Differences in Circadian Pattern of Ambulatory Pulse Pressure Between Healthy and Complicated Pregnancies

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Abstract—With the use of ambulatory monitoring, a circadian blood pressure pattern has been shown to characterize normotensive as well as hypertensive pregnant women. However, the potential differences between healthy and complicated pregnancies in pulse pressure, an independent marker of cardiovascular risk in the general population, have not yet been investigated. We analyzed 2523 blood pressure series sampled for 48 hours once every 4 weeks from the first obstetric visit until delivery in 245 women with uncomplicated pregnancies, 140 with gestational hypertension, and 49 who developed preeclampsia. Compared with uncomplicated pregnancies, a statistically significant elevation in the 24-hour mean of pulse pressure is found in complicated pregnancies in all trimesters (P<0.001). Results further indicate similar 24-hour mean of pulse pressure between gestational hypertension and preeclampsia in the first trimester of pregnancy (P=0.158). The increase in pulse pressure among women who developed preeclampsia compared with women with gestational hypertension, although small, was statistically significant in the second trimester (1.4 mm Hg; P=0.010) and, to a larger extent, in the third trimester of pregnancy (1.8 mm Hg; P<0.001). The differences in pulse pressure between healthy and complicated pregnancies, observed already in the first trimester of gestation, are found when systolic and diastolic blood pressure for women with a later diagnosis of gestational hypertension or preeclampsia are within the accepted range of normotension. Moreover, ambulatory pulse pressure provides higher sensitivity than clinic measurements for the diagnosis of hypertension in pregnancy. (Hypertension. 2004;44:316-321)

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

With the use of ambulatory blood pressure (BP) monitoring, a circadian pattern has been shown to characterize BP in clinically healthy pregnant women as well as in women who develop gestational hypertension or preeclampsia.1,2 Changes in the circadian pattern of BP could be used either to predict preeclampsia or to assess its severity.3,4 However, only a few studies have been conducted on the normal pattern of ambulatory BP monitoring (ABPM) in uncomplicated pregnancies,5,6 most of them without comparison with the circadian pattern of BP in complicated pregnancies, an issue only addressed occasionally.1,2,7 None of these studies so far investigated a potential difference between healthy and complicated pregnancies in the circadian pattern of pulse pressure (PP), a recognized independent marker of cardiovascular risk.8

As in general nonpregnancy practice, current guidelines for diagnosis and management of hypertension in pregnancy rest almost completely on systolic BP (SBP) and diastolic BP (DBP), 2 specific inflection points of the BP wave.9,10 However, BP propagates through the arterial tree as a repetitive continuous wave and is more accurately described as consisting of a pulsatile component (PP) and a steady component (mean arterial BP). We have examined and compared characteristics of circadian variability in PP 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 434 (218 nullipara) untreated, white, pregnant women (245 normotensive, 140 who developed gestational hypertension, and 49 who developed preeclampsia) who fulfilled all required criteria for this trial. Gestational hypertension was defined as conventional clinic BP values >140 or 90 mm Hg for SBP or DBP, respectively, after the 20th week of gestation without clinical record of hypertension before pregnancy8 or a hyperbaric index (area of BP excess above the upper limit of a time-varying tolerance interval computed as a function of gestational age)11 consistently above the threshold for diagnosis of hypertension in pregnancy9,12 after the 20th week of gestation for further corroboration. This index has been shown prospectively to provide higher sensitivity and specificity than office BP measurements or mean BP values derived from ABPM for diagnosing hypertension and predicting the outcome of pregnancy.5,6,12 Preeclampsia was defined as gestational hypertension and proteinuria, >300 mg per 24-hour urine excretion diag-

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nosed after the 20th week of gestation in a previously normotensive woman. Diagnosis of gestational hypertension and preeclampsia was done with information from the conventional obstetric examinations, including monthly ABPM, and routine analyses of urine, including 24-hour urine collection in women with suspicion of proteinuria from dipsticks. Gestational age and fetal growth were determined by monthly ecography assessments. Office BP measurements (3 to 6 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 maternal age (18 to 40 years) and gestational age (>16 weeks at the time of inclusion). Exclusion criteria were multiple pregnancy, chronic hypertension, chronic liver disease, renal disease, any disease requiring the use of anti-inflammatory medication, diabetes or any other endocrine disease such as hyperthyroidism, and intolerance to the use of an ABPM device. The state ethics committee of clinical research approved the study. All women signed consent forms before entering the study.

**ABPM Assessment**

The SBP and DBP of each woman were measured by ABPM every 20 minutes from 7 AM to 11 PM and every 30 minutes during the night for 48 consecutive hours with a validated SpaceLabs 90207 device (SpaceLabs Inc) at the time of recruitment, and then every 4 weeks until delivery. Women were instructed to go about their usual activities with minimal restrictions but to follow a similar schedule during the 2 consecutive days of ABPM and to avoid use of over-the-counter and any other medication for the duration of the trial. During monitoring, each woman maintained a diary listing the time of going to bed at night and awakening in the morning and of meals, exercise, and unusual physical activity, plus events and mood/emotional states that might affect BP. BP series were not considered valid for analysis (a total of 81) when a woman showed an irregular rest/activity schedule during the 2 days of sampling, a duration of sampling <42 hours, an odd sampling with spans of >2 hours without BP measurement, or a nighttime resting span <6 hours or >12 hours. The total number of valid BP series following these criteria and with ≥80% of valid BP measurements provided by the 434 women under investigation fulfilling all mentioned requirements set a priori was 2523.

**Statistical Methods**

Each individual’s clock hour BP values were first rereferenced from clock time to hours after awakening from nocturnal sleep according to the information obtained from the diaries. This transformation avoided the introduction of bias in the shape and phasing of the 24-hour BP pattern because of differences among subjects in their sleep/activity routine. BP values were then edited according to commonly used criteria for removal of outliers and measurement errors. The circadian rhythm of PP for each group of women in each trimester of gestation was established by population multiple-component analysis. The circadian rhythm parameters of the midline estimating statistic of rhythm (MESOR; average value of the rhythmic function fitted to the data), overall amplitude (one half the difference between the maximum and the minimum values of the best fitted curve), and orthophase (peak time, expressed as a lag from the time of awakening from nocturnal sleep) were compared between groups of women in each trimester of pregnancy with a nonparametric test developed to assess differences in parameters derived from population multiple-components analysis. Hourly means of PP were compared between groups by t test corrected for multiple testing with the Holm procedure. Sensitivity and specificity (as defined previously) of the test for diagnosing hypertension in pregnancy based on PP were evaluated as a function gestational age.
Results

Modeling the Circadian BP Variability

Individually, a statistically significant 24-hour component was obtained for 97% of the SBP, 94% of the DBP, and 41% of the PP profiles sampled from normotensive pregnant women, with a significant 12-hour component characterizing 53%, 56%, and 11% of the profiles for SBP, DBP, and PP, respectively. For women with complicated pregnancies, the 24-hour component was statistically significant for 91%, 92%, and 43% of the profiles for SBP, DBP, and PP, respectively, whereas the 12-hour component was significant for 55%, 57%, and 11% of the profiles. Other higher-frequency harmonic components were significant in <16% of the BP profiles and in <4% of the PP profiles for any group or trimester of pregnancy. From the population point of view, 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 PP in normotensive and hypertensive pregnant women at all stages of gestation.

Circadian Rhythm in PP and Its Evolution During Pregnancy

Compared with uncomplicated pregnancies, a significant elevation of the 24-hour mean of PP is found in pregnancies with gestational hypertension or preeclampsia in all trimesters (Figures 1, 2, and 3, left). Figure 3 also includes (on the right) a graph comparing the circadian pattern of PP between women who developed gestational hypertension and those who developed preeclampsia. The comparison of circadian characteristics indicates that the 24-hour mean, although slightly elevated in preeclampsia (48.9 versus 47.5 mm Hg), is not significantly different between these 2 groups of women sampled in the first trimester of gestation ($P=0.158$). Results further indicate a significant increase in circadian amplitude in women who developed preeclampsia compared with those with gestational hypertension ($P=0.038$), mainly because of the elevation of PP during diurnal active hours in the former group (Figure 1, right).

In the second trimester (Figure 2), the differences between normotensive and hypertensive women are significant at all circadian times after correcting for multiple testing ($P<0.001$ for each of the 24 hourly means). The 24-hour mean BP for normotensive pregnant women is slightly although not statistically lower in the second compared with the first trimester (42.3 versus 42.6 mm Hg; $P=0.190$). For women with a final diagnosis of gestational hypertension or preeclampsia, PP slightly increases from the first to the second trimester (47.6 versus 47.9 mm Hg; $P=0.574$). In this second trimester of pregnancy, a statistically significant difference in 24-hour mean between gestational hypertension and preeclampsia is demonstrated for PP ($P=0.010$).

The differences in PP between healthy and complicated pregnancies sampled in the third trimester of gestation are larger than those found for the first and second trimesters.
Besides the significant difference in 24-hour mean between both groups, the hourly means of PP are significantly higher in women with gestational hypertension or preeclampsia at all sampling times. Compared with the second trimester, BP significantly increases for normotensive pregnant women ($P<0.001$), reaching a 24-hour mean value (42.9 mm Hg) greater than that obtained in the first trimester for the same subjects (Figure 1). For women with complicated pregnancies, BP continues to increase with gestational age from the second to the third trimesters of pregnancy (47.9 versus 48.5; $P=0.008$). The trend of increasing PP with gestational age during the second half of pregnancy is larger for women who developed preeclampsia compared with those who developed gestational hypertension. In the third trimester, the difference in 24-hour mean of PP between gestational hypertension and preeclampsia is statistically significant ($P<0.001$), the differences being consistently greater during the hours of nocturnal rest compared with the differences between groups found during the hours of diurnal activity (Figure 3, right).

The Table provides information on the test for diagnosing hypertension in pregnancy based on the mean of 3 to 6 clinic BP measurements obtained on the same day just before starting ABPM, using the constant critical thresholds for BP common to all current definitions of gestational hypertension and preeclampsia (140/90 mm Hg for SBP/DBP). Results indicate a very poor sensitivity at all stages of gestation, mainly for DBP. Specificity, on the contrary, is very high, because just a very small percentage of women in this study, including those with proteinuric preeclampsia, had conventional BP values $>140/90$ mm Hg even during most of the third trimester of pregnancy. The relative risk is also very small. Sensitivity is increased slightly and specificity decreased by the use of a constant threshold of 60 mm Hg for clinic PP measurements, a value chosen here just for comparative purposes. For the women investigated here, the critical threshold for the 24-hour mean of ambulatory PP providing higher sensitivity and specificity at all stages of pregnancy was found to be $\approx 45$ mm Hg. For this cutoff value, the table indicates a marked increase in sensitivity with a minor decrease in specificity compared with clinic BP measurements.

**Discussion**

Despite the available evidence correlating increasing values of PP with cardiovascular risk, the potential predictive or diagnostic value of PP in pregnant women has not yet been evaluated. Results from Figure 1 indicate a significant difference in the 24-hour mean of PP between women with complicated and uncomplicated pregnancies sampled by ABPM during the first 14 weeks of gestation. This difference is found several months before the clinical diagnosis of gestational hypertension can be made by relying on office BP measurements, usually obtained well in advance of the third trimester of pregnancy. Moreover, the difference of $\approx 5$ mm Hg (12% of the daily mean) in the 24-hour mean of PP is found when 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 in pregnancy (24-hour mean of 115 and 68 mm Hg for SBP and DBP, respectively). The comparison of circadian PP variability between gestational hypertension and preeclampsia indicates similar patterns in the first trimester of pregnancy (Figure 1). However, differences between these 2 groups of pregnant women are already significant in the second trimester of gestation (Figure 2) and, to a larger extent, in the third trimester (Figure 3).

Results shown in Figures 1 through 3 could somehow be related to a higher diagnostic value in pregnancy of ambulatory SBP compared with DBP. Among several other authors, Kyle et al.\(^7\) have investigated the effectiveness of second-trimester 24-hour mean of BP as a screening test for hypertension in pregnancy. They reported that the awake SBP was significantly higher at 18 and 28 weeks of gestation in those women who subsequently developed gestational hyperten-

sion. Bellomo et al.\(^8\) also showed that 24-hour SBP was superior to office BP for prediction of the outcome of pregnancy in women sampled on just 1 occasion during their third trimester of pregnancy. Brown et al.\(^9\) suggested that 125 mm Hg for 24-hour mean of SBP and 106 mm Hg for the nocturnal mean of SBP were predictive of later gestational hypertension or preeclampsia. In a previous independent study, we found a sensitivity for SBP \(>26\%\) above that of DBP at all stages of gestation, with specificity \(\approx 40\%\) to 50\% greater for SBP.\(^1^7\) Apart from the advantages of SBP compared with DBP, all of these studies also have in common to demonstrate a higher sensitivity and specificity of ABPM over clinic BP values for the diagnosis of hypertension in pregnancy. This conclusion seems to apply also to ambulatory PP. Differences in ambulatory PP between normotensive and hypertensive pregnant women sampled during the early stages of gestation (Figure 1) could not be demonstrated on the basis of conventional PP values (Table). Moreover, the documented differences in ambulatory PP between women who developed gestational hypertension and those with preeclampsia, significant already during the second trimester of pregnancy (Figure 2), could not be observed in clinic PP even at the time of delivery.

### Perspectives

The differential changes in the circadian pattern of PP with advancing gestational age in normal pregnancy, gestational hypertension, and preeclampsia demonstrated here offer new end points for early diagnosis of gestational hypertension and preeclampsia based on information obtained from ABPM that could also be used as a guide for establishing preventive interventions.\(^2^0\) Apart from the potential value of mean values of PP (Table), other indexes derived from ABPM have been shown to identify early in pregnancy those women who subsequently will develop gestational hypertension or preeclampsia.\(^3,4,1^2\) In particular, the hyperbaric index defined above has been shown prospectively to provide high sensitivity and specificity for diagnosis of hypertension in pregnancy as well as for the prediction of the outcome of pregnancy,\(^4,1^2\) rendering ABPM a useful technique for evaluation of women during gestation. The potential benefit of using a similar parameters derived from PP (area of PP excess above the upper limit of a time-specified reference threshold) alone or in combination with the hyperbaric index of BP deserves further investigation.

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