Differences in Circadian Blood Pressure Variability During Gestation Between Healthy and Complicated Pregnancies

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

Background: Changes in circadian variation of blood pressure (BP) could be used either to predict preeclampsia or to assess its severity. We examined and compared characteristics of circadian variability in BP in women with both healthy and complicated pregnancies who were systematically monitored throughout gestation.

Methods: We analyzed 2430 BP series sampled by ambulatory monitoring for 48 h once every 4 weeks from the first obstetric visit until delivery in 235 women with uncomplicated pregnancies, 128 with gestational hypertension, and 40 with preeclampsia. The circadian pattern of BP variation for each group and trimester of gestation was established by population multiple-components analysis.

Results: The differences in 24-h mean and amplitude between healthy and complicated pregnancies were highly significant in all trimesters (P < 0.001). Results further indicated similar circadian characteristics between gestational hypertension and preeclampsia in the first trimester of pregnancy. The difference between these two groups in 24-h mean was statistically significant for systolic (P = 0.002) and diastolic BP (P = 0.038) in the second trimester and, to a larger extent, in the third trimester (P < 0.001).

Conclusions: The differences in BP between healthy and complicated pregnancies that can be observed as early as in the first trimester of pregnancy are found when both systolic and diastolic BP for women with a later diagnosis of gestational hypertension or preeclampsia are well within the accepted range of normotension. These differences 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. Am J Hypertens 2003;16:200–208 © 2003 American Journal of Hypertension, Ltd.

Key Words: Blood pressure, ambulatory monitoring, circadian rhythm, pregnancy, normotension, gestational hypertension, preeclampsia.

Despite their extremely poor sensitivity and specificity, the diagnosis of gestational hypertension still relies on office blood pressure (BP) measurements and the use of arbitrary constant critical thresholds, 140/90 mm Hg for systolic BP (SBP)/diastolic BP (DBP) after 20 weeks of gestation in a previously normotensive woman.1,2 Recent studies have tried to overcome the poor results from isolated BP measurements in detecting hypertension in pregnancy by relying on ambulatory BP monitoring (ABPM).3 With use of ABPM, a circadian BP variability has been shown to characterize clinically healthy pregnant women as well as women who developed gestational hypertension or preeclampsia.4–6 During gestation, another source of variability comes from the predictable pattern of BP changes along the course of pregnancy.7 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 pregnancy and then continuously increases until delivery.7

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From the Bioengineering and Chronobiology Laboratories (RCH, DEA, AM, JRF, IA), University of Vigo, Vigo, Spain; and Obstetrics and Gynecology Department (MFA, RU, MI), Hospital Clínico Universitario and Medical School, University of Santiago, Santiago de Compostela, Spain.
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Address correspondence and reprint requests to Professor Ramón C. Hermida, Bioengineering and Chronobiology Laboratories, E.T.S.I. Telecomunicación, Campus Universitario, VIGO (Pontevedra) 36200, Spain; e-mail: rhermida@tsc.uvigo.es
Changes in the circadian pattern of BP could be used either to predict preeclampsia or to assess its severity. However, 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. Few studies have used ABPM to assess the circadian pattern of BP in complicated pregnancies, an issue only occasionally addressed. With use of ABPM, several authors have found a reduced drop in BP by night in preeclamptic patients, whereas others report an inversion of the circadian pattern of change in BP associated with preeclampsia. Most of the later studies have usually been carried out during the last stages of pregnancy. Limitations of these studies derive also from the inability to properly describe the nonsinusoidal waveform of circadian BP variability. In an attempt to corroborate and extend conclusions from previous studies, we report here results from a prospective study of BP variability during pregnancy. In particular, we have examined and compared characteristics of circadian variability in BP of clinically healthy pregnant women, as well as women who developed gestational hypertension or preeclampsia and who were systematically monitored throughout gestation.

## Methods

### Subjects

We studied 403 (207 primipara) untreated white pregnant women (235 normotensive, 128 of whom developed gestational hypertension and 40 of whom developed preeclampsia), who fulfilled all required criteria for this trial. Gestational hypertension was defined as conventional BP values >140 or 90 mm Hg for SBP or DBP, respectively, after week 20 of gestation without clinical record of hypertension previous to pregnancy or a hyperbaric index (HBI; area of BP excess above the upper limit of a time-varying tolerance interval computed as a function of gestational age) that was consistently above the threshold for diagnosis of hypertension in pregnancy after week 20 of gestation. This index has been shown to provide a much better approach than office BP measurements or mean BP values derived from ABPM for prediction of pregnancy outcomes. Preeclampsia was defined as gestational hypertension and proteinuria, > 300 mg/24 h urine excretion, with or without edema, diagnosed after week 20 of gestation in a previously normotensive woman. The demographic characteristics of the women investigated are included in Table 1. Gestational age and fetal growth were determined by monthly echography assessments. Office BP measurements (three to six at each obstetric visit) were always obtained by the same midwife to avoid examiner bias. Women were seated during BP determination, and Korotkoff phase V was used for DBP measurement.

Inclusion criteria were absence of any condition requiring the use of antihypertensive medication; maternal age (18 to 40 years); and gestational age (<16 weeks at the time of inclusion). Exclusion criteria included multiple...
pregnancy, chronic hypertension, chronic liver disease, any disease requiring use of anti-inflammatory medication, diabetes or any other endocrine disease such as hyperthyroidism, and intolerance to ABPM device. Apart from the 403 women providing all required information, 23 subjects who provided < 4 profiles of ABPM (five spontaneous abortions and 18 who withdrew from the trial at the early stages of gestation) were eliminated from the study. The State Ethics Committee of Clinical Research approved the study. All women signed consent forms before entering the study.

**BP Assessment**

In this trial, the SBP and DBP of each woman were scheduled to be measured by ABPM every 20 min during the day (7 AM to 11 PM) and every 30 min during the night for 48 consecutive h with a SpaceLabs 90207 device (SpaceLabs, Redmond, WA) at the time of recruitment (usually within the first trimester of pregnancy), and then every 4 weeks until delivery. Women were assessed while adhering to their usual diurnal activity (9 AM to midnight for most) and nocturnal sleep routine. They were instructed to go about their usual activities with minimal restrictions but to follow a similar schedule during the 2 days of ABPM and to avoid the use of medication for the duration of the trial. The BP series were eliminated from analysis if the women showed an irregular rest–activity schedule during the 2 days of sampling, an odd sampling with spans of > 3 h without BP measurement, or a night resting span < 6 h or > 12 h. The total number of BP series provided by the 403 women under investigation fulfilling all requirements a priori was 2430.

The clinical evaluation of this oscillometric monitor for use in pregnancy according to the standards published by the Association for Advancement of Medical Instrumentation and the British Hypertension Society has been previously established. In addition to the woman’s routine antenatal care, ABPM was performed, and none of the women were hospitalized during monitoring. The BP cuff was worn on the nondominant arm, with cuff size determined by upper arm circumference at each study visit. The ABPM always started between 10 AM and 1 PM. During monitoring, each subject maintained a diary listing the times at which they went to bed at night, woke in the morning, ate meals, engaged in exercise or unusual physical activity, and experienced events or mood/emotional states that might affect BP.

**Statistical Methods**

Each individual’s clock hour BP values were first rerereferenced from clock time to hours after awakening from nocturnal sleep. This transformation avoided the introduction of bias in the shape and phasing of the 24-h BP pattern due to differences among subjects in their sleep/activity routine. The BP values were then edited according to commonly used criteria for the removal of outliers and measurement errors. The circadian rhythm in BP for each group of 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 applicable to nonsinusoidal hybrid time series data (time series of data collected from a group of subjects) consisting of values distributed at equal or unequal intervals. Circadian parameters thus obtained were compared between groups of women in each trimester of pregnancy with a nonparametric test developed to compare parameters obtained from population multiple components analysis. Hourly means of BP were compared between groups of women by test corrected for multiple testing using Holm’s procedure. In addition, the demographic and perinatal characteristics included in Table 1 were compared between groups of pregnant women by analysis of variance (quantitative variables) or nonparametric $\chi^2$ testing (incidence of complications).

**Results**

**Baseline Characteristics and Evolution During Pregnancy**

The baseline characteristics of the three groups of pregnant women investigated differed in regard to maternal weight ($P < 0.001$) but not age ($P = .077$) or height ($P = .348$). Maternal weight was characterized by a continuous linear increase along the course of gestation for the three groups of women investigated. There was no significant difference between women who developed gestational hypertension and those who developed preeclampsia with regard to maternal weight at the time of inclusion ($P = .811$; Table 1) or in their linear pattern of increasing weight throughout pregnancy ($P > 0.387$). Weight was statistically significantly higher in women with complicated pregnancies as compared to those of normotensive women at all times during gestation. The comparison of the linear models obtained for these two groups of women indicates, however, that the slopes of increasing weight with gestational age are similar ($P = .497$).

The comparison of the average office BP measurements obtained at the time of the first visit to the hospital indicates statistically significant differences between healthy and complicated pregnancies ($P < 0.001$ for both SBP and DBP), but similar BP for women who later developed gestational hypertension as compared to those who developed preeclampsia ($P = .735$ for SBP and $P = .512$ for DBP). Table 1 also indicates statistically significant differences between the three groups of women in office BP measurements taken at the last obstetric visit shortly before delivery ($P < .001$ for both SBP and DBP), as well as in gestational age at delivery ($P < .001$, mostly due to the earlier mean delivery time of women who develop preeclampsia), newborn weight ($P < .001$), and Apgar scores at 1, 5, and 10 min after birth ($P = .014$, <.001 and <.002, respectively).
Pregnancy Outcomes

Results from Table 1 indicate statistically significant differences between the three groups of women in preterm delivery and intrauterine growth retardation \( (P < .001 \text{ in both cases}) \). Differences in the incidence of these two complications are also significant when comparing normotensive women with those who developed gestational hypertension \( (P = .031 \text{ and } < .001, \text{ respectively}) \). The incidence of delivery by cesarean section was double for women with gestational hypertension and those with preeclampsia in regard to women with gestational hypertension or preeclampsia at the last obstetric visit \( (P < .001) \), incidence of intrauterine growth retardation \( (P < .001) \) and preterm delivery \( (P = .011) \), and Apgar scores of newborns \( (P < .025) \).

Modeling the Circadian BP Variability

For the normotensive pregnant women, no difference was found between circadian BP characteristics obtained as a function of parity or maternal 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-h component was obtained for 97% of the SBP and 95% of the DBP profiles sampled from normotensive pregnant women, with a significant second harmonic (12-h component) characterizing 54% and 57% of the profiles for SBP and DBP, respectively. For women with complicated pregnancies, the 24-h component was statistically significant for 91% and 92% of the profiles for SBP and DBP, respectively. For women with complicated pregnancies, the 24-h component was statistically significant for 91% and 92% of the profiles for SBP and DBP, respectively, whereas the 12-h component was significant for 55% of the SBP profiles and for 58% of the DBP profiles. Other higher frequency (ultradian) harmonic components were significant in less than 16% of the profiles for any group or trimester of pregnancy. From the population point of view, although other ultradian components can be demonstrated as statistically significant in a small percentage of women, a rather simple model including only the two first harmonics of the 24-h period describes sufficiently well, at the specified sampling rate, the circadian pattern of BP in both healthy and complicated pregnancies. The same model was found previously to describe also the circadian pattern of BP variability in clinically healthy subjects of both sexes.

Circadian Rhythm in BP and Their Evolution During Pregnancy

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 Figs. 1 through 3. Compared with uncomplicated pregnancies, a statistically significant elevation of the 24-h mean of BP is found in pregnancies with gestational hypertension or preeclampsia in all trimesters \( (P < .001 \text{ for both SBP and DBP}) \). There is also a statistically significant difference in the circadian amplitude (half of the difference between the maximum and minimum values of the best fitted curve) of both SBP and DBP between healthy and complicated pregnancies in all trimesters of gestation \( (P < .001 \text{ for both variables in all trimesters}) \).

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 to clinically healthy pregnant women is shown in Fig. 1 (top); Fig. 1 (bottom) includes graphs comparing the circadian pattern of SBP (left) and DBP (right) between women who developed gestational hypertension and preeclampsia. The comparison of circadian characteristics indicates that the rhythm parameters are similar in these two groups of complicated pregnant women sampled in the first trimester of gestation \( (all P > .108) \).

Fig. 2 (top) represents the circadian variation of SBP (left) and DBP (right) of women undergoing sampling during the second trimester of pregnancy. The differences between normotensive and hypertensive women are highly statistically significant at all circadian times after correcting for multiple testing. The 24-h mean of BP for normotensive pregnant women is statistically lower in the second trimester \( (P < .001 \text{ for both SBP and DBP}) \). 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 24-h mean between gestational hypertension and preeclampsia is demonstrated for both SBP \( (P = .002) \) and DBP \( (P = .038) \). The bottom graphs of Fig. 2 further indicate the lack of differences in circadian amplitude between these two groups of women \( (P > .280) \).

The graphs at the top of Fig. 3, comparing SBP and DBP between healthy and complicated pregnancies sampled in the third trimester of gestation, indicate larger differences than those shown in Figs. 1 and 2 for the first and second trimesters of pregnancy. Besides the statistically significant difference in 24-h mean 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 to the second trimester, BP increases slightly for normotensive pregnant women, reaching a 24-h mean value comparable to that computed in the first trimester for the same women (Fig. 1). For women with complicated pregnancies, 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 to those who developed gestational hypertension. In the third trimester, the difference in 24-h mean between gestational hypertension and preeclampsia is statistically significant for both SBP and DBP \( (P < .001) \). The comparison of circadian
amplitude indicates no difference in either SBP ($P = .084$) or DBP ($P = .372$).

**Discussion**

Results from Fig. 1 indicate a highly statistically significant difference in the circadian variability of SBP and DBP between women with complicated and uncomplicated pregnancies who underwent sampling ABPM during the first 14 weeks of gestation. The differences in BP during the first trimester of pregnancy are statistically significant at all of the hourly intervals in which the 24-h span was divided for comparative analysis. These differences are
found several months before the clinical diagnosis of gestational hypertension can be made by relying on office BP measurements (usually obtained well advance of the third trimester of pregnancy). Moreover, the differences of approximately 12 mm Hg in the 24-h mean of SBP and of approximately 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 physiologic range of BP variability. As in the first trimester, the highly statistically significant differences between healthy and complicated pregnancies documented in the second trimester (Fig. 2), exceeding 13 mm Hg in the 24-h mean of SBP and 7 mm Hg in that of DBP, are found with hourly BP values well below criteria used to make the diagnosis of hypertension by office measurements (140/90 mm Hg for SBP/DBP), even for the hypertensive women. The documented differences in the 24-h mean of BP between women with healthy and complicated pregnancies are well within the accepted normal physiologic range of BP variability. As in the first trimester, the highly statistically significant differences between healthy and complicated pregnancies documented in the second trimester (Fig. 2), exceeding 13 mm Hg in the 24-h mean of SBP and 7 mm Hg in that of DBP, are found with hourly BP values well below criteria used to make the diagnosis of hypertension by office measurements (140/90 mm Hg for SBP/DBP), even for the hypertensive women. The documented differences in the 24-h mean of BP between women with healthy and complicated pregnancies are well within the accepted normal physiologic range of BP variability.
pregnancies undergoing sampling during the third trimester are approximately 15 mm Hg for SBP and 9 mm Hg for DBP.

The comparison of circadian BP variability between gestational hypertension and preeclampsia indicates similar patterns for both SBP and DBP in the first trimester of pregnancy (Fig. 1, bottom). Differences between these two later groups is shown on the bottom. #Indicates the number of BP time series analyzed for each group. P value from testing the zero amplitude assumption. Dark bar in the lower horizontal axis indicates the average resting span. Curve represented for each group corresponds to the best fitted model obtained by population multiple components analysis (with corresponding characteristics given in the table below each chronogram). Arrows descending from the upper horizontal axis point to the circadian orthophase for each group. †Hours after awakening. Abbreviations as in Figs. 1 and 2.

FIG. 3. Circadian variation of systolic (left) and diastolic (right) BP in normotensive pregnant women and women with a final diagnosis of gestational hypertension or preeclampsia sampled in the third trimester of pregnancy (top). A comparison between these two later groups is shown on the bottom. #Indicates the number of BP time series analyzed for each group. P value from testing the zero amplitude assumption. Dark bar in the lower horizontal axis indicates the average resting span. Curve represented for each group corresponds to the best fitted model obtained by population multiple components analysis (with corresponding characteristics given in the table below each chronogram). Arrows descending from the upper horizontal axis point to the circadian orthophase for each group. †Hours after awakening. Abbreviations as in Figs. 1 and 2.

A larger increase in BP with advancing gestational age during the second half of pregnancy characterizes preeclampsia as compared to gestational hypertension.¹ Differences in 24-h BP mean are therefore highly statistically significant for both SBP and DBP in the third trimester (Fig. 3, bottom).

Figs. 1 through 3 also show differences in circadian amplitude between healthy and complicated pregnancies in all trimesters of gestation. Figs. 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, especially for the subgroup of women who developed preeclampsia. An increase in circadian amplitude of BP before the actual onset of hypertension (elevation in 24-h mean) was also noted in several previous studies.\footnote{25} Fig. 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 women with complicated pregnancies, 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 women who developed preeclampsia. The differences in amplitude between healthy and complicated pregnancies in this last trimester stem from the lack of reduction in amplitude for the women who developed gestational hypertension but not preeclampsia (Figs. 1 through 3, bottom graphs).

In summary, the differential changes in the circadian pattern of BP with advancing gestational age in normal pregnancy, gestational hypertension, and preeclampsia that have been demonstrated here offer new end points for the early diagnosis of gestational hypertension and preeclampsia based on information obtained from ABPM, which could also be used as a guide for establishing preventive interventions.\footnote{26,27} Despite the significant differences between healthy and complicated pregnancies shown in Figs. 1 through 3, the use of the 24-h mean of BP does not provide a proper approach for an individualized early diagnosis of hypertensive complications in pregnancy.\footnote{28,29} 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.\footnote{5,16,17} In particular, the HBI defined above has been shown prospectively to provide high sensitivity and specificity for diagnosis of gestational hypertension as well as for the prediction of pregnancy outcomes.\footnote{16,17} rendering ABPM a useful technique for evaluating women during pregnancy.

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References


