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Renal hemodynamic and tubular responses to salt in women using oral contraceptives

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Background. The use of oral contraceptives is associated with an increased risk of developing hypertension but the mechanisms of this hypertensive effect are not completely defined. The purpose of the present study was to assess prospectively the systemic and renal hemodynamic and tubular responses to salt in women taking oral contraceptives.

Methods. Twenty seven young healthy normotensive women taking oral contraceptives containing monophasic combination of 30 μg ethynilestradiol and 150 μg desogestrel for >6 months were enrolled. All women were assigned at random to receive a low (40 mmol/day) or a high (250 mmol/day) sodium diet for 1 week on two consecutive menstrual cycles during the active oral contraceptive phase. At the end of each diet period, 24-hour ambulatory blood pressure, renal hemodynamics, sodium handling, and hormonal profile were measured.

Results. The blood pressure response to salt on oral contraceptives was characterized by a salt-resistant pattern with a normal circadian rhythm. Salt loading results in an increase in glomerular filtration rate (GFR) ($P < 0.05$ vs. low salt), with no change in the renal plasma flow, thus leading to an increase in the filtration fraction ($P < 0.05$). At the tubular level, women on oral contraceptives responded to a low salt intake with a marked increased in proximal sodium conservation ($P < 0.01$ vs. high salt) and with an almost complete reabsorption of sodium reaching the distal tubule. After sodium loading, both the proximal and the distal reabsorption of sodium decreased significantly ($P < 0.01$).

Conclusion. The use of oral contraceptives is not associated with an increased blood pressure response to salt in young normotensive women. However, oral contraceptives affect the renal hemodynamic response to salt, a high salt intake leading to an increase in GFR and filtration fraction. This effect is possibly mediated by the estrogen-induced activation of the renin-angiotensin system. Oral contraceptives also appear to increase the tubular responsiveness to changes in sodium intake. Taken together, these data point out evidence that synthetic sex steroids have a significant impact on renal function in women. The renal effects of oral contraceptives should be taken into account when managing young women with renal diseases.

Key words: blood pressure, sodium, lithium, renal, hemodynamics, oral contraceptives.

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The use of oral contraceptives is known to increase blood pressure in a large proportion of women and is associated with an increased risk of developing hypertension [1, 2]. The mechanisms whereby oral contraceptives trigger a blood pressure elevation are not well understood. In early studies, elevated plasma levels of renin and angiotensinogen were found in women receiving estrogens [3–5]. It was concluded from these observations that the renin-angiotensin system plays a major role in mediating the changes in blood pressure in oral contraceptive users. However, similar increases in angiotensinogen were measured in both normotensive and hypertensive women taking oral contraceptives, suggesting that the hepatic stimulation of angiotensinogen by estrogens is probably not the only determinant of the change in blood pressure [6, 7]. An impaired negative feedback on renin secretion induced by oral contraceptives represents another mechanism that could lead to the rise in blood pressure in hypertensive women receiving oral contraceptives [8]. Yet, a more recent study failed to confirm that the renin-angiotensin system plays a prominent role in maintaining a high blood pressure in women with oral contraceptive–associated hypertension [9].

Sodium retention is yet another potential mechanism whereby oral contraceptives could lead to an increase in blood pressure. In Dahl salt-sensitive rats, female sex hormones appear to protect against the development of sodium-dependent and -independent hypertension as ovariectomized Dahl salt-sensitive rats exhibit an exaggerated development of hypertension [10, 11]. In humans, the incidence of hypertension clearly increases in postmenopausal females, when female sex hormones decrease [12] and this may again be related to a greater sodium retention. Indeed, we have reported recently that meno-

pausal women not on hormonal replacement therapy are salt-sensitive, their blood pressure increasing significantly on high salt diet [abstract; Pechère-Bertschi A et al, *J Am Soc Nephrol* 10:369, 1999].

This contrasts markedly with nonmenopausal women who are rather salt-resistant whatever the phase of the menstrual cycle [13]. The relative contribution of estrogens and progesterone in mediating these various responses to salt in nonmenopausal and menopausal women is still unclear because the direct effects of female sex hormones on renal sodium handling have not been investigated in great details. Several studies have demonstrated that progesterone is natriuretic but the effects of endogenous as well as exogenous estrogens on sodium excretion are not clearly defined. Ribstein et al [9] have recently suggested that there is an altered autoregulation of renal sodium handling in hypertensive women taking oral contraceptives. However, women included in this study were not investigated under different salt diets. Thus, whether oral contraceptives affect the blood pressure by influencing the renal response to salt is still unknown.

The goals of the present study were therefore to investigate prospectively the blood pressure and the renal hemodynamic and tubular responses to salt in young normotensive healthy women taking oral contraceptives using a standard protocol that has been used previously in noncontraceptive users [13, 14].

METHODS

Subjects

The study population consisted of 27 young white normotensive female volunteers recruited mostly among the medical students and the hospital staff of the University Hospital of Geneva. All women were healthy and had been on oral contraceptives containing 30 μg ethynilestradiol plus 150 μg desogestrel for >6 months. They were nonsmokers and were not taking any medication known to affect blood pressure and renal function. At the initial visit, a full medical history and a clinical examination were undertaken. The volunteers were randomly assigned to be studied at the beginning (day 4 to day 12) and at the end (day 21 to day 28) of the treatment cycles. The study protocol has been reviewed and approved by the Institutional Ethics Committee (University Hospital, Geneva) and all subjects gave their written informed consent.

Clinical investigation

The volunteers were randomly allocated to receive a low (40 mmol sodium per day) and a high (250 mmol sodium per day, achieved by adding 6 g of salt in their usual diet) sodium diet for a 7-day period during two consecutive months. The diets were conducted at home and all women received detailed recommendations on how to follow a low salt diet. After each 7-day diet period, 24-hour urines were collected separately during the day (from 8:00 a.m. to 10:00 p.m.) and during the night (from 10:00 p.m. to 8:00 a.m.) in order to measure sodium excretion. Concomitantly, 24-hour blood pressure was recorded using ambulatory blood pressure monitoring (Diasys, Physicor, Geneva, Switzerland). This device has been validated by the British Hypertension Society and was rated B/A. Ambulatory blood pressure was measured at 20-minute intervals during the day (from 8:00 a.m. to 10:00 p.m.) and every 60 minutes during the night (from 10:00 p.m. to 8:00 a.m.). On the next day, the volunteers were admitted to the hospital at 8:30 a.m. after an overnight fast to measure their renal function. Renal hemodynamics was measured using sinistrin (an analog of inulin) and paraaminohippuric acid (PAH) clearances as described previously [15]. After lying quietly for a 90-minute period of equilibration in supine position and administration of an oral water load of 5 mL/kg to ensure a stable urine output, the glomerular filtration rate (GFR), and the effective renal plasma flow (ERPF) were measured twice, in two 90-minute clearance intervals.

Analytic procedures

Sodium excretion was expressed as $U_{Na} \cdot V$ in mmol/day or μmol/min, where U_{Na} is the urinary sodium concentration and V is the urinary volume expressed either in mL/24 hours or in mL/min. Proximal renal sodium handling was assessed by the determination of endogenous lithium in plasma and urine using graphite furnace atomic absorption spectrophotometry [16, 17] and by the fractional excretion of lithium and sodium using the standard formula (FE_X = clearance of x divided by the GFR). In addition, the fractional distal reabsorption of sodium (i.e., the percentage of the distally delivered sodium reabsorbed in the postproximal nephron segments) was calculated as $[(FE_{Li} - FE_{Na})/FE_{Li}] \cdot 100$. Plasma catecholamines were determined by high-performance liquid chromatography [18] and plasma renin activity (PRA) and aldosterone by radioimmunoassay [19, 20]. Plasma progesterone levels were measured using an enzyme immunoassay (Kryptor, CIS Bio, Saclay, France). Sinistrin (Inutest®) was purchased from Laevosan Gesellschaft (Zürich, Switzerland) and PAH from SERB, Laboratoires Pharmaceutiques (Paris, France).

Statistics

All results are expressed as mean ± standard error (SEM). Data were then analyzed using a paired or unpaired Student *t* test for independent samples when appropriate. A one-way analysis of variance was used for comparison between oral contraceptive users and nonusers.

Table 1. Characteristics of oral contraception users ($N = 27$)

Age *years*	26 (range, 20–40)
Family history of hypertension	14/27
Weight *kg*	58.5 ± 1.5
Body mass index kg/m^2	20.8 ± 0.5
Premenstrual symptoms	20/27
Cycle study day	5.3 ± 0.3 (range, 4–12, $N = 13$) 15 ± 0.4 (range, 14–21, $N = 14$)[a]
Oral contraceptives	Ethinylestradiol 30 μg + desogestrel 150 μg
Serum creatinine *μmol/L*	76 ± 2

[a] Thirteen women were studied during the first week of taking oral contraceptives and 14 women were studied during the third week of the treatment. The results were exactly of the same magnitude, which is why the two groups were pooled.

Values are mean ± SE.

Table 2. Ambulatory blood pressure response to salt on oral contraceptives

	Day		Night	
Sodium diet	Low	High	Low	High
Systolic blood pressure *mm Hg*	107 ± 2	108 ± 2	91 ± 2[a]	93 ± 2[a]
Diastolic blood pressure *mm Hg*	73 ± 1	71 ± 1	59 ± 2[a]	60 ± 1[a]
Pulse pressure *mm Hg*	34 ± 1	37 ± 2	32 ± 2	33 ± 1[a]
Heart rate *beats/min*	84 ± 2	80 ± 2	64 ± 2[a]	67 ± 2[a]

[a] $P < 0.01$ vs. daytime

Values are mean ± SE.

RESULTS

The baseline characteristics of the women included in this study are presented in Table 1. More than half of the subjects suffered from mild premenstrual symptoms. There was a family history of hypertension in about half of the volunteers.

Blood pressure and heart rate response to salt

The changes in 24-hour urinary sodium excretion induced by the two diets were significantly different. On a low salt diet, $U_{Na} \cdot V$ was 26 ± 3 mmol/24 hours, and on a high salt diet, the mean sodium excretion was 322 ± 20 mmol/24 hours ($P < 0.01$). The salt-induced changes in daytime and nighttime ambulatory blood pressure, heart rate, and pulse pressure on oral contraceptives are presented in Table 2. No significant differences in daytime or nocturnal ambulatory blood pressure or heart rate were observed on high compared with low sodium intake on oral contraceptives. A significant nocturnal dip in both systolic and diastolic blood pressures was found whatever the diet ($P < 0.01$ nighttime compared with daytime). Figure 1 illustrates the pressure-natriuresis relationship in subjects on oral contraceptives in comparison with women not receiving contraceptives and evaluated either during the follicular or during the luteal phase of a normal menstrual cycle. The graph demonstrates that blood pressure on oral contraceptives is essentially salt-resistant, as found in the two phases of the normal menstrual cycle without oral contraceptives [13].

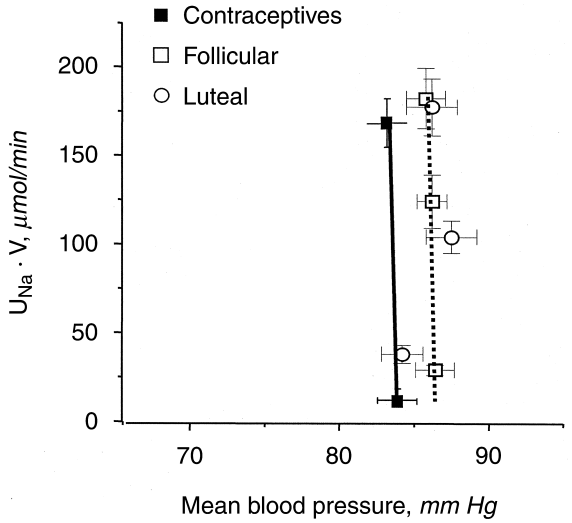

Fig. 1. Relationship between mean ambulatory blood pressure (mm Hg) and sodium excretion (μmol/min) in normotensive women studied on oral contraceptive agents and in oral contraceptive nonusers. All values are mean ± SE.

Table 3. Renal hemodynamic and hormonal responses to salt on oral contraceptives

	Sodium diet	
	Low	High
GFR *mL/min/1.73 m²*	96 ± 4	117 ± 4[a]
ERPF *mL/min/1.73 m²*	446 ± 18	485 ± 19
FF *%*	22 ± 1	24 ± 0.5[a]
PRA *ng/mL/hour*	2.8 ± 0.3	1.0 ± 0.1[b]
Aldosterone *nmol/L*	0.6 ± 0.2	0.1 ± 0.02[b]
Adrenaline *nmol/L*	0.3 ± 0.2	0.3 ± 0.1
Noradrenaline *nmol/L*	2.0 ± 0.5	1.5 ± 0.3
Progesterone *ng/mL*	0.4 ± 0.1	0.5 ± 0.1

Abbreviations are: GFR, glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction; PRA, plasma renin activity.

[a] $P < 0.05$; [b] $P < 0.01$ vs. low salt diet

Values are mean ± SE.

Renal hemodynamic and hormonal response to salt

The effects of changing the sodium intake on renal hemodynamics and hormonal profile on oral contraceptives are presented in Table 3. Salt loading induced a significant increase in GFR ($P < 0.05$) and no significant change in ERPF compared with low salt intake, consequently filtration fraction was significantly increased ($P < 0.05$). The effects of changing sodium intake on the vasoactive hormones profile in oral contraceptive users are also presented in Table 3. As expected, PRA and aldosterone levels decreased significantly ($P < 0.01$) after sodium loading. Plasma noradrenaline and adrenaline levels were not significantly changed by the different sodium diets. On oral contraceptives, plasma progesterone levels were low and not affected by the sodium content of the diet.

Table 4. Segmental tubular renal sodium response to salt on oral contraceptives ($N = 27$)

	Sodium diet	
	Low	High
Body weight *kg*	58.3 ± 1.4	59.7 ± 1.5[a]
Urinary volume *L*		
Day	1.3 ± 0.1	1.3 ± 0.1
Night	0.4 ± 0.05[b]	0.4 ± 0.03[b]
$U_{Na} \cdot V$ *μmol/min*		
Day	17 ± 2	168 ± 12[c]
Night	18 ± 4	128 ± 8[b,c]
FE_{Na} %		
Day	0.12 ± 0.02	1.01 ± 0.06[c]
Night	0.14 ± 0.03	0.88 ± 0.07[c]
Cl_{Li} mL/min		
Day	14.9 ± 1.4	25.7 ± 2.7[c]
Night	12.8 ± 1.2	21.0 ± 1.9[c]
FE_{Li} %		
Day	14.0 ± 1.4	21.5 ± 2[c]
Night	13.8 ± 1.3	19.4 ± 1.7[c]
FDR_{Na} %		
Day	99.1 ± 0.1	94.7 ± 0.4[c]
Night	99.0 ± 0.2	94.9 ± 0.4[c]
FE_K %		
Day	16.1 ± 0.9	12.0 ± 0.9[c]
Night	8.9 ± 0.7	5.0 ± 0.34[c]

Abbreviations are: U, urinary; FE_{Na}, fractional excretion of sodium; Cl, clearance; FE_{Li}, fractional excretion of lithium; FDR_{Na}, fractional distal reabsorption of sodium; K, potassium.

[a] $P < 0.05$; [b] $P < 0.01$ daytime vs. nighttime; [c] $P < 0.01$ vs. low salt diet

Values are mean ± SE.

Segmental renal sodium handling on oral contraceptives and the effect of salt

On oral contraceptives, administration of high sodium diet caused a significant increase in body weight (+ 1.4 ± 0.2 kg). Table 4 shows the diet-induced changes in sodium excretion and proximal and distal renal sodium handling. The urinary volume did not change significantly from a low to a high salt diet. As expected from the diets, the daytime and nighttime urinary sodium excretion increased significantly from a low to a high sodium intake ($P < 0.01$), indicating that compliance to the regimen was excellent. On a high salt diet, sodium excretion decreased significantly during the night ($P < 0.01$, day vs. night). The fractional excretion of endogenous lithium (FE_{Li}), a marker of proximal excretion, increased significantly on a high sodium diet ($P < 0.01$), and the fractional distal reabsorption of sodium (FDR_{Na}) decreased significantly, indicating that sodium balance is maintained by both a decrease in proximal and distal sodium reabsorption in women on oral contraceptives.

DISCUSSION

The main objective of the present study was to evaluate the effect of oral contraceptives on the blood pressure and the renal response to salt. Our results show that the blood pressure response to salt in young normotensive women on oral contraceptives is characterized by a salt-resistant pattern, with a normal circadian rhythm. In the kidney, chronic salt loading results in a significant increase in GFR with no change in ERPF, thus leading to an increase in filtration fraction. At the tubular level, women on oral contraceptives respond to a low salt intake with increased proximal sodium conservation and with an almost complete reabsorption of the sodium reaching the distal level of the tubule. After sodium loading, both the proximal and the distal reabsorption of sodium decreases significantly.

The administration of oral contraceptives has been associated with a rise in blood pressure and some women may even develop a significant but reversible hypertension [1, 2]. Activation of the renin-angiotensin system is generally considered as the main factor leading to the increase in blood pressure since estradiol administration stimulates the hepatic synthesis of angiotensinogen [21, 22]. The exogenous female sex hormones can also cause a decrease in sodium excretion accompanied by water retention, two factors that may further contribute to increase blood pressure [23]. In this study, we show for the first time that the pressure-natriuresis relationship of women taking oral contraceptives is of the salt-resistant pattern, as it is in oral contraceptive nonusers in both phases of the menstrual cycle [13] (Fig. 1). Interestingly, the salt-resistant pattern is observed despite the relative stimulation of the renin-angiotensin system. As expected, PRA in our oral contraceptive users is higher than the activity measured in oral contraceptive nonusers studied at comparable levels of salt intake [13] and the changes in PRA induced by the changes in sodium intake is significantly greater in oral contraceptive users than in nonusers as shown in Table 5. Yet, in oral contraceptive users, PRA can still be partially suppressed on a high salt intake. The salt-resistant pattern in face of an activated renin-angiotensin system is therefore in accordance with the findings of Hall et al [23] who have shown in dogs that salt sensitivity develops primarily when the activity of the renin-angiotensin cascade cannot be modulated.

The results of the present study suggest that *exogenous* female sex hormones influence markedly the renal hemodynamic response to salt without affecting systemic blood pressure. Indeed, salt loading in oral contraceptive users induced a significant increase in GFR with no change in ERPF, hence filtration fraction increased. The salt-induced changes in GFR and ERPF are shown in Table 5 for oral contraceptive users and nonusers. A comparable but nonsignificant trend was observed in oral contraceptive nonusers studied during the follicular phase [14]. In contrast, during the luteal phase of the normal menstrual cycle, we found that salt loading induces a renal vasodilatation with no change in GFR. There are few data on the renal hemodynamic effects of oral contraceptives. An early study by Hollenberg et

Table 5. Renal response to salt: Comparison between oral contraceptive users and nonusers[a]

Sodium diet	Oral contraceptive ($N = 27$) High-low	Follicular ($N = 17$) High-low	Luteal ($N = 18$) High-low	ANOVA
GFR *mL/min/1.73 m²*	22 ± 6	4.9 ± 3.9	−1.6 ± 6[b]	$P = 0.009$
ERPF *mL/min/1.73 m²*	28 ± 23	−5 ± 30	64 ± 36[c]	P = NS
PRA *ng/mL/hour*	1.9 ± 0.3	0.83 ± 0.16[b]	0.76 ± 0.21[b]	$P = 0.007$
FE_{Na} %	0.89 ± 0.05	1.16 ± 0.13	0.97 ± 0.1	$P = 0.06$
FE_{Li} %	7.9 ± 2.3	12.1 ± 7.1	−1.2 ± 2.2[d]	$P = 0.06$

Abbreviations are: GFR, glomerular filtration rate; ERPF, effective renal plasma flow; PRA, plasma renin activity.
[a]All values have been obtained by subtracting the result of the low salt diet from that of the high salt diet.
[b]$P < 0.01$ vs. oral contraceptive (unpaired t test); [c]$P < 0.05$; [d]$P < 0.01$ vs. follicular (paired t test)
Values are mean ± SE.

al [24] showed that oral contraceptives in healthy young women reduced the ERPF and reported a negative correlation between plasma angiotensin II levels and ERPF with a significant activation of the renin-angiotensin system. The administration of oral contraceptives has been found to increase creatinine clearance in young women studied on a free sodium intake [25]. Kang et al [26] found significant increases in systolic blood pressure, renal vascular resistance, and filtration fraction in oral contraceptive users compared to nonusers, and showed that these differences were at least partially abolished by angiotensin II blockade. At the glomerular level, an increase in GFR and filtration fraction can result either from a vasodilatation of afferent arterioles associated or not with an increase in the tonus of the efferent arteriole or to a vasoconstriction of the efferent arteriole with no change in the afferent tone. A direct effect on the glomerulus may also produce an increase in filtration fraction. To explain the salt-induced renal vasodilatation and fall in filtration fraction in women studied during the luteal phase, we had proposed the hypothesis that estrogens modulate the renal hemodynamics indirectly via the nitric oxide pathway and perhaps prostaglandin formation [13, 14], thereby inhibiting the effects of angiotensin II on glomerular hemodynamics. Through this mechanism, estrogens could cause a renal vasodilatation and a decrease in filtration fraction. The same mechanism may actually be operating to explain the salt-induced increase in GFR in oral contraceptive users but with one important difference (i.e., the baseline activity of the renin-angiotensin system). Thus, we hypothesize that the vasodilatory effect of estrogens in oral contraceptive users may be more prominent at the level of afferent arteriole, thereby leading to an increase in GFR and filtration fraction. Of course, we realize that this hypothesis is very speculative and deserves further investigations with more direct measurements. Of note, high plasma estrogen levels have been reported to augment endothelial nitric oxide synthesis [27, 28].

The apparent difference between endogenous and exogenous female sex hormones as reflected by the more pronounced effect of salt loading on renal hemodynamic in oral contraceptive users than in nonusers could be attributed to differences in potency between endogenous and exogenous female sex hormones. Indeed, combined oral contraceptive agents deliver pharmacologic levels of estrogens that exhibit 6 to 10 times the estrogenic activity provided by endogenous estrogens [29]. Finally, the observation of a salt-induced increase in GFR and filtration fraction in oral contraceptive users may have a long-term clinical impact and implications for use in patients with renal disease. Indeed, in a recent study, a significant increase in 24-hour urinary albumin excretion was found in normotensive as well as in hypertensive women using oral contraceptives when compared with nonusers with a similar blood pressure [9]. In this clinical situation, a low sodium intake may lower intraglomerular pressure and hence reduce urinary protein excretion.

The effects of exogenous female sex hormones on renal tubular function are not known. Endogenous progesterone is known to be natriuretic, but synthetic derivatives of progesterone may not have similar natriuretic properties. Indeed, early studies have demonstrated that synthetic progestins had a decreased affinity for renal mineralocorticoid receptors, explaining a lack of natriuretic activity of these compounds [30]. Whether estrogen affects tubular sodium handling is not known. In our oral contraceptive users, the tubular response to changes in sodium intake was relatively comparable to that obtained in normotensive men [31] and in women studied during the follicular phase of the menstrual cycle (Table 5) [14]. Indeed, the proximal reabsorption of sodium increased markedly on a low sodium diet, as reflected by a decrease in FE_{Li}, and decreased significantly on a high sodium diet. As shown in Figure 2, the FE_{Li}/FE_{Na} relationship is parallel but shifted to lower levels of FE_{Li} in women receiving oral contraceptives when compared to women studied in the follicular phase. This shift may again be attributed to the activation of the renin-angiotensin system leading to an increased proximal reabsorption of sodium. A high reabsorption of sodium was also found to occur in the distal tubule as reflected by the

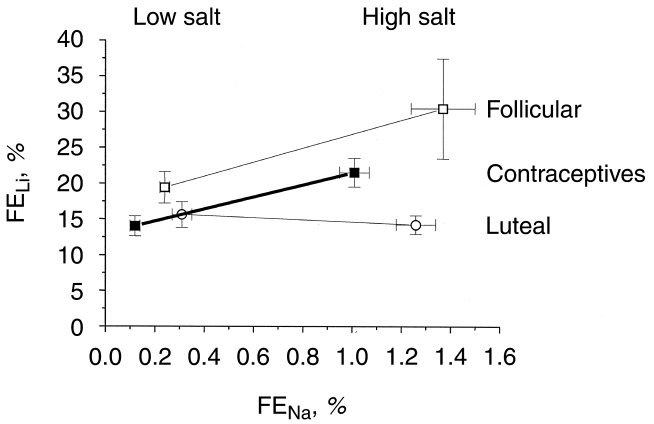

Fig. 2. Salt-induced variations in daytime fractional excretion of sodium (FE_{Na}) and endogenous lithium (FE_{Li}) in normotensive women studied on oral contraceptives. For comparison, the same parameters studied in the follicular and luteal phases of the normal menstrual cycle published previously are presented [14]. Low salt, 40 mmol/day; high salt, 250 mmol/day.

very high FDR_{Na}. Thus, combined oral contraceptives do not appear to affect the balance between the proximal and the distal nephron segments. However, because of the activation of the renin-angiotensin system, women on oral contraceptives may have a greater tubular responsiveness. Interestingly, in our study, chronic oral contraceptive administration resulted in a positive sodium balance when diet changes from a low to a high salt diet, reflected in a mean weight gain of 1.5 kg.

CONCLUSION

This study shows that the use of hormonal contraceptives is not associated with an increased blood pressure response to salt, and women on oral contraceptives have a salt-resistant pattern like oral contraceptive nonusers. However, oral contraceptives do affect the renal hemodynamic response to salt, an effect that appears to be mediated by the combined effects of estrogens on the renin-angiotensin system and on vasodilatory factors such as nitric oxide and prostaglandins. The increase in filtration fraction observed with the administration of contraceptives in women receiving a high salt diet may be of clinical concern since a high filtration fraction has been associated with an increased incidence of microalbuminuria and proteinuria as well as with an increased risk of glomerular sclerosis. At last, exogenous female sex hormones appear to increase the tubular responsiveness to changes in sodium intake leading to an increased reabsorption of sodium. Taken together, these data point out evidence that synthetic sex steroids differ in their effects on kidney from endogenous steroids. In a general point of view, it implicates that in women on oral contraceptives suffering from any kidney problem, sodium restriction should be encouraged.

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REFERENCES

1. Chasan-Taber L, Willett WC, Manson JAE, *et al*: Prospective study of oral contraceptives and hypertension among women in the United States. *Circulation* 94:483–496, 1996
2. Williamson PM, Buddle ML, Brown MA, *et al*: Ambulatory blood pressure monitoring in the normal menstrual cycle and in women using oral contraceptives. Comparison with conventional blood pressure measurement. *J Hypertens* 9:953–958, 1996
3. Skinner SL, Lumbers ER, Symonds EM: Alteration by oral contraceptives of normal menstrual changes in plasma renin activity, concentration and substrate. *Clin Sci* 36:67–76, 1969
4. Laragh JH, Sealey JE, Ledingham JGG, *et al*: Oral contraceptives: Renin, aldosterone, and high blood pressure. *JAMA* 201:918–922, 1967
5. Weinberger MH, Collins D, Dowdy AJ, *et al*: Hypertension induced by oral contraceptives containing estrogen and gestagen. *Ann Intern Med* 71:891–902, 1969
6. Weir RJ: When the pill causes a rise in blood pressure. *Drugs* 16:522–527, 1978
7. Derkx FMH, Stuenkel C, Visser W, *et al*: Immunoreactive renin, prorenin, and enzymatically active renin in plasma during pregnancy and in women taking oral contraceptives. *J Clin Endocrinol Metab* 63:1008–1015, 1986
8. Saruta T, Saade GA, Kaplan MN: A possible mechanism for hypertension induced by oral contraceptives: Diminished feedback suppression of renin. *Arch Intern Med* 126:621–626, 1970
9. Ribstein J, Halimi JM, Du Cailar G, *et al*: Renal characteristics and effect of angiotensin suppression in oral contraceptive users. *Hypertension* 33:90–95, 1999
10. Hinojosa-Laborde C, Lange DL, Haywood JR: Role of female sex hormones in the development and reversal of Dahl hypertension. *Hypertension* 35:484–489, 2000
11. Otsuka K, Suzuki H, Sasaki T, *et al*: Blunted pressure natriuresis in ovariectomized Dahl-Iwai salt-sensitive rats. *Hypertension* 27: 119–124, 1996
12. Reckelhoff JF: Gender differences in the regulation of blood pressure. *Hypertension* 37:1199–1212, 2001
13. Pechère-Bertschi A, Maillard M, Stalder H, *et al*: Blood pressure and renal hemodynamic response to salt during the normal menstrual cycle. *Clin Sci* 98:697–702, 2000
14. Pechère-Bertschi A, Maillard M, Stalder H, *et al*: Renal segmental tubular response to salt during the normal menstrual cycle. *Kidney Int* 61:425–431, 2002
15. Pechère-Bertschi A, Nussberger J, Decosterd L, *et al*: Renal response to the angiotensin II receptor subtype 1 antagonist irbesartan versus enalapril in hypertensive patients. *J Hypertens* 16: 385–393, 1998
16. Magnin JL, Decosterd LA, Centeno C, *et al*: Determination of trace lithium in biological fluids using graphite furnace atomic absorption spectophotometry. Variability of urine matrices circumvented by cation exchange solid phase extraction. *Pharm Acta Helv* 71:237–246, 1996
17. Steinhauslin F, Burnier M, Magnin JL, *et al*: Fractional excretion of trace lithium and uric acid in acute renal failure. *J Am Soc Nephrol* 4:1429–1437, 1994
18. Bauersfeld W, Ratge D, Knoll E, *et al*: Determination of catecholamines in plasma by HPLC and amperometric detection. Comparison with a radioenzymatic method. *J Clin Chem Clin Biochem* 24:185–188, 1986
19. Bakiri F, Benmiloud M, Vallotton MB: The renin-angiotensin

system in panhypopituitarism dynamic studies and therapeutic effects in Sheehan's syndrome. *J Clin Endocrinol Metab* 56:1042–1047, 1983
20. Kubasik NP, Warren K, Sine HE: Evaluation of a new commercial radioassay kit for aldosterone using an iodinated tracer. *Clin Biochem* 12:59–61, 1979
21. Helmer OM, Griffith RS: Effect of the administration of estrogens on the renin-substrate (hypertensinogen) content of rate plasma. *Endocrinology* 51:421–426, 1952
22. Dignam WS, Voskian J, Assali NS: Effects of estrogens on renal hemodynamics and excretion of electrolytes in human subjects. *J Clin Endocrinol* 16:1032–1041, 1956
23. Hall JE, Guyton AC, Smith MJ, Jr, *et al*: Blood pressure and renal function during chronic changes in sodium intake: role of angiotensin. *Am J Physiol* 239:F271–F280, 1980
24. Hollenberg NK, Williams GH, Burger B, *et al*: Renal blood flow and its response to angiotensin II. An interaction between oral contraceptive agents, sodium intake, and the renin-angiotensin system in healthy young women. *Circ Res* 38:35–40, 1976
25. Brandle E, Gottwald E, Melzer H, *et al*: Influence of oral contraceptive agents on kidney function and protein metabolism. *Eur J Clin Pharmacol* 43:643–646, 1992
26. Kang AK, Duncan JA, Cattraran DC, *et al*: Effect of oral contraceptives on the renin angiotensin system and renal function. *Am J Physiol Regul Integr Comp Physiol* 280:R807–R8013, 2001
27. Mendelsohn M: Genomic and nongenomic effects of estrogen in the vasculature. *Am J Cardiol* 90(1A):3F–6F, 2002
28. John S, Jacobi J, Schlaich MP, *et al*: Effects of oral contraceptives on vascular endothelium in premenopausal women. *Am J Obstet Gynecol* 183:28–33, 2000
29. Stachenfeld NS, Silva C, Keefe DL, *et al*: Effects of oral contraceptives on body fluid regulation. *J Appl Physiol* 87:1016–1025, 1999
30. Wambach G, Higgins JR, Kenn DC, *et al*: Interaction of synthetic progestagens with renal mineralocorticoids receptors. *Acta Endocrinol (Copenh)* 92:560–567, 1979
31. Burnier M, Monod ML, Chiolero A, *et al*: Renal sodium handling in acute and chronic salt loading/depletion protocols: The confounding influence of water loading. *J Hypertens* 18:1657–1664, 2000