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Ambulatory Blood Pressure in Mild Hypertensive Women Taking Oral Contraceptives

A Case-Control Study

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The aim of the present study was to compare the ambulatory blood pressure levels in mild (stage 1) hypertensive women using oral contraceptives and respective values in nonusers of oral contraceptives with similar office blood pressure. The study group consisted of 24 mild hypertensive patients taking low dosage estrogen–progestogen oral contraceptives. Seventy women of similar age and body mass index who had never used oral contraceptives served as a control group.

Both daytime and nighttime systolic blood pressure values were significantly higher in oral contraceptive users. There was an average 8.3 mm Hg difference (95% confidence interval, 3.0 to 13.7 mm Hg; $P = .003$) for the daytime and 6.1 mm Hg difference (95% confidence interval, 0.4 to 11.8 mm Hg; $P = .04$) for the nighttime. No significant differences in ambulatory diastolic blood pressure between the two groups were found.

These data provide evidence that hypertensive oral contraceptive users with the same office blood pressure as that in hypertensive noncontraceptive users have a significantly higher ambulatory systolic blood pressure. Our results support the opinion that alternative methods of contraception should be considered for hypertensive women in place of oral contraceptives. Am J Hypertens 1995; 8:249–253

KEY WORDS: **Ambulatory blood pressure, hypertension, oral contraceptives, women.**

The negative cardiovascular effects of oral contraceptives are well established.[1–6] Several cross-sectional and longitudinal studies have reported some elevation of office blood pressure among oral contraceptive users.[7–11] Cook et al[7] found an increase of 4.1 mm Hg in office systolic blood pressure after the initiation of oral contraceptive use, whereas the office diastolic blood pressure increase was significantly related to the duration of use and estimated at 0.5 mm Hg per year. Fisch and Frank[8] reported an average increase of 5 to 6 mm Hg systolic blood pressure and 1 to 2 mm Hg diastolic blood pressure. In their study, in spite of the small average blood pressure elevation among oral contraceptive users, about three times as many oral contraceptive users as nonusers had office blood pressure levels more than 140/90 mm Hg. Stern et al[9] found an average increase of 7.2 mm Hg and 1.0 mm Hg for systolic blood pressure and diastolic blood pressure, respectively, in white users versus nonusers. Much

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larger average elevations have been observed in other studies; for example, 14 mm Hg for systolic blood pressure over 4 years.[10] It has been suggested by Prentice[5] that relative risk functions that relate the disease incidence to the measured office blood pressure may be much flatter than those that would arise if disease rates were studied as a function of some "true" blood pressure levels.

Casual blood pressure measurements obtained in a physician's office or clinic are not necessarily representative of blood pressure level throughout a 24-h period. Ambulatory blood pressure monitoring overcomes this problem by providing multiple readings over time, with minimal intrusion into the patient's daily activities.[12,13] Surprisingly, no published study has yet investigated the effects of oral contraceptives on the diurnal blood pressure profile.

The aim of the present study was to compare the ambulatory blood pressure levels in stage 1 (mild) hypertensive women using oral contraceptives and respective values in noncontraceptive users with similar office blood pressure.

METHODS

The study group consisted of 24 white mild hypertensive patients taking low dosage estrogen–progestogen oral contraceptives. The most common preparations were those containing 30 μg of ethinyloestradiol with 75 μg of gestoden. The mean duration of oral contraceptives use was 3.0 years (range, 4 months to 10 years). Fourteen women reported that their blood pressure was normal (<130/85 mm Hg) before they started to take the pill. In the remaining 10 women blood pressure occasionally exceeded 140/90 mm Hg before using the pill, but after introduction of the pill it did not rise by more than 10/5 mm Hg. In these 10 women other contraceptive methods were not suitable and the risks of unwanted pregnancy were considered by the family doctor to be greater than the risks of stage 1 hypertension.

Seventy women of similar age and office blood pressure who had never used oral contraceptives served as a control group. Both oral contraceptive users and nonusers participated in the Harvest study,[14] a trial on the predictive value of ambulatory blood pressure monitoring. The inclusion criteria for the Harvest trial are as follows: aged 18 to 45 years, supine diastolic blood pressure from 90 to 99 mm Hg, body weight within 30% of the ideal, smoking of fewer than 20 cigarettes/day, and no prior treatment for essential hypertension.

The clinical characteristics of the two groups are presented in Table 1. The oral contraceptive and control groups were of comparable age, height, weight, and body mass index. There were 6 smokers (25%) in the oral contraceptives group and 13 smokers (18.6 %) in the controls (P = NS by χ^2 test).

TABLE 1. CLINICAL CHARACTERISTICS OF PATIENTS USING CONTRACEPTIVES (OC) AND CONTROLS

Variables	OC Patients (n = 24)	Controls (n = 70)	P
Age (yr)	30.6 (6.5)	32.7 (5.8)	NS
Height (cm)	164.4 (6.4)	162.6 (6.5)	NS
Weight (kg)	60.9 (8.7)	61.8 (7.8)	NS
Body mass index (kg/m^2)	22.5 (2.6)	23.3 (2.4)	NS

Values presented as means (SD).

Office blood pressure was measured following the recommendations of the British Society of Hypertension,[15] six times during two visits after a 5-min rest in the supine position. The mean of the six readings was defined as office blood pressure. At the second visit office blood pressure was measured just before the application of the ambulatory blood pressure monitoring device. Twenty-four-hour ambulatory blood pressure and heart rate monitoring was performed with either the A&D TM-2420 model 7 (A&D Company, Tokyo, Japan) or the ICR Spacelabs 90207 (Spacelabs Inc., Redmond, WA), which were previously validated.[16,17] Ambulatory blood pressure reproducibility proved to be similar with the two devices.[18] Before the recording was started, the device was checked against a mercury sphygmomanometer by means of a Y tube. The patients were instructed to remain motionless during cuff inflation and to maintain their usual habits. Blood pressure was measured every 10 min during waking hours (6 AM to 11 PM) and every 30 min at night. All ambulatory blood pressure monitoring data were screened for editing of artifactual values based on previously described criteria.[19] The mean 24-h awake and asleep blood pressures were calculated for each patient.

Statistics Differences between the oral contraceptive group and controls were assessed with unpaired t test. Confidence intervals (95%) for the difference between the means of office and ambulatory blood pressure were determined. Multiple regression analysis was performed to assess the effect of age, body mass index, duration of use of oral contraceptives, and cigarette smoking status on 24-h ambulatory blood pressure in the oral contraceptive group. Two-tailed tests were used throughout. Values of $P < .05$ were considered significant. Data are presented as means ± SD.

RESULTS

The office, daytime, and nighttime blood pressure values of the two groups are shown in Table 2. Although the office blood pressure values of the oral contraceptive group and controls were similar, the

TABLE 2. OFFICE AND AMBULATORY BLOOD PRESSURE IN ORAL CONTRACEPTIVES (OC) PATIENTS AND CONTROLS

Variables	OC Patients	Controls	Difference	*t*	*P*
Systolic blood pressure (mm Hg)					
Office	139.3 (12.4)	141.0 (9.7)	−1.7 (−6.6, 3.2)	−0.68	NS
Daytime	136.8 (11.9)	128.5 (11.3)	8.3 (3.0, 13.7)	3.08	.003
Nighttime	117.5 (12.6)	111.4 (11.8)	6.1 (0.4, 11.8)	2.13	.04
Diastolic blood pressure (mm Hg)					
Office	92.3 (4.8)	93.9 (4.6)	−1.6 (−3.8, 0.6)	−1.46	NS
Daytime	84.4 (8.8)	84.1 (7.0)	0.4 (−3.2, 3.9)	0.20	NS
Nighttime	71.8 (8.5)	71.5 (8.2)	0.3 (−3.6, 4.2)	0.15	NS

Values presented as means (SD), differences as means (95% confidence intervals).

daytime and nighttime systolic blood pressure values of oral contraceptive users were significantly higher than those of controls. Consequently, also the mean 24-h systolic was significantly higher in oral contraceptive users than that of nonusers (Figure 1).

No significant differences in ambulatory diastolic blood pressure between the oral contraceptive group and controls were found (Table 2). Daytime and nighttime heart rate values were similar in the oral contraceptive and control groups. Daytime heart rate averaged 79.3 ± 7.7 beats/min in oral contraceptive users and 79.3 ± 6.8 beats/min in nonusers. Mean nighttime heart rate was 66.6 ± 8.1 beats/min in the oral contraceptive group and 67.7 ± 7.4 beats/min in controls.

Multiple regression analysis for 24-h systolic blood pressure and 24-h diastolic blood pressure as the dependent variable in the oral contraceptives group (Table 3) revealed no significant effect for age, body mass index, duration of oral contraceptive use, or smoking status.

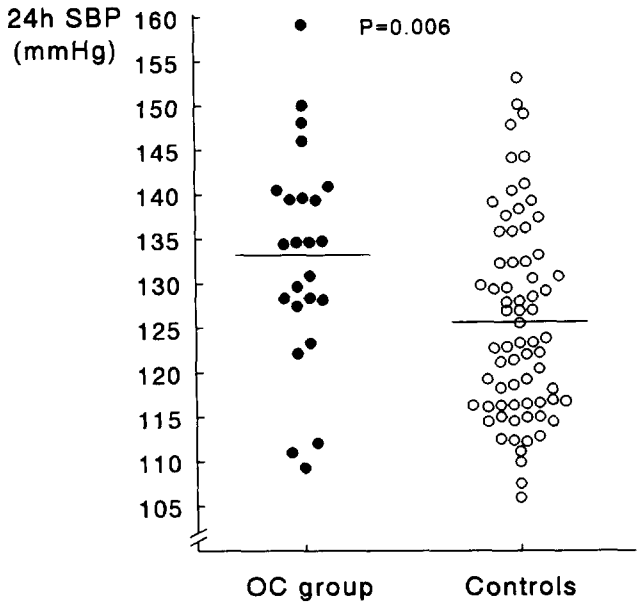

FIGURE 1. *Twenty-four-hour systolic blood pressure (in mm Hg) in oral contraceptive (OC) users and controls. The mean of each group is depicted by a horizontal line.*

DISCUSSION

As summarized by Prentice,[5] the majority of cross-sectional and longitudinal studies report increases of approximately 5 mm Hg in office systolic blood pressure and 2 mm Hg in office diastolic blood pressure among oral contraceptive users. Ambulatory monitoring provides a measure of blood pressure that is significantly more reproducible than traditional office measurement,[12,18] and therefore, it is more representative of an individual's usual pressure. There is increasing evidence that the target organ damage correlates best with data derived from ambulatory blood pressure monitoring.[20–22]

The most significant finding of the present study is that hypertensive oral contraceptive users with the same office blood pressure as that in hypertensive nonusers had a significantly higher ambulatory systolic blood pressure. This finding was particularly striking during daytime with a difference of 9 mm Hg; however, a significant difference was observed also throughout the night.

There are several potential mechanisms by which oral contraceptives might induce a substantial increase in blood pressure. First, activation of the renin-angiotensin system by estrogens is well documented in both animal and human studies.[3,23] Second, oral contraceptives can alter erythrocyte cation transport.[24] Third, recently some evidence for effects of estrogen on cardiac remodeling has been obtained in animal model.[25] The administration of a single large intramuscular dose of 17β-estradiol resulted in the left ventricular chamber enlargement and increased stroke volume in the ewe. Furthermore, the elevated estrogen during ovulation induction has been associated with the increased left ventricular chamber and stroke volume in humans.[26]

In the present study, the finding of an upward shift of the 24-h systolic blood pressure in oral contracep-

TABLE 3. MULTIPLE LINEAR REGRESSION IN PATIENTS USING ORAL CONTRACEPTIVES (OC) WITH 24-H AMBULATORY BLOOD PRESSURE AS A DEPENDENT VARIABLE

Variables	Coefficient	Standard Error	*t*	*P*
Dependent variable: 24-h systolic blood pressure				
Independent variables:				
Age (yr)	0.15	0.43	0.37	NS
Body mass index (kg/m^2)	−1.41	1.04	−1.36	NS
Duration of OC use (mo)	0.06	0.08	0.79	NS
Smoking status (0 for nonsmokers, 1 for smokers)	−0.12	6.16	−0.02	NS
Dependent variable: 24-h diastolic blood pressure				
Independent variables				
Age (yr)	−0.10	0.31	−0.33	NS
Body mass index (kg/m^2)	0.10	0.74	0.14	NS
Duration of OC use (mo)	0.04	0.06	0.66	NS
Smoking status (0 for nonsmokers, 1 for smokers)	−2.34	4.39	−0.53	NS

tive users without an increase in ambulatory heart rate may suggest a volume-dependent rather than a neurogenic elevation of blood pressure. The study of Manheim et al[27] is of some help in explaining our findings. They found that in both normotensive and hypertensive women 24-h ambulatory systolic blood pressure was significantly higher during the luteal phase than during the follicular phase. Both groups had significantly higher serum estradiol and progesterone levels in the luteal phase. In the present study we did not take into account the phase of menstrual cycle in which the women were at the moment of ambulatory blood pressure measurement or the day of the oral contraceptive cycle in the subjects taking the estrogen–progestogen pill. Thus, we cannot say whether the effect of oral contraceptives on ambulatory blood pressure might vary within a cycle.

The risk of cardiovascular complications among oral contraceptive users was found primarily in women more than 35 years old and in those who smoke.[3] In the present study we found no significant relation between the ambulatory blood pressure levels and age, smoking status, duration of oral contraceptive use, and body mass index. The value of this finding is limited, however, owing to a small number of subjects.

Because many of the previous studies on blood pressure and oral contraceptives involved higher doses of both estrogen and progesterone than are presently in use, the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure[28] suggested that the current incidence of oral contraceptive-induced hypertension is probably smaller than reported earlier. The present study indicates that office measurements underestimate the effect of 30-μg estrogenic oral contraceptives on blood pressure in mild hypertensive women. Whether this finding may be observed in normotensive women remains to be investigated.

The present data do not permit to draw any conclusions as to the implications of the observed elevation of ambulatory systolic blood pressure in oral contraceptive users. It would probably be misleading to try to extrapolate the present findings to explain the well-known increase in cardiovascular disease risk among oral contraceptives users.[1,2,5] However, our results indicate that oral contraceptives use should be taken into account in population studies on ambulatory blood pressure.

In conclusion, our data provide evidence that ambulatory systolic blood pressure is significantly increased in mild hypertensive women using oral contraceptives in comparison to nonusers with similar office blood pressure. Longitudinal prospective studies using ambulatory blood pressure monitoring are needed for full understanding of the effects of oral contraceptives on blood pressure. Our results support the opinion[28] that alternative methods of contraception should be considered for mild hypertensive women in place of oral contraceptives.

APPENDIX

List of centers participating in the study:

Belluno—Cardiologia: P. Pellegrini, S. Gregori; Conegliano V—Divisione Lungodegenza: M. Santonastaso, C. Mognol; Cremona—Divisione Medica: G. Garavelli; Dolo—Divisione Medica: L. Borsato, F. Pegoraro; Mirano—Cardiologia: D. D'Este, P. Borella; Padova—Clinica Medica 1: P. Palatini, C. Canali; Padova—Servizio Cardiologia: G. Maraglino, V. Accurso; Piove di Sacco—Cardiologia: C. Martines, R. Businaro; Pordenone—Centro Cardioreumatologico: G. Cignacco, G. Zanata; Portogruaro—Divisione Medica: S. Zotti, R. Gelisio; Rovereto—Ala—Divisione Medica: M. Mattarei, T. Biasion; Rovigo—Cardiologia: P. Zonzin, A. Bortolazzi, E. Ferrarese; San Daniele del Friuli—Area di Emergenza: L. Mos, O. Vriz; San Donà di Piave—Cardiologia: A. Sanson, L. Milani; Trento—Divisione Medica: G. Devenuto, M. Dal Follo; Treviso—Divisione Nefrologia: C. dalla Rosa, P. Gatti, A. Camarotto; Vittorio Veneto—Divisione Medica: F. Sanzuol, E. Cozzutti; Presi-

dent: C. Dal Palù; Vice President: A.C. Pessina; Trial Coordinator: P. Palatini.

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