood pressure, and this response was reversed after withdrawal of OC. These findings are consistent with an altered autoregulation of renal sodium handling in hypertensive patients taking OC. No pertinent data were generated in this study regarding the mechanisms of a putative sodium retention associated with OC administration. In addition, no change in body weight (taken as a rough index of extracellular fluid volume) was observed after OC withdrawal, in contrast with previous observations.

Increased UAE is observed in 15% to 20% of never-treated, lean patients with essential hypertension, and systolic pressure was shown to be the major determinant of albuminuria in such patients. Although conducted in a rather small number of patients, this study indicated that OC administration resulted in a slightly increased prevalence and mean level of albuminuria when compared with subjects with similar blood pressure. Of note, a mild difference in systolic blood pressure was observed between normotensive OC users and nonusers. Interestingly, ambulatory blood pressure monitoring disclosed a slightly higher systolic blood pressure in OC users when compared with control subjects with similar and apparently normal casual blood pressure. Thus, it cannot be excluded that small, undetected differences in ambulatory blood pressure may explain part of the excess albuminuria observed in OC users. Of note, no known risk factor for albuminuria such as diabetes mellitus, obesity, or increased prevalence of smoking history was associated with OC use in the current study. The findings of similar values for filtration fraction and urinary excretion of β₂-microglobulin in OC users and nonusers suggested that increased albuminuria was not mediated by an alteration in intraglomerular hemodynamics or tubular reabsorption. In fact, albuminuria might result from renal endothelial dysfunction. Subtle changes in renal albumin permeability during OC administration might be the early event potentially leading to intra-renal vascular damage.

It is of interest that the present population of women with OC hypertension had an increased waist/hip ratio. This index of visceral (android) adiposity was associated with higher blood pressure and albuminuria in diabetic patients. Whether an increased waist/hip ratio could be a marker of susceptibility to blood pressure, or a consequence of, administration of OC remains to be studied. OC use was also associated with an increased level of circulating triglycerides (but no hyperglycemia), a finding usually attributed to the progestogenic component. Whether specific metabolic alterations and endothelial dysfunction are linked to OC-associated hypertension deserves further study.

In conclusion, this study failed to demonstrate a role for the renin-angiotensin system in the maintenance of OC hypertension. However, long-term treatment based on blockade of the renin system should be assessed specifically in OC users when no alternate form of contraception is feasible—inasmuch as the repeatedly advocated use of diuretics, including spironolactone, in the treatment of such patients has never been substantiated in a controlled trial. In addition, the reported data indicate that OC use is associated with increased albuminuria, possibly resulting from endothelial dysfunction. Further studies are needed to delineate the markers of individual susceptibility to OC hypertension and to evaluate whether the excessive albuminuria with respect to the level of arterial pressure observed in OC hypertensive users is a predictor of an increased probability of cardiovascular morbidity events or further development of renal deterioration.

References
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