Influence of Parity and Age on Ambulatory Monitored Blood Pressure During Pregnancy

Diana E. Ayala, Ramón C. Hermida

Abstract—Studies based on casual blood pressure measurements concluded that both age and parity have significant effects on blood pressure during pregnancy. We have tested these results on clinically healthy normotensive women who were systematically studied by ambulatory blood pressure monitoring during their pregnancies. We analyzed 1254 blood pressure series sampled for 48 consecutive hours every 4 weeks from the first obstetric visit (usually within the first trimester of pregnancy) until delivery in 205 normotensive pregnant women. Data were divided for comparative analysis by parity (nulliparous versus multiparous), age (≤25, 26 to 30, 31 to 35, and ≥36 years), and trimester of gestation. Circadian parameters established by population multiple-component analysis were compared between groups with a nonparametric test. Effects of age and parity on blood pressure were also tested by ANOVA. A highly statistically significant circadian pattern described by a 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 (always $P<0.001$). There was no significant difference in 24-hour mean among groups divided by parity at any age or stage of pregnancy (always $P>0.160$). A trend of increasing blood pressure with age was found for diastolic but not systolic blood pressure. Although statistically significant, differences in the 24-hour mean of diastolic blood pressure among groups divided by age were always <1.5 mm Hg. Data obtained from systematic ambulatory monitoring in normotensive pregnant women indicate the lack of differences in blood pressure according to parity. The small, although significant, increase in diastolic blood pressure with age may have little influence in the proper identification of women with gestational hypertension. Reference thresholds for blood pressure to be used in the early identification of hypertensive complications in pregnancy could thus be developed as a function of rest-activity cycle and gestational age, independent of parity or maternal age. **(*Hypertension*. 2001;38[part 2]:753-758.)**

Key Words: blood pressure ■ pregnancy ■ age ■ blood pressure monitoring, ambulatory ■ circadian rhythm

Previous studies have shown the prognostic significance of parity in the differential diagnosis of various hypertensive diseases of pregnancy.[1–5] On long-term follow-up, multiparous patients with preeclampsia or eclampsia seem to differ from nulliparous women with the same complications in pregnancy.[1,6,7] Moreover, clear differences have been demonstrated between nulliparous and multiparous women in both maternal presentation and impact of maternal disease on fetal growth and development.[2,8–10] It has been thus concluded from these observations that multiparous and nulliparous patient groups should be analyzed separately whenever hypertensive diseases of pregnancy are evaluated. On the other hand, the incidence of preeclampsia seems to be higher at both ends of the age scale.[6] Therefore, it is of interest to examine the underlying variations of blood pressure (BP) during pregnancy by both age and parity.

In a cohort study on >6500 women, Christianson[11] showed that both maternal age and parity have highly significant effects on casual BP measurements during pregnancy. Although other studies based on office BP determinations have also provided similar conclusions,[12,13] results are still controversial because of the lack of correlation between parity and BP shown in several other trials.[14–16] The controversy could come from, among other factors, the inclusion in some studies of both healthy and complicated pregnancies and from the shortcomings of casual BP values. These provide a measurement that represents only a fraction of the 24-hour BP profile, usually under circumstances that may have a pressor effect, and the technique is fraught with potential errors, including instrument defects and examiner technique.[17] The use of a reliable and accurate automated device for ambulatory BP monitoring (ABPM) has been suggested as the logical approach to overcoming many of the problems associated with office BP measurement.[18,19]

By the use of ABPM, predictable patterns of BP variation along gestation have been identified for both clinically healthy and hypertensive pregnant women.[20] 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

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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.[20] Moreover, differences between healthy and complicated pregnancies in the circadian pattern of BP, previously documented for the second trimester of pregnancy,[21] can be observed by ABPM as early as in the first trimester of pregnancy, before the actual clinical diagnosis of gestational hypertension or preeclampsia takes place for the women investigated.[22] Therefore, healthy and complicated pregnancies should be studied separately when investigating other possible factors influencing BP during gestation. Accordingly, we studied the possible influence of parity and maternal age on BP in clinically healthy normotensive pregnant women who were systematically sampled by 48-hour ABPM from the first obstetric visit to the hospital until delivery.

Methods

Subjects

We studied 205 (112 nulliparous) untreated white pregnant women with uncomplicated pregnancies who fulfilled all required criteria for this trial. They were 30.2±5.4 (mean±SD) years of age at the time of the study. All women received obstetric care at the Obstetric Physiopathology Unit, Hospital Clínico Universitario, Santiago de Compostela, Spain. All issues related to ABPM, including handling and preparation of the monitors, individualized explanation about their use to each patient, and processing of the data provided by any given pregnant woman after monitoring, were always performed by the same member of the research group in 1 room of the unit. Conventional obstetric examinations of the pregnant women, usually done on the same day just before starting ABPM, were performed by other members of the research group in different rooms of the unit.

Inclusion criteria were the absence of any condition requiring the use of antihypertensive medication, maternal age between 18 and 40 years, gestational age <16 weeks at the time of inclusion, casual BP measurements <140/90 mm Hg for systolic/diastolic BP (SBP/DBP) for the duration of pregnancy, and hyperbaric index (area of BP excess above the upper limit of a tolerance interval specified as a function of gestational age and rest-activity cycle[23,24]) consistently below the previously established threshold for diagnosing hypertension in pregnancy,[23] as an added measure to corroborate normotension in all women investigated. Exclusion criteria were, among others, gestational hypertension, preeclampsia, multiple pregnancy, chronic hypertension, chronic liver disease, any disease requiring 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 205 women providing all required information, 17 subjects who provided <4 profiles of ABPM (2 who had spontaneous abortions and 15 who withdrew from the trial) 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 minutes during the day (7:00 AM to 11:00 PM) and every 30 minutes during the night for 48 consecutive hours at the time of recruitment (usually within the first trimester of pregnancy) and then every 4 weeks until delivery with an SpaceLabs 90207 device. BP series were eliminated from analysis when the subjects showed an irregular rest-activity schedule during the 2 days of sampling, an odd sampling with spans of >3 hours without BP measurement, or a night resting span <6 or >12 hours. The total number of BP series provided by the 205 women under investigation fulfilling all mentioned requirements set a priori was 1254.

During sampling, all women were living on their usual diurnal waking (≈9:00 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 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.[25] 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 10:00 AM and 1:00 PM. During monitoring, each subject maintained a diary listing the times of going to bed at night and awakening in the morning; of meals, exercise, and unusual physical activity; and of events and mood/emotional states that might affect BP.

Statistical Methods

Each individual's clock-hour BP values were first re-referenced from clock time to hours before and after awakening from nocturnal sleep. This transformation avoided the introduction of bias caused by differences among subjects in their sleep/activity routine.[26] BP values were then edited according to commonly used criteria for the removal of outliers and measurement errors.[27] The remaining data were analyzed by the use of Chronolab,[28] a software package for biologic signal processing by linear and nonlinear least-squares estimation. Data were divided for comparative analysis by parity (nulliparous versus multiparous), age (≤25, 26 to 30, 31 to 35, and ≥36 years), and trimester of gestation. The actual number of women investigated within each age group was as follows: 19 nulliparous and 14 multiparous women ≤25 years; 43 nulliparous and 33 multiparous women 26 to 30 years; 31 nulliparous and 30 multiparous women 31 to 35 yearse; and 19 nulliparous and 16 multiparous women ≥36 years. The circadian rhythm of BP for each group of pregnant women in each trimester of gestation was established by population multiple-component analysis,[29] a method designed for analysis of nonsinusoidal hybrid data (time series of data collected from a group of subjects) with unequidistant observations.

The method produces estimates of the rhythm-adjusted mean or MESOR (midline estimating statistic of rhythm, average value of the rhythmic function fitted to the data), as well as the amplitude (one half the extent of change explainable by the rhythmic fitted curve) and acrophase (crest time expressed as a lag from a designated reference) 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 (one half the difference between the maximum and the minimum of the best fitted curve) and the orthophase and the bathyphase (peak and trough times, respectively; here expressed as a lag from the time of awakening from nocturnal sleep).[29] Circadian parameters were subsequently compared between groups of women in each trimester of pregnancy with parametric and nonparametric tests developed to compare parameters obtained from population multiple components analysis.[29] Additionally, the distributions of 24-hour mean BP were compared for groups of women divided by parity and age for each trimester of gestation by ANOVA.

Results

Figure 1 represents the histograms with the distributions of the 24-hour mean of SBP (top) and DBP (bottom) for nulliparous and multiparous pregnant women divided according to age and trimester of gestation. Results from Figure 1 indicate the lack of statistically significant differences in BP as a function of parity for each age group and trimester of pregnancy. The larger, but not significant (P=0.160), difference between nullipara and multipara was found for the SBP of women ≥36 years of age sampled in the second trimester

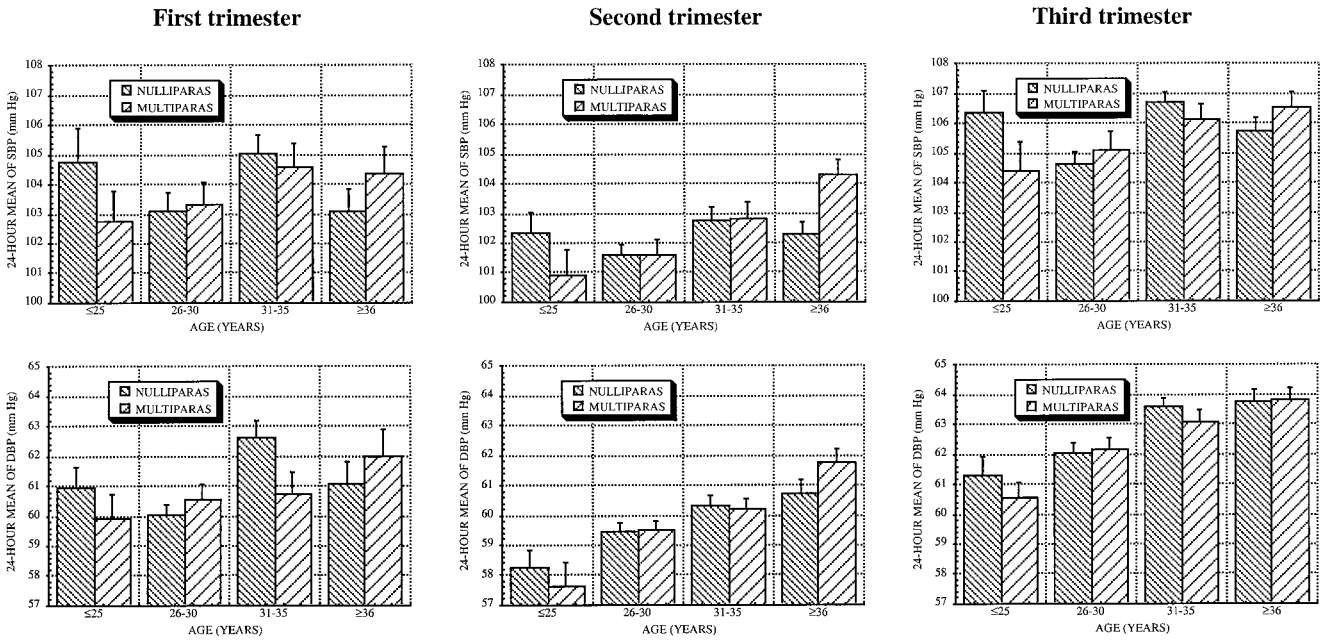

Figure 1. Influence of parity and age in the 24-hour mean of SBP (top) and DBP (bottom) of clinically healthy pregnant women sampled by 48-hour ABPM in different trimesters of their gestation.

of pregnancy. Figure 1 also indicates that as previously documented,[20,22] in normotensive pregnant women BP decreases from the first to the second trimester and raises again in the third, independent of parity or maternal age. Results from ANOVA indicate that there is no significant difference in BP as a function of maternal age in the first trimester of pregnancy ($P>0.274$ for the 24-hour mean of SBP and DBP). In the second trimester, there is a significant increase of DBP ($P<0.001$) with increasing maternal age, but there is no significant change of SBP as a function of age ($P=0.296$). Although statistically significant, the difference in the 24-hour mean of DBP between groups of pregnant women with <30 and >30 years of age sampled in the second trimester of pregnancy was, however, of only 1.5 mm Hg. The trend of increasing DBP with maternal age was smaller, although still statistically significant ($P=0.016$), in the third trimester, mainly for nulliparous women.

The parameters of the circadian rhythm (obtained by population multiple component analysis) for SBP and DBP in each trimester of pregnancy for nulliparous and multiparous clinically healthy women are indicated in the tables at the bottom of Figures 2 and 3. The graphs show the lack of differences in 24-hour mean, amplitude, and orthophase of BP as a function of parity in normotensive women systematically sampled throughout gestation by 48-hour ABPM. These graphs represent circadian population chronograms (display of data as a function of time), with hourly mean±SD computed as follows. First, hourly means are computed from each individual series, after stacking all data sampled during a 48-hour monitoring span in 1 idealized 24-hour span (given the highly statistically significant rhythm with a period of 24 hours demonstrated in about 97% 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 awakening; 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 waveform 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. Differences or similarities in rhythm characteristics, and the general waveform of circadian variability in BP, can be readily seen from this graphic representation. The characteristics of the circadian rhythm, including information on the number of series analyzed for each group, are represented in the tables below each graph.

The comparison of SBP (Figure 2, left) and DBP (Figure 3, left) between nulliparous and multiparous pregnant women sampled in the first trimester of gestation indicates that not only is the circadian MESOR of BP similar but also all 24-hour averages are practically overlapped for both groups. In the second trimester (Figures 2 and 3, center), the small and not significant difference in 24-hour mean between the 2 groups of women being compared seems to be reversed, in the sense that multiparous women are now characterized by a higher BP compared with that of nulliparous subjects. Differences in the 24-hour mean of BP in the third trimester of pregnancy between nullipara and multipara (Figures 2 and 3, right) are as small as 0.05 and 0.03 mm Hg for SBP and DBP, respectively.

Discussion

Results from this study on normotensive women systematically measured by 48-hour ABPM during different stages of their pregnancies indicate the lack of differences in BP according to parity, in contrast with conclusions from earlier reports based on routine prenatal visit BP measurements.[11–13]

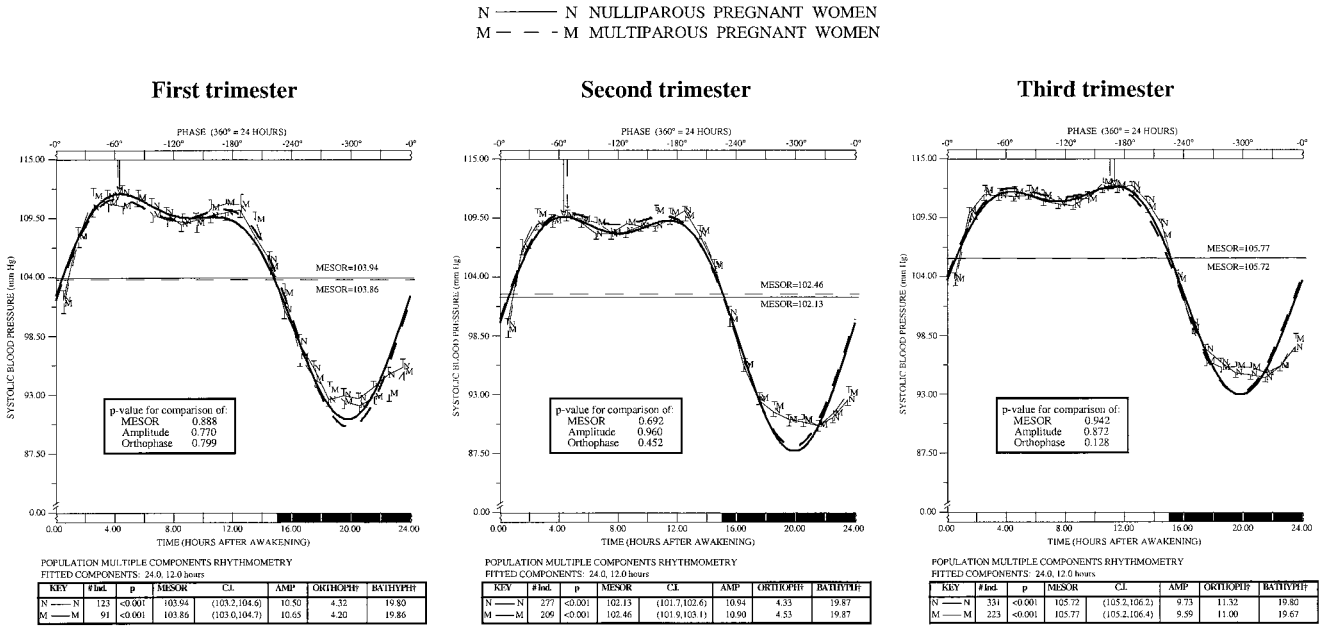

Figure 2. Circadian variation of SBP in clinically healthy pregnant women who were assessed by 48-hour APBM in different trimesters of their gestation. Each graph shows the hourly mean±SD collected from nullipara (solid line) and multipara pregnant women (dashed line), respectively. The nonsinusoidal shaped curve represented for each group corresponds to the best-fitting waveform model determined by population multiple-component analysis (with corresponding characteristics given in the table below each graph). The arrow descending from the upper horizontal time axis points to the circadian orthophase (rhythm's crest time, in hours after awakening).

These reports indicated that for a given maternal age, nulliparas had a higher BP than did parous women. This observation was usually related to the prognostic significance of parity in the differential diagnosis of gestational hypertension, preeclampsia, and eclampsia.[2–5] The larger, although not statistically significant, differences as a function of parity in our study were found for women ≥36 years of age; surprisingly, for both SBP and DBP measured at all 3 trimesters of pregnancy in this age group, multiparous women tend to have a slightly higher BP than do nulliparous women, in opposition to previous reports based on casual measurements. A slightly higher BP can also be observed for all multiparous women compared with nulliparous women, independent of maternal age for data sampled by ABPM in the second trimester of pregnancy, although differences are not statistically significant (Figures 2 and 3, center).

Not all previous studies have shown, however, a significant relation between parity and casual BP measurements. Moutquin et al[15] conducted a prospective study on 366 pregnant women whose BP was measured at each antenatal visit, using an automatic random-zero sphygmomanometer. They found no difference in BP during pregnancy between nulliparous and multiparous women who remained normotensive. Lee Feldstein et al[14] analyzed the BP values measures in 755 females in relation to parity, race, and residential stress; none of the regression relationships between BP and parity was found to be significant in the race-stress groups included in their study. In a more recent trial, Okonofua et al[16] monitored the BP of 189 women from early pregnancy up to term, during labor, and 24 hours after delivery. They also found no significant correlation of BP with parity, but there was a significant positive correlation with maternal age. These results also agreed with those from Margulies et al[30] from a prospective study that included follow-up throughout gestation of 249 normal pregnant women (129 nulliparous and 120 multiparous) with a weekly BP control under the same experimental conditions. The results of this trial demonstrated that there was only a low correlation between maternal age and DBP, but no correlation was found with SBP.

Along these lines, results from Figure 1 indicate a trend of increasing DBP, but not SBP, with age, mainly during the second trimester of gestation. Although statistically significant, differences in the 24-hour mean of DBP among groups of women divided according to age were always <1.5 mm Hg. The increase of BP with maternal age in our study is small in absolute value; it can only be demonstrated for DBP, and it is only statistically significant for data sampled in the second trimester of gestation in both nulliparous and multiparous women and in the third trimester for nulliparous pregnant women. With all these limitations, the potential correlation of DBP with maternal age could have little influence in the proper identification of women with potential hypertensive complications in pregnancy.

Results from this study are based on data systematically measured by 48-hour ABPM. Although most studies assessing the circadian BP profile have used 24-hour ABPM as a compromise with practicability, monitoring over at least 48 hours has been shown to present advantages in the analysis of BP variability,[26,31–33] diagnosis of disease,[24] and evaluation of a patient's response to treatment.[32] The individualized estimation of rhythm characteristics becomes more reliable, and new end points, such as the circadian period, are obtained that cannot usually be estimated from 24-hour records.[34] More-

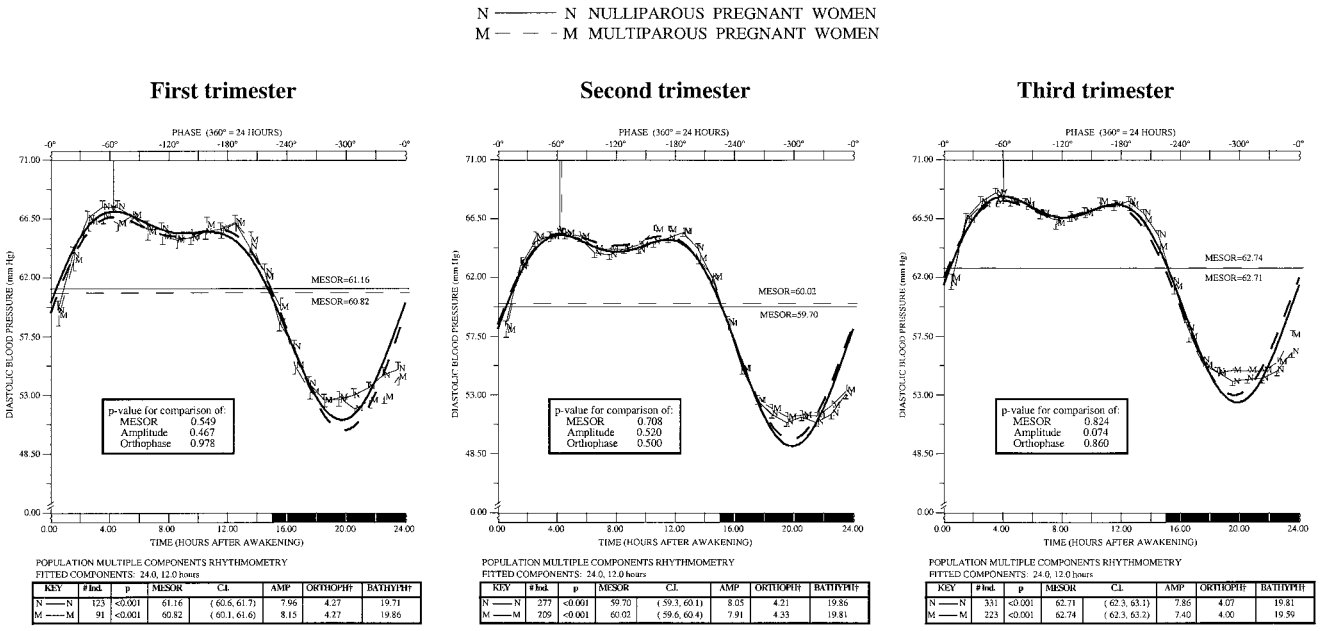

Figure 3. Circadian variation of DBP in clinically healthy pregnant women who were assessed by 48-hour ABPM in different trimesters of their gestation. Each graph shows the hourly mean±SD collected from nullipara (solid line) and multipara pregnant women (dashed line), respectively. The nonsinusoidal shaped curve represented for each group corresponds to the best-fitting waveform model determined by population multiple-component analysis (with corresponding characteristics given in the table below each graph). The arrow descending from the upper horizontal time axis points to the circadian orthophase (rhythm's crest time, in hours after awakening).

over, there may be relatively large day-to-day changes in BP, in part caused by differences in day-to-day schedule, that are at least partly accounted for by sampling over ≥2 days.[26,31] Finally, a highly statistically BP reduction during the second day of monitoring compared with the first day for the initial 5 to 6 hours of monitoring has been recently described in hypertensive patients who used an ABPM device for the first time but not the successive times 3 months apart.[35] This "ABPM effect," which has been shown to be independent of any change or modification in physical activity between consecutive days of monitoring, affects both treated as well as untreated patients and represents a significant pressor response to the novelty of the ABPM device,[35] supporting the need for monitoring over spans of time >24 hours.

The circadian pattern with large amplitude that characterize BP in healthy pregnancies at all gestational ages[22] suggests that the constant threshold currently used for diagnosing hypertension in pregnancy[36,37] should be replaced by a time-specified reference limit reflecting the mostly predictable BP variability.[26,38] The ideal reference interval for a variable of clinical interest would be specific for all deterministic factors affecting that variable. Results from Figures 1 to 3 corroborate previous reports showing a predictable pattern of BP variation with gestational age in normotensive women independently of parity or maternal age.[20] Moreover, Figures 2 and 3 also show the expected highly significant circadian variation in BP for all groups of women and stages of gestation. This circadian pattern, here expressed in hours after awakening from nocturnal sleep, was demonstrated as statistically significant in 97% of all pregnant women studied by 48-hour ABPM who participated in this trial.

This study on women systematically sampled by 48-hour ABPM throughout gestation confirms the predictable pregnancy-associated variability in BP, shows the lack of any significant influence of parity on BP, and provides proper information for the establishment of reference limits for BP to be used in the early diagnosis of hypertensive complications in pregnancy.[38] Those limits could thus be developed as a function of rest-activity cycle and gestational age, independent of parity or maternal age.

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