Ambulatory Blood Pressure Monitoring (ABPM) in the Normal Menstrual Cycle and in Women Using Oral Contraceptives
Comparison With Conventional Blood Pressure Measurement

Paula M. Williamson, Megan L. Buddle, Mark A. Brown, and Judith A. Whitworth

This study was undertaken to determine if blood pressures (BP) assessed by routine sphygmomanometry and 24 h ambulatory monitoring (ABPM) alter throughout the normal menstrual cycle or in the cycle of women using oral contraceptive pills (OCP), and the interrelationships between urinary sodium (Na) and potassium (K) excretion and ABPM throughout the menstrual cycle.

Eleven women with a normal ovulatory cycle (ovulatory) and ten age-matched women taking an oral contraceptive pill (OCP) were studied three times in random order during their menstrual cycle, within days 1 to 5, 13 to 16, and 25 to 28. Twenty-four hour urine Na, K, and creatinine (Cr) excretion and serum Na, K, Cr, cortisol, estradiol, progesterone and plasma renin, angiotensinogen, and aldosterone concentrations were measured. BP was measured by a mercury sphygmomanometer and by 24 h BP (Accutracker II).

On days 1 to 5, daytime systolic BP was higher in OCP [mean: 123 mm Hg, 95% confidence interval: 117, 128] than ovulatory women [114 mm Hg (109, 118); P = .011] though daytime diastolic BPs were similar [OCP: 71 (68, 75), ovulatory: 69 (66, 72)]. This difference in daytime systolic BP between groups was also apparent at both of the other stages of the menstrual cycle. Nighttime systolic BPs were significantly higher in OCP users on days 13 to 16 (P < .05) and days 25 to 28 (P < .01). In women taking OCPs, daytime ABPM for days 1 to 5 were higher than their office readings by 15 (7, 23)/11 (7, 15) mm Hg (P = .001), whereas office and ABPM readings were similar in ovulatory women. This pattern was evident at all three stages. There was no significant change in BP throughout the menstrual cycle within either group, and no correlation between urine Na or K and BP.

Systolic BPs are higher throughout the menstrual cycle in women who take OCPs than in ovulatory women but this difference is only detected when ambulatory blood pressure is assessed. Blood pressure does not change subsequently in either ovulatory or OCP-taking women throughout the menstrual cycle. Am J Hypertens 1996;9:953–958

KEY WORDS: Ambulatory blood pressure measurement, menstrual cycle, oral contraceptives, renin-angiotensin system, progesterone.
There are known hypertensinogenic effects in virtually all women taking combined estrogen-progestagen oral contraceptives for 6 months or longer, though there is conflicting evidence as to whether low dose estrogen-progestagen combinations affect blood pressure (BP). It is probable that they have an effect but to a lesser extent than higher dose preparations. Recent data suggest that administration of combination oral contraceptives is associated with an increase in office systolic BP of between 2 and 7 mm Hg and an increase in office diastolic BP of between 1 and 3 mm Hg.

Interpreting the effects of oral contraceptive pills (OCP) requires comparison with age-matched women who are not taking these medications. It is possible, however, that BP may vary during a normal menstrual cycle, as found in one study that used 24 h ambulatory blood pressure monitoring (ABPM), but this was not found by others. ABPM is regarded as more representative of BP throughout a 24 h period than casual BP measurements obtained in a physician’s office or clinic setting, by providing multiple readings over time. One recent study examined office BP and ambulatory BP in Stage 1 (mild) hypertensive women taking OCP and nonpregnant, mildly hypertensive women, but this was not extended to include assessments at different stages of the menstrual cycle. As yet no published study has investigated the effects of oral contraceptives on the diurnal BP profile of normotensive women.

In documenting hypertension in women taking OCP it may be that elevated BP is more obvious at some stages of the cycle than at others, particularly when the components of the OCP vary throughout the menstrual cycle. In addition, there are hormonal changes occurring throughout the menstrual cycle, several of which (e.g., renin, aldosterone, and cortisol) are involved in the regulation of renal sodium, potassium excretion, and BP.

The aim of this study was to compare blood pressures, using ‘office’ and 24 h ABPM assessments, at different stages of the menstrual cycle in women using oral contraceptives and normally ovulating age matched women.

MATERIALS AND METHODS

Subjects Normal volunteers were 11 nonpregnant women with regular menstruation (ovulatory) and 10 age-matched women taking low dose estrogen-progestagen oral contraceptives. The OCPs contained ethinyl estradiol, the dose of which ranged from 30 to 50 μg; the most common preparation contained 30 μg combined with 50 to 150 μg levonorgestrel. All the women were healthy, not taking medication, and were not restricted in diet. Entry into the study was based upon BP measured using a routine sphygmomanometer (4 to 5 readings taken over a 20 min interval) and only those women with BP < 135/85 mm Hg were enrolled. Informed consent was obtained from each subject and the study was approved by the Southern Sydney Area Health Service Ethics Committee.

Clinical Studies Studies were conducted at 3 times during the menstrual cycle, days 1 to 5 (follicular), days 13 to 16 (ovulatory), and days 25 to 28 (luteal). Subjects entered the study at different stages of their menstrual cycle. The stage of the cycle on entry was calculated from the date of onset of menstruation. On each occasion subjects collected urine for 24 h for measurement of sodium (Na), potassium (K), creatinine (Cr), and albumin excretion the day prior to attending our clinical research room between 8:00 and 10:00 AM. After lying quietly for 30 min BP was recorded using a mercury sphygmomanometer (three readings over 10 min) and blood was collected for serum Na, K, Cr, plasma active renin (pPRC), plasma angiotensinogen (ANG), plasma aldosterone (Aldo), serum cortisol, serum estradiol, and serum progesterone concentrations. An ambulatory blood pressure monitoring device (Accutracker II, Suntech Medical Instruments, Raleigh, NC) was then placed around the right arm and worn for 24 h with BP readings every 30 min in the day and hourly readings during sleep at night. The recordings were analyzed with interactive software (Accusoft, Suntech Medical Instruments). All subjects were encouraged to carry out their normal daily routine although they were asked to avoid heavy exercise during this period. In addition, all women were instructed to remain motionless during ABPM measurements. Day and night periods corresponded to awake and asleep periods as determined from the subject’s diary. Ovulation was confirmed in each ovulatory subject by a rise in serum progesterone concentration.

Laboratory Measurements We measured pPRC as the generation of angiotensin I (AI) and Aldo by direct radioimmunoassay, as described previously. The interassay coefficients of variation (CV) for these assays were 10.6% and 10.3% for renin and Aldo, respectively, and the intraassay CVs were 7.1% and 8.9%. ANG was measured indirectly as the amount of AI released enzymatically by human renin, as described. Serum estradiol was measured by radioimmunoassay for the direct determination of 17β-estradiol (Sorin Biomedica SpA, Saluggia, Italy) and serum progesterone by Spectra Progesterone (Orion Diagnostica, Espoo, Finland). Serum cortisol was measured by direct radioimmunoassay, using an Amerlex kit (Amersham Radiochemical, Amersham, Buckinghamshire, England). Plasma and urinary electrolytes and creatinine were measured by an autoanalyzer (Perspective Analyzer, American Monitor, Indianapolis, IN). Urinary albumin concentration was mea-
asured by radioimmunoassay (Pharmacia, Uppsala, Sweden) as described previously.20

Samples from all three occasions for individual subjects were measured in the same assay to minimize variability.

**Statistics** Data for aPRC, ANG, and progesterone were expressed as median and interquartile range and all other data as mean and standard deviation (SD). Data were analyzed across the three occasions using repeated measure analysis of variance using subjects and time as factors. If data were not distributed normally these were log transformed prior to analysis. Significance of within-subject factors was examined by the method of Greenhouse and Geisser,21 as implemented by the SYSTAT statistical program (Systat Inc., Evanston, IL). If significant, the Mann-Whitney or Wilcoxon signed rank test was used if data were not normally distributed or Student's paired or unpaired t test for the other data. A correction for multiple comparisons using Hochberg and Benjamini's method was performed.22

**RESULTS**

**Subject Characteristics** Subjects were of similar age with an age range from 21 to 36 years (ovulatory mean, 27 years; and OCP mean, 25 years). Both groups had similar body mass index (BMI) values (ovulatory mean, 21.4; and OCP mean, 22.4) and two (18%) ovulatory and one woman taking OCP (10%) smoked (not significant). Serum and urinary Na were similar in the two groups throughout the menstrual cycle (Table 1). Serum and urinary K were higher in the women taking OCP than the ovulatory women in the follicular phase (P < .01 and P < .05, respectively). Urinary albumin decreased at days 13 to 16 in the OCP group (P < .05), but did not change in the ovulatory women (Table 1). There was no correlation between urine Na, K, and BP.

**Blood Pressures** Twenty-four hour ABPM systolic BP was higher in the OCP than the ovulatory group in all three phases (Figure 1). This was true for all daytime BPs and for nighttime BPs with the exception of the follicular phase. There was no difference between the two groups in diastolic BP or heart rate at any stage. Office BPs also did not differ between groups at any stage of the cycle.

In women taking OCPs, daytime and 24 h ambulatory BPs were higher than their office mercury sphygmomanometer readings whereas these readings were similar in ovulatory women (Figure 2). Ambulatory and office blood pressures did not change throughout the cycle in either group.

A power calculation using the method of Bach and Sharpe23 demonstrated sufficient power to detect a change within subjects of 7 to 8 mm Hg systolic BP

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**TABLE 1. METABOLIC AND HORMONAL MEASUREMENTS IN OVULATORY WOMEN (URINARY ALBUMIN WHERE n = 9) AND WOMEN TAKING OCP AT DAYS 1 TO 5, DAYS 13 TO 16, AND DAYS 25 TO 28 OF THE MENSTRUAL CYCLE**

<table>
<thead>
<tr>
<th>Days</th>
<th>Ovulatory (n = 9)</th>
<th>OCP (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5</td>
<td>1.4 (1.5, 3.3)</td>
<td>2.5 (1.5, 2.6)*</td>
</tr>
<tr>
<td>13–16</td>
<td>3.2 (2.5, 5.3)*</td>
<td>4.2 (1.2, 2.4)*</td>
</tr>
<tr>
<td>25–28</td>
<td>3.4 (2.7, 5.3)*</td>
<td>4.1 (1.2, 2.4)*</td>
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* Values are expressed as median (interquartile range).

**aPRC, Angiotensin II, and Progesterone (mg/mL) Compared to Days 1-5**

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<td>61 (53, 81)</td>
<td>668 (569, 703)</td>
<td>118 (105, 134)</td>
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<tr>
<td>13–16</td>
<td>349 (221)</td>
<td>406 (34, 510)</td>
<td>119 (114, 137)</td>
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<td>359 (221)</td>
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through the menstrual cycle (Power = 80% at α = 5%), a clinically meaningful BP difference.

**Plasma and Serum Hormone Concentrations (Table 1)** In ovulating women serum estradiol concentration increased at ovulation (P < .01) and fell in the luteal phase, but was still significantly higher than in the follicular phase (P < .05). Serum progesterone concentration increased at ovulation (P = .05) and was highest in the luteal phase (P < .01).

The level of aPRC increased at ovulation and in the luteal phase (P < .05) in the normal menstrual cycle but there was no change in ANG concentrations. In contrast, women taking OCP had lower aPRC at days 13 to 16 and 25 to 28 and no change in aPRC throughout the cycle. ANG concentrations were higher in the OCP group at all stages and increased significantly from days 1 to 5 to days 13 to 16 and 25 to 28 (P < .01). Serum cortisol concentration was higher at all stages in women taking OCP as compared with ovulatory women (days 1 to 5: P < .01; days 13 to 16 and 25 to 28: P < .001). In the OCP group cortisol rose further at days 13 to 16 (P < .01) and days 25 to 28 (P < .05), whereas no change occurred in ovulatory women. Aldo was initially higher in OCP women but did not change through their cycle. In contrast, aldosterone (like aPRC) rose significantly by the luteal phase in ovulatory women.

Twenty-four hour systolic BP correlated only with ANG on days 1 to 5 and days 13 to 16 when the two groups were combined. Blood pressures did not correlate with any of the above hormones when the groups were analyzed separately.

**DISCUSSION**

Twenty-four hour and daytime ambulatory systolic BP were higher at the commencement and throughout the menstrual cycle in women who took OCP than in ovulatory women. However, there was no change during the cycle in either ambulatory or office BP within groups, despite changes in vasoactive hormones.

Even though these normotensive oral contraceptive users had a 10 mm Hg greater daytime ambulatory systolic BP than ovulatory women, they had similar office BPs, as Narkiewicz et al. found in their study of mildly hypertensive women. In our study, the observation that daytime ambulatory systolic BPs were higher than corresponding office BP (taken after 30 min of recumbent rest) was not observed in ovulatory women. Therefore, this study confirms that normotensive women using combination OCP have increased systolic BP that is not evident in their office BP results.

We could not explain this on the basis of lower office BP in women using OCPs compared to ovulating...
women. An increase in activity in women on OCP during 24 h ABPM was also unlikely as heart rate was similar in the two groups. The observation that BPs are similar at rest yet disparate during normal activity implies greater vasoreactivity in OCP women during ambulation. This cannot be the sole explanation as nocturnal systolic BP was also higher in the OCP group.

In our study, 24 h ambulatory systolic BP was about 10 mm Hg higher in OCP women than in ovulatory women, a greater difference than in studies that used mercury sphygmomanometry in larger numbers of subjects. Our ambulatory diastolic BP findings were more consistent with previous studies that found a difference of 1 to 3 mm Hg, though in our study this was a numerical rather than a statistically significant difference. We found that this increase in systolic BP in women using OCPs was sustained throughout the cycle though ambulatory BPs did not change within ovulatory women or those taking OCPs throughout the menstrual cycle. This is in keeping with the observations of two other studies examining only ovulatory women. Karpanou et al used 24 h ABPM on day 5, at ovulation (measured by luteinizing hormone in urine) and a week after ovulation; Hjertberg et al likewise measured 24 h ABPM in the follicular and luteal phases, as measured by serum progesterone levels. Both studies found no difference in any BP parameter between these time points in 27 and 21 normotensive women, respectively. Manhem et al reported that in both normotensive and hypertensive women 24 h systolic BP was significantly higher during the luteal than follicular phase, though their actual ABPM values were not included. Overall, there have been few studies assessing ambulatory blood pressure throughout the menstrual cycle and as yet no published study has investigated the effect of oral contraceptives on the diurnal BP profile through the menstrual cycle in normotensive women. We have confirmed the observation of Narkiewicz et al that ambulatory systolic BP is higher in OCP users and extended their findings to show that this occurs in normotensive OCP users, not only in hypertensives. Furthermore, this effect is independent of the stage of the menstrual cycle in which the blood pressure is measured.

The hormonal results confirmed previous studies and did not provide new information on the mechanisms involved in different blood pressures between women taking OCP and ovulatory women during the menstrual cycle. The increased serum cortisol concentrations in women taking OCP is thought to be due to an increase in serum free cortisol as well as corticosteroid-binding globulin. Serum cortisol increased at days 13 to 16 and days 25 to 28 with no subsequent rise in BP in women taking oral contraceptives. This result was consistent with a previous study where women given 0.3 mg/day ethinyl estradiol over a 5 day period showed no rise in BP despite increased concentrations of serum cortisol and plasma ANG.

In summary, this study demonstrates that com-
bined estrogen and progestagen oral contraceptives raise systolic blood pressure by about 10 mm Hg in normotensive women, an effect that is not apparent unless ambulatory blood pressure monitoring is employed. Subtle and long-term effects of slight increases in blood pressure within the normal range on cardiovascular morbidity in normotensive women taking low dose oral contraceptives have not been examined and so cannot be ignored. Secondly, we have found that 24 h blood pressure does not vary in the normal menstrual cycle or in the cycle of women taking the oral contraceptive pill despite changes in cortisol, renin, and aldosterone. Thus, it is reasonable that blood pressure assessment in women be carried out at any stage of their menstrual cycle.

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REFERENCES


