Blood Pressure Patterns in Normal Pregnancy, Gestational Hypertension, and Preeclampsia

Ramón C. Hermida, Diana E. Ayala, Artemio Mojón, José R. Fernández, Ignacio Alonso, Inés Silva, Rafael Ucieda, Manuel Iglesias

Abstract—With the aim to describe the daily pattern of blood pressure during the trimesters of pregnancy in clinically healthy women as well as in pregnant women who developed gestational hypertension or preeclampsia, we analyzed 1494 blood pressure series systematically sampled by ambulatory monitoring for 48 hours every 4 weeks after the first obstetric visit in 124 women with uncomplicated pregnancies, 55 with gestational hypertension, and 23 with a final diagnosis of preeclampsia. The circadian pattern of blood pressure variation for each group and trimester of gestation was established by population multiple-component analysis. A highly statistically significant circadian pattern represented by a linear model that includes components with periods of 24 and 12 hours is demonstrated for systolic and diastolic blood pressure for all groups of pregnant women in all trimesters (P<0.001 in all cases). The differences in circadian rhythm–adjusted mean between complicated and uncomplicated pregnancies are highly statistically significant in all trimesters (always P<0.001). There is also a statistically significant difference in circadian amplitude (extent of daily change) of blood pressure between healthy and complicated pregnancies in all trimesters (always P<0.004). Results further indicate similar circadian characteristics between women who later developed gestational hypertension or preeclampsia in the first trimester of pregnancy. The difference between these 2 groups in circadian mean is statistically significant in the second trimester for systolic (P=0.022) but not for diastolic blood pressure (P=0.986). In the third trimester, the difference in circadian mean is highly statistically significant for both variables (P<0.001). The differences in blood pressure between healthy and complicated pregnancies can be observed as early as in the first trimester of pregnancy. Those highly significant differences are found when both systolic and diastolic blood pressure for women with a later diagnosis of gestational hypertension or preeclampsia are well within the accepted normal physiological range of blood pressure variability. These differing changes in the circadian pattern of blood pressure with advancing gestational age between healthy and complicated pregnancies offer new end points that may lead to an early identification of hypertensive complications in pregnancy as well as to the establishment of prophylactic intervention. (Hypertension. 2000;36:149-158.)

Key Words: blood pressure ■ circadian rhythm ■ pregnancy ■ hypertension, gestational ■ normotension ■ preeclampsia

Blood pressure (BP) assessment in pregnant women has relied mostly on a few measurements taken in the physician’s office. These casual time-unspecified measurements perform poorly, even in the third trimester of pregnancy, in selection of a population for potential detection of preeclampsia. Isolated BP measurement is, however, still the mainstay of the diagnosis of preeclampsia. The use of a reliable and accurate automated device for ambulatory BP monitoring (ABPM) is the logical approach to overcoming many of the problems associated with conventional BP measurement. ABPM has the added advantage that in addition to the immediate presentation of absolute BP values, it gives the extra dimension of facilitating analysis of the circadian variation of BP in pregnancy. Both systolic BP (SBP) and diastolic BP (DBP) vary in adulthood on the average >50 mm Hg within each day. Such circadian BP variability also characterizes clinically healthy pregnant women as well as women who developed gestational hypertension or preeclampsia. During gestation, another source of variability comes from the predictable pattern of BP changes along pregnancy. In clinically healthy pregnant women, BP steadily decreases up to the middle of gestation and then increases up to the day of delivery, with final BP values similar to those found early in pregnancy in the same women. For women who developed gestational hypertension or preeclampsia, BP is stable during the first half of preg-
nancy and then continuously increases until delivery. These predictable patterns of BP variability during pregnancy are somehow independent from the continuous linear increase in maternal weight with gestational age.

Changes in circadian variation of BP could be used either to predict preeclampsia or to assess its severity. Although reference values are now available for 24-hour ABPM in nonpregnant patients, only a few studies have been made on the normal pattern of ABPM in uncomplicated pregnancies, most of them without comparison with the circadian pattern of BP in complicated pregnancies, an issue only occasionally addressed. Normal values for 24-hour ABPM have been determined in at least 2 of the most extensive studies done so far in pregnancy, the first in a primigravid population of 98 women sampled at 5 different gestational ages and the second in 71 normotensive pregnant women systematically sampled every 4 weeks starting on the first trimester of pregnancy. This later study also provided comparison for the circadian BP variation between healthy and complicated pregnancies. Results indicated statistically significant differences in BP between healthy and complicated pregnancies as early as in the first trimester of pregnancy; at this stage of gestation, both SBP and DBP for healthy and complicated pregnancies were still within the accepted normal physiological range of BP variability. Moreover, by the use of ABPM, several authors have found a reduced drop in BP by night in preeclamptic patients, whereas others even report an inversion of the circadian pattern of change in BP associated with preeclampsia. Most of the later studies have usually been performed during the last stages of pregnancy. Limitations of these studies came also from the inability to properly describe the nonsinusoidal waveform of circadian BP variability. In the attempt to corroborate and extend conclusions from previous studies, we report results from a prospective study of BP variability during pregnancy. In particular, we have used a recently developed method for analysis of nonsinusoidal time series with unequidistant sampling to examine and compare characteristics of circadian variability in BP of clinically healthy pregnant women as well as women with gestational hypertension or preeclampsia who were systematically monitored throughout gestation.

Methods

Subjects
We studied 202 (126 primipara) white pregnant women (124 with uncomplicated pregnancies, 55 who developed gestational hypertension, and 23 who developed preeclampsia) who fulfilled all required criteria for this trial (see below). Diagnosis of gestational hypertension (conventional BP values >140/90 mm Hg for SBP/DBP after the 20th week of gestation without clinical record of hypertension previous to pregnancy) or preeclampsia (gestational hypertension and proteinuria, >300 mg in 24 hours of urine; hypertension, >149/95 mm Hg for SBP/DBP at the 20th week of gestation, presence of proteinuria, defined as >300 mg of protein in 24 hours of urine collection with or without edema, diagnosed after the 20th week of gestation in a previously normotensive woman) was done with information from the conventional obstetric examinations and routine analyses of urine. The demographic baseline characteristics of the women investigated are included in the Table. All women received obstetric care at the Obstetric Physiopathology Unit, Hospital Clinico Universitario, Santiago de Compostela, Spain. Reasons for receiving medical care at this unit include, among others, family or personal history of either gestational hypertension, preeclampsia or chronic hypertension; cardiovascular, endocrine, bleeding, or metabolic diseases; personal history of spontaneous abortion; and no other endocrine disease such as hyperthyroidism, and intolerance to the use of antiinflammatory medication, diabetes or any other endocrine disease such as hyperthyroidism, and intolerance to the use of an ABPM device. Apart from the 202 women providing all required information, 11 subjects who provided <5 profiles of ABPM (3 spontaneous abortions and 8 who withdrew from the trial) were eliminated from the study. The State Ethics Committee of Clinical Research approved the study. All volunteers signed consent forms before entering the study.

BP Assessment
The SBP and DBP of each of the 202 subjects who completed the trial were automatically monitored every 30 minutes during the day (9 AM to 10 PM) and hourly during the night for 48 hours with an ABPM-630 Colin device at the time of recruitment and then every 4 weeks until delivery. BP series were eliminated from analysis when they showed an irregular schedule during the days of sampling, an odd sampling with spans of >3 hours without BP measurement, or a night resting span <6 hours or >12 hours. The total number of BP series provided by the women under investigation fulfilling all mentioned requirements set a priori was 1494. During sampling, all women were living on their usual diurnal waking (~9 AM to approximately midnight) and nocturnal resting routine, following everyday life conditions with minimal restrictions. They were told to follow a similar schedule during the days of sampling and to avoid the use of medication for the duration of the trial. The monitor measures BP by dual microphone auscultation by means of Korotkoff phase 1 for SBP and phase 5 for DBP; it also provides a more sensitive oscillometric mode to assess BP. The clinical evaluation of the monitor according to the standards published by the Association

Demographic Characteristics of Subjects Investigated

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects, n</th>
<th>BP Series, n</th>
<th>Age, y</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>SBP at Inclusion, mm Hg</th>
<th>DBP at Inclusion, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotension</td>
<td>124</td>
<td>971</td>
<td>30.0±5.5</td>
<td>62.8±9.5</td>
<td>161.9±5.5</td>
<td>119.6±9.8</td>
<td>65.0±7.2</td>
</tr>
<tr>
<td>Gestational hypert</td>
<td>55</td>
<td>382</td>
<td>30.6±4.9</td>
<td>74.2±18.3</td>
<td>162.4±6.9</td>
<td>121.3±9.1</td>
<td>66.2±7.7</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>23</td>
<td>141</td>
<td>32.2±5.6</td>
<td>76.5±12.8</td>
<td>162.9±5.1</td>
<td>120.4±8.8</td>
<td>64.3±8.5</td>
</tr>
</tbody>
</table>

All values given in mean±SD, when appropriate.
for Advancement of Medical Instrumentation has been previously established. The BP cuff was worn on the nondominant arm. ABPM was performed in addition to the woman’s routine antenatal care, and no person was hospitalized during monitoring. Cuff size was determined by upper arm circumference at the time of each visit. ABPM always started between 10 AM and 1 PM. During monitoring, each subject maintained a diary regarding information about their activity cycle, dietary consumption, physical activity, emotional state, and other external or internal stimuli possibly affecting BP.

### Statistical Methods

Original oscillometric data from each BP series were first synchronized according to the rest-activity cycle of each individual by recomputing all times of sampling in hours from bedtime to avoid differences among subjects in actual times of daily activity and to express results in circadian time rather than in less meaningful clock hours. After synchronization, BP values were edited according to commonly used criteria for the removal of outliers and measurement errors. The remaining data were analyzed by the use of Chronolab, a software package for biological signal processing by linear and nonlinear least-squares estimation. The circadian rhythm in BP for each group of pregnant women (healthy or complicated pregnancies, as well as gestational hypertension and preeclampsia separately) in each trimester of gestation was established by population multiple-component analysis. A method designed for analysis of nonsinusoidal hybrid data (time series of data collected from a group of subjects) with unequidistant observations.

The method provides estimates of the rhythm-adjusted mean or MESOR (midline estimating statistic of rhythm, defined as the average value of the rhythmic function fitted to the data), as well as the amplitude, defined as half the difference between the maximum and the minimum of the fitted curve in one fundamental period; the orthophase, defined as the lag from a defined reference time point of the crest time in the curve fitted to the data for every fitted component. When all fitted components are harmonics from a fundamental period, the method of multiple components also provides 3 additional parameters: the overall amplitude, defined as half the difference between the maximum and the minimum of the best fitted curve in one fundamental period; the orthophase, defined as the lag from a defined reference time point of the crest time, within a fundamental period, in the curve of multiple components fitted to the data; and the bathyphase, defined as the lag from a defined reference time point of the time of the lowest value, within a fundamental period, in the curve of multiple components fitted to the data.

The parameters of the circadian rhythm (obtained by population multiple component analysis) for SBP and DBP were subsequently compared between groups of women in each trimester of pregnancy with a nonparametric test developed to compare parameters obtained from population multiple components analysis. Additionally, the demographic characteristics included in the Table were compared between groups of pregnant women by ANOVA.

### Results

Results from ANOVA for the data included in the Table indicate statistically significant differences in baseline characteristics between the 3 groups of pregnant women investigated in maternal weight (P=0.001) but not in age (P=0.219), height (P=0.749), or casual BP values at the time of the first visit to the hospital (P=0.624 and 0.588 for SBP and DBP, respectively). The Table further indicates statistically significant differences in casual BP at the time of delivery (P<0.001 for both SBP and DBP), gestational age at delivery (P=0.024), newborn weight (P=0.007), and Apgar scores at 1, 5, and 10 minutes after birth (P=0.074, 0.003, and 0.003, respectively).

For the normotensive pregnant women, no difference was found between circadian BP characteristics obtained as a function of parity or age for any trimester of pregnancy. Data from the whole database were therefore pooled for subsequent analysis and only divided according to gestational age and pregnancy outcome. Individually, a statistically significant 24-hour component was obtained for 96% of the SBP and 94% of the DBP profiles sampled from normotensive pregnant women, with a significant second harmonic (12 hours component) characterizing 55% and 57% of the profiles for SBP and DBP, respectively. For women with complicated pregnancies, the 24-hour component was statistically significant for 91% and 92% of the profiles for SBP and DBP, respectively, whereas the 12-hour component was significant for 56% of the SBP profiles and for 59% of the DBP profiles. Other ultradian harmonic components were significant in <17% of the profiles for any group or trimester of pregnancy. A statistically significant increase in the coefficient of determination (percentage of overall variability explained by the function fitted to the data) was only obtained after including in the model of multiple components periods of 24 and 12 hours for both SBP and DBP for any group of women and trimester of gestation. From the population point of view, although other ultradian components can be demonstrated as statistically significant in a small percentage of subjects, a rather simple model including only the 2 first harmonics of the 24-hour period describes sufficiently well, at the specified sampling rate, the circadian pattern of BP in both healthy and complicated pregnancies.

The parameters of the circadian rhythm (obtained by population multiple component analysis) for SBP and DBP in each trimester of pregnancy for clinically healthy women as well as for pregnant women with a final diagnosis of gestational hypertension or preeclampsia are indicated in the tables at the bottom of Figures 1 through 3. Compared with uncomplicated pregnancies, a statistically significant elevation of the circadian MESOR of BP is found in pregnancies with gestational hypertension or preeclampsia in all trimesters (P<0.001 for both SBP and DBP). There is also a statistically significant difference in the circadian amplitude of both SBP and DBP between healthy and complicated pregnancies.

### Table

<table>
<thead>
<tr>
<th>SBP at Delivery, mm Hg</th>
<th>DBP at Delivery, mm Hg</th>
<th>Gestational Age at Delivery, wk</th>
<th>Newborn Wt, g</th>
<th>Newborn Apgar Score at 1 min</th>
<th>Newborn Apgar Score at 5 min</th>
<th>Newborn Apgar Score at 10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>118.3±12.2</td>
<td>67.2±9.7</td>
<td>39.7±1.4</td>
<td>3315±457</td>
<td>8.86±0.94</td>
<td>9.92±0.31</td>
<td>9.98±0.14</td>
</tr>
<tr>
<td>126.6±13.0</td>
<td>72.0±10.5</td>
<td>39.0±3.7</td>
<td>3139±542</td>
<td>8.96±0.21</td>
<td>9.91±0.28</td>
<td>10</td>
</tr>
<tr>
<td>130.2±12.5</td>
<td>75.8±10.7</td>
<td>38.2±2.8</td>
<td>2918±844</td>
<td>8.26±2.60</td>
<td>9.16±2.50</td>
<td>9.37±2.31</td>
</tr>
</tbody>
</table>
Figure 1. Circadian variation of systolic (left) and diastolic (right) BP in normotensive pregnant women and women with final diagnosis of gestational hypertension or preeclampsia sampled in first trimester of pregnancy (top). Comparison between these 2 later groups is shown at bottom. Probability value is from testing zero-amplitude assumption. MESOR indicates average value of rhythmic function fitted to data (in mm Hg); AMP, amplitude, half the difference between maximum and minimum of fitted curve (in mm Hg); ORTHOPH, orthophase, lag from defined reference time point (here, bedtime) of crest time in curve fitted to data (in angular degrees, with 360°=24 hours); BATHYPH, bathyphase, lag from same reference time point of time of lowest value in curve fitted to the data; and CI, 95% confidence intervals. Curve represented for each group corresponds to best fitted model obtained by population multiple components analysis (with corresponding characteristics given in table below each chronogram). Arrows from upper horizontal axis indicate circadian orthophases for each group.
pregnancies in all trimesters of gestation ($P<0.004$ for both cardiovascular variables in all trimesters).

The elevation of SBP and DBP during the first trimester of pregnancy in subjects with a later diagnosis of gestational hypertension or preeclampsia as compared with clinically healthy pregnant women is shown in Figure 1 (top). This figure represents a circadian population chronogram (display of data as a function of time), with hourly means and standard errors of data computed as follows: First, hourly means are computed from each individual series, after stacking all data sampled during a 48-hour monitoring span in only 1 idealized 24-hour span (given the highly statistically significant rhythm with a period of 24 hours demonstrated in about 94% of all BP series studied). In a second step, the average of those individual means at each interval is computed averaging across the total number of series for any given population. The lower horizontal axis represents circadian time in hours after bedtime; the resting span is indicated by the dark bar in the lower horizontal axis. The nonsinusoidal curve represented for each group corresponds to the best fitted model obtained by population multiple components analysis applied to all original BP values (not just to the hourly means). The arrow from the upper horizontal axis indicates the circadian orthophase for each group. Statistically significant differences between hourly means for each group (detected by $t$ test adjusted for multiple testing) at any given interval are indicated by an asterisk above the lower horizontal axis. Differences in rhythm characteristics (as is the case here for the circadian MESOR and amplitude) as well as the general waveform of circadian variability in SBP and DBP can be readily seen from this graphic representation. The characteristics of the circadian rhythm, including information on the number of BP series analyzed for each group, are represented in the tables below each chronogram. Figure 1 also includes, on the bottom, chronograms comparing the circadian pattern of SBP (left) and DBP (right) between women who developed gestational hypertension and preeclampsia. The comparison of circadian characteristics indicates similar parameters between these 2 groups of complicated pregnant women sampled in the first trimester of their gestation (always $P>0.189$ for comparisons of MESOR and amplitude of SBP and DBP).

Figure 2 (top) represents the circadian chronograms of SBP (left) and DBP (right) of women sampled during the second trimester of pregnancy. The differences between normotensive and hypertensive women are highly statistically significant at all circadian times. The circadian MESOR of BP for normotensive pregnant women is statistically lower in the second as compared with the first trimester ($P<0.001$ for both SBP and DBP). The decrease in BP cannot be demonstrated, however, for women with a final diagnosis of gestational hypertension or preeclampsia. In this second trimester of pregnancy, a statistically significant difference in circadian MESOR between gestational hypertension and preeclampsia is demonstrated for SBP ($P=0.022$) but not for DBP ($P=0.986$). The bottom chronograms of Figure 2 further indicate the lack of differences in circadian amplitude between these 2 groups of women (always $P>0.158$).

The chronograms at the top of Figure 3, comparing SBP and DBP between healthy and complicated pregnancies sampled in the third trimester of gestation, indicate larger differences than those shown in Figures 1 and 2 for the first and second trimesters of pregnancy. Besides the statistically significant difference in circadian MESOR between both groups, the hourly means of SBP and DBP are statistically significantly higher in women with gestational hypertension or preeclampsia at all sampling times. As compared with the second trimester, BP slightly increases for normotensive pregnant women, reaching a circadian MESOR comparable to that computed in the first trimester for the same subjects (Figure 1). For women with complicated pregnancies, however, BP increases greatly from the second to the third trimester. The trend of increasing BP with gestational age during the second half of pregnancy is larger for women who developed preeclampsia as compared with gestational hypertension without proteinuria. In the third trimester, the difference in circadian MESOR between gestational hypertension and preeclampsia is highly statistically significant for both SBP and DBP ($P=0.001$). The comparison of circadian amplitude indicates no difference in either SBP ($P=0.188$) or DBP ($P=0.742$). There was no significant difference in circadian orthophase between groups of pregnant women compared at any trimester.

Despite the differences observed in Figures 1 through 3, diagnosis of hypertensive complications in pregnancy cannot rely on BP measurements obtained at any given individual circadian time.$^{1,2,4}$ To illustrate this point, we focused the analysis of all BP values sampled between 10 AM and 1 PM, the usual timing of most scheduled visits of pregnant women to the obstetrician at Spanish hospitals, including our own setting. Results indicate the high degree of overlap between the distributions of SBP and DBP values obtained from healthy and complicated pregnancies. During the first trimester, there was a total overlap of 97% of all 1920 SBP values sampled between 10 AM and 1 PM (98% overlap for DBP). Women who later developed gestational hypertension or preeclampsia had at those times SBP values as low as 75 mm Hg, with only 48 out of a total of 548 SBP values actually exceeding 140 mm Hg. During the second trimester, BP decreases for healthy pregnant women but not for those who develop gestational hypertension.$^{12,13}$ The degree of overlap in SBP is of 97%; only 153 of the 1886 SBP values obtained from complicated pregnancies exceeded 140 mm Hg. Results were almost similar during the third trimester, when most of the pregnant women investigated actually developed gestational hypertension or preeclampsia. In this last trimester of pregnancy, the overlap between normotensive and hypertensive pregnant women in casual values of SBP was 98%; only 288 of 2113 values sampled from pregnant women with gestational hypertension or preeclampsia exceeded 140 mm Hg. The use of these casual measurements for diagnostic purposes indicates a very poor sensitivity consistently $<10\%$. These results are comparable to those reported previously from other studies based on conventional casual BP sampling.$^{3,6}$ Specificity is, however, very high, because a very small number of BP samples
Figure 2. Circadian variation of systolic (left) and diastolic (right) BP in normotensive pregnant women and women with final diagnosis of gestational hypertension or preeclampsia sampled in second trimester of pregnancy (top). Comparison between these 2 later groups is shown at bottom. Probability value is from testing zero-amplitude assumption. MESOR indicates average value of rhythmic function fitted to data (in mm Hg); AMP, amplitude, half the difference between maximum and minimum of fitted curve (in mm Hg); ORTHOPH, orthophase, lag from defined reference time point (here, bedtime) of crest time in curve fitted to data (in angular degrees, with 360°=24 hours); BATHYPH, bathyphase, lag from same reference time point of time of lowest value in curve fitted to data; and CI, 95% confidence intervals. Curve represented for each group corresponds to best-fitted model obtained by population multiple components analysis (with corresponding characteristics given in table below each chronogram). Arrows from upper horizontal axis indicate circadian orthophases for each group.
Figure 3. Circadian variation of systolic (left) and diastolic (right) blood pressure in normotensive pregnant women and women with final diagnosis of gestational hypertension or preeclampsia sampled in third trimester of pregnancy (top). Comparison between these 2 later groups is shown at bottom. Probability value is from testing zero-amplitude assumption. MESOR indicates average value of rhythmic function fitted to data (in mm Hg); AMP, amplitude, half the difference between maximum and minimum of fitted curve (in mm Hg); ORTHOPH, orthophase, lag from defined reference time point (here, bedtime) of crest time in curve fitted to data (in angular degrees, with 360° = 24 hours); BATHYPH, bathyphase, lag from same reference time point of time of lowest value in curve fitted to data; and CI, 95% confidence intervals. Curve represented for each group corresponds to best-fitted model obtained by population multiple components analysis (with corresponding characteristics given in table below each chronogram). Arrows from upper horizontal axis indicate circadian orthophases for each group.
actually exceeds the limit of 140/90 mm Hg for SBP/DBP, even in the third trimester.

Discussion
The fit of multiple components that are statistically and biologically significant accounts for nonsinusoidal waveforms and provides parameters characterizing them. When the data are nonsinusoidal, as in the case of BP, the least-squares fit of a cosine curve, frequently used before also in the context of pregnancy, may be used for rhythm detection, although this approach is not as powerful as the simultaneous fit of all statistically significant components. The probability value obtained in testing the zero-amplitude assumption in fitting a unique component by population-mean cosinor should thus be regarded as reflecting whether the data are better approximated by a cosine curve than by a horizontal line. When more than 1 period is statistically significant over the span of time investigated or when the waveform is nonsinusoidal, the use of a population multiple components analysis to fit a model consisting of several cosine functions, preferably harmonics from 1 fundamental period, to data sampled from several individuals is recommended. The use of multiple components analysis has been limited by the fact that the method was only applicable for the analysis of longitudinal time series (data sampled from only 1 individual). On the other hand, the advantages of using rhythm parameters (MESOR and amplitude) compared with usual statistics (mean and range) when describing the pattern of circadian BP variability have already been described.

Since the data were obtained at an unequalidistant sampling rate covering 2 cycles (48 hours), the MESOR provides a better estimation of the true 24-hour mean than the average of all BP values (usually overestimating the true mean as the result of the denser sampling during activity). The MESOR and the mean are only mathematically equal when the data are obtained at an equidistant sampling rate covering an integer number of cycles, a situation far from real in most clinical applications. The double amplitude provides information about the extent of total predictable change in BP along the 24 hours. Since the amplitude but not the range is computed from the best fitted curve to original values, it contains information about BP variability obtained from the whole data series. The range, on the contrary, only reflects the difference between the maximum and minimum single values. These extreme values are too frequently associated to measurement errors or samples influenced by external stimuli.

Results from Figure 1 indicate a highly statistically significant difference in the circadian variability of SBP and DBP between complicated and uncomplicated pregnant women sampled by ABPM during the first 14 weeks of gestation. These differences could not be demonstrated, however, by relying on the casual BP measurements obtained at the time of the first visit to the hospital (Table). The differences in BP during the first trimester of pregnancy are statistically significant at each and every hourly interval in which the 24-hour span was divided for comparative analysis. These differences are found several months before the actual clinical diagnosis of gestational hypertension was made (usually obtained well advanced the third trimester of pregnancy). Moreover, the differences of about 12 mm Hg in the circadian MESOR of SBP and of 7 mm Hg in DBP are found when both SBP and DBP for women with a later diagnosis of gestational hypertension or preeclampsia are well within the accepted normal physiological range of BP variability. The circadian MESOR for the group of women with complicated pregnancies was 115.3/67.2 mm Hg for SBP/DBP; the hourly means were always <127/76 mm Hg for the same variables. Although women with a final diagnosis of gestational hypertension or preeclampsia have higher weight at the time of recruitment than normotensive pregnant women (Table), maternal weight alone cannot explain the highly statistically significant differences in BP found as early as in the first trimester of pregnancy among those 2 groups of women (Figure 1, top). On the one hand, for normotensive pregnant women, the correlation between the circadian MESOR of BP and maternal weight or body mass index, although significant (P = 0.008) is very small (correlation coefficient r = 0.132).

On the other hand, weight increases linearly with gestational age in all groups of pregnant women; as indicated before, BP is characterized, however, by predictable patterns of variation along pregnancy markedly different for healthy and complicated pregnant women. Thus, although weight increases, for normotensive pregnant women, BP steadily decreases up to the middle of gestation, whereas for women with hypertensive complications in pregnancy, BP is stable during the first half of pregnancy.

As in the first trimester, the highly statistically significant differences between healthy and complicated pregnancies documented in the second trimester (Figure 2), exceeding 13 mm Hg in the circadian MESOR of SBP and 7 mm Hg in the circadian MESOR of DBP, are found with BP values well below 140/90 mm Hg even for the hypertensive women. The documented differences in the circadian MESOR between healthy pregnant women and pregnant women with complications sampled during the third trimester are, however, inverse similar patterns for both SBP and DBP in the first trimester of pregnancy (bottom of Figure 1). Differences are statistically significant in the second trimester for the circadian MESOR of SBP but not for DBP (bottom of Figure 2). A larger increase in BP with advancing gestational age during the second half of pregnancy characterizes preeclampsia as compared with gestational hypertension. Differences in circadian MESOR are therefore statistically significant for both SBP and DBP in the third trimester (bottom of Figure 3), which may be too late for a proper early identification and further prophylactic intervention of preeclampsia as compared with gestational hypertension.

Figures 1 through 3 also show differences in circadian amplitude between healthy and complicated pregnancies in all trimesters of gestation. Figures 1 and 2 indicate that during the first and second trimesters of pregnancy, before the clinical diagnosis of disease for most women investigated, the circadian amplitude of BP is statistically higher in complicated pregnancies, specially for the subgroup of women who developed preeclampsia. An increase in circadian amplitude...
of BP before the actual onset of hypertension (elevation in circadian MESOR) was also noted in several previous studies. The circadian amplitude of BP is statistically higher in neonates with a family history of hypertension and cardiovascular disease as compared with those without such history. By 14 years of age, correlations are found between the circadian amplitude of DBP and target organ involvement, namely the thickness of the interventricular cardiac septum determined by M-mode echocardiography. Figure 3 indicates that in the third trimester of pregnancy, the difference in circadian amplitude of BP between the groups compared is still statistically significant. For the pregnant women with complications, the amplitude decreases from the second to the third trimester. This is mainly due to the reduced drop in BP by night (and therefore reduced circadian amplitude) with advancing gestational age in the patients who developed preeclampsia. The differences in amplitude between healthy and complicated pregnancies in this last trimester stand from the lack of reduction in amplitude for the women who developed gestational hypertension but not preeclampsia (bottom graphs of Figures 1 through 3). A decrease in BP amplitude could then provide useful information in the identification of those women with an elevated BP in pregnancy that could also develop proteinuria, an issue that needs further investigation in larger groups of women studied longitudinally throughout gestation.

Results from this prospective study on pregnant women systematically sampled by ABPM along gestation corroborate earlier conclusions indicating that diagnosis of hypertensive complications in pregnancy cannot rely on casual BP measurements obtained at the physicians office. Moreover, despite the highly statistically significant differences in the circadian MESOR of BP between healthy and complicated pregnancies illustrated in Figures 1 through 3, results from previous retrospective and prospective studies indicate that due to the large overlap in the distributions of the circadian MESOR between these 2 groups of pregnant women, an individualized diagnosis cannot rely on just the 24-hour mean of BP. These poor results from the use of a test based on mean BP values have led many authors to extrapolate erroneously that ABPM is not a valid approach in pregnancy.

Other indexes obtained from the BP series have been shown, however, to identify early in pregnancy those women who subsequently will develop gestational hypertension or preeclampsia. The circadian pattern with large amplitude that characterizes BP in healthy pregnancies, as indicated in Figures 1 through 3, suggests that the constant threshold currently used for diagnosing hypertension in pregnancy should be replaced by a time-specified reference limit reflecting the mostly predictable BP variability. This circadian pattern of BP also indicates that diagnosis should not be based on average values, such as the daily, diurnal, or nocturnal means, which do not take into account most of the variability in BP. Once the time-varying threshold, given for instance by the upper limit of a tolerance interval, is available, the hyperbaric index, as a proper determinant of BP excess, can be calculated as the total area of any given patient’s BP above the threshold. This so-called tolerance-hyperbaric test has been shown prospectively to provide high sensitivity and specificity for the very early identification of subsequent hypertensive complications in pregnancy. For the women investigated in this study, sensitivity of the tolerance-hyperbaric test was 94% for women sampled during the first trimester of gestation and increased up to 99% in the third trimester. The positive and negative predictive values were >97% in all trimesters. The relative risk was 44 in the first trimester and increased 5-fold in the third trimester of pregnancy. However, results from the use of this test did not provide information on an individualized diagnosis of preeclampsia as compared with gestational hypertension only. Along these lines, the differing changes in the circadian pattern of BP with advancing gestational age in normal pregnancy, gestational hypertension, and preeclampsia demonstrated offer new end points for the design and future prospective evaluation of a test for the early diagnosis of preeclampsia based on information obtained from ABPM, which could also be used as a guide for establishing preventive interventions.

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References


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Ramón C. Hermida, Diana E. Ayala, Artemio Mojón, José R. Fernández, Ignacio Alonso, Inés Silva, Rafael Ucieda and Manuel Iglesias

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