Predictable Blood Pressure Variability in Healthy and Complicated Pregnancies

Ramón C. Hermida, Diana E. Ayala, Manuel Iglesias

Abstract—With the aim of describing the predictable pattern of blood pressure (BP) variability during gestation, we analyzed 2430 BP series systematically sampled by ambulatory monitoring for 48 consecutive hours every 4 weeks from the first obstetric visit (usually within the first trimester of pregnancy) until delivery in 235 normotensive women, 128 women who developed gestational hypertension, and 40 women who had a final diagnosis of preeclampsia. The pattern of variation along gestation of the 24-hour means of BP and heart rate was established for each group of women by polynomial regression analysis. For normotensive women, results indicate a steady decrease in BP up to 20 weeks of pregnancy, followed by an increase in BP up to the day of delivery, with an average 8% BP increase between the middle of gestation and delivery. In complicated pregnancies, BP is stable until the 22nd week of gestation and then increases linearly for the remainder of the pregnancy. Complicated pregnancies are characterized by a 9% and 13% increase in systolic and diastolic BPs, respectively, during the second half of gestation. Results also indicate that during the first half of pregnancy, systolic but not diastolic BP is slightly elevated in women who developed preeclampsia compared with those who developed gestational hypertension. During the second half of gestation, the linear trend of increasing BP for women who developed preeclampsia has a significantly higher slope than the trend for women with gestational hypertension. For both healthy and complicated pregnancies, heart rate increases until the end of the second trimester and slightly decreases thereafter. This study of women systematically sampled by 48-hour ambulatory BP monitoring throughout gestation confirms the predictable pregnancy-associated variability in 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. Those limits should be developed as a function of gestational age, taking into account the trends in BP throughout pregnancy demonstrated here. (Hypertension. 2001;38[part 2]:736-741.)

Key Words: blood pressure • heart rate • pregnancy • hypertension, pregnancy induced • preeclampsia • blood pressure monitoring, ambulatory

Pregnancies complicated by an elevated blood pressure (BP) or preeclampsia contribute markedly to perinatal morbidity and mortality. Gestational hypertension and preeclampsia are mostly diagnosed during the third trimester of pregnancy. Many of the physiological changes of preeclampsia are essentially a reversal of those that accompany a healthy pregnancy (lack of increase in plasma volume, elevation of BP, increase in peripheral vascular resistance, reduced production of aldosterone compared with a healthy pregnancy). Although the exact cause of preeclampsia is unknown, several mechanisms have been suggested, including enhanced sensitivity to vasopressors, an abnormal maternal immunological reaction, and an imbalance in the production of vasoactive prostaglandins (thromboxane A₂ and prostacyclin), resulting in vasoconstriction of small arteries, platelet activation, and uteroplacental insufficiency.

Because an elevated BP after 20 weeks of gestation in a previously normotensive woman is common to the definition of both gestational hypertension and preeclampsia, the issue of whether the development of these complications may be predicted on the basis of BP obtained during conventional antenatal visits has been addressed in several retrospective and prospective studies. Recent studies have tried to overcome the poor results from isolated BP measurements in detecting hypertensive complications in pregnancy by relying on ambulatory BP monitoring (ABPM). With this approach, predictable patterns of BP changes along gestation have been identified for both clinically healthy and hypertensive pregnant women. 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. Despite these predictable differing patterns of BP variation,
Diagnosis of hypertension in pregnancy still relies mostly on constant thresholds for BP not specified as a function of gestational age.

In an attempt to corroborate and extend conclusions from previous studies, we report here the results from a prospective study of BP variability during pregnancy. In particular, we established and compared patterns of variability in BP along gestation in clinically healthy pregnant women and women with gestational hypertension or preeclampsia who were systematically studied by 48-hour ABPM from the first visit to the hospital until delivery.

**Methods**

**Subjects**

We studied 403 (207 primiparous) untreated white pregnant women (235 normotensive, 128 who developed gestational hypertension, and 40 who developed preeclampsia) who fulfilled all required criteria for this trial (see below). Gestational hypertension was defined as conventional BP values >140 or >90 mm Hg for systolic (SBP) or diastolic (DBP) BP, respectively, after the 20th week of gestation without clinical record of hypertension previous to pregnancy, with a hyperbaric index (area of BP excess above the upper limit of a time-varying tolerance interval computed as a function of gestational age) consistently above the threshold for diagnosis of hypertension in pregnancy after the 20th week of gestation for further corroboration of hypertension in pregnancy. Preeclampsia was defined as gestational hypertension and proteinuria, >300 mg in 24 hours of urine collection, with or without edema, diagnosed 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. The demographic characteristics of the women investigated are included in the Table.

All women received obstetric care at the Obstetric Physiopathology Unit, Hospital Clínico 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 disease; a personal history of spontaneous abortion; and multiple pregnancy, obesity, and adolescent or middle-aged nulliparous women (<18 or >35 years). The relative risk of gestational hypertension and preeclampsia in this unit is ~3.5 times that of the general obstetric population in our setting. Thus, all women participating in this trial were highly motivated and of relatively high risk for developing complications in pregnancy; the actual percentage of women with complicated pregnancies in this study does not necessarily reflect the actual incidence of hypertension in pregnancy in our setting. Despite a higher epidemiological risk according to the factors given above, women used as control subjects in this trial were normotensive at the time of inclusion and remained normotensive for the duration of pregnancy. 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 ABPM was begun, were performed by other members of the research group in different rooms of the unit.

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 were, among others, 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 of an ABPM device. Apart from the 403 women providing all required information, 23 subjects who provided <4 profiles of ABPM (5 who had spontaneous abortions and 18 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.

**Demographic Characteristics of Subjects Investigated**

<table>
<thead>
<tr>
<th>Variable</th>
<th>NT</th>
<th>GH</th>
<th>PE</th>
<th>P, 3 Groups</th>
<th>P, GH Versus PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>235</td>
<td>128</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP series, n</td>
<td>1408</td>
<td>800</td>
<td>222</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>30.4±5.5</td>
<td>29.7±5.0</td>
<td>31.8±5.0</td>
<td>0.077</td>
<td>0.019</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63.1±9.7</td>
<td>74.1±17.0</td>
<td>73.3±12.2</td>
<td>&lt;0.001</td>
<td>0.811</td>
</tr>
<tr>
<td>Height, cm</td>
<td>161.9±5.5</td>
<td>162.9±7.1</td>
<td>162.5±5.5</td>
<td>0.348</td>
<td>0.766</td>
</tr>
<tr>
<td>SBP at first visit, mm Hg*</td>
<td>119±10</td>
<td>125±10</td>
<td>124±10</td>
<td>&lt;0.001</td>
<td>0.735</td>
</tr>
<tr>
<td>DBP at first visit, mm Hg*</td>
<td>65±7</td>
<td>70±8</td>
<td>69±10</td>
<td>&lt;0.001</td>
<td>0.512</td>
</tr>
<tr>
<td>SBP at last visit, mm Hg*</td>
<td>118±9</td>
<td>138±10</td>
<td>146±13</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP at last visit, mm Hg*</td>
<td>66±7</td>
<td>82±7</td>
<td>86±8</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Gestational age at delivery, wk</td>
<td>39.4±1.1</td>
<td>38.8±3.4</td>
<td>37.7±3.1</td>
<td>&lt;0.001</td>
<td>0.069</td>
</tr>
<tr>
<td>Newborn weight, g</td>
<td>3334±446</td>
<td>3087±630</td>
<td>2967±859</td>
<td>&lt;0.001</td>
<td>0.368</td>
</tr>
<tr>
<td>Delivery by cesarean section, %</td>
<td>18.29</td>
<td>36.72</td>
<td>35.00</td>
<td>&lt;0.001</td>
<td>0.844</td>
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<tr>
<td>Intrauterine growth retardation, %</td>
<td>5.10</td>
<td>16.41</td>
<td>27.50</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preterm delivery (&lt;37 wk), %</td>
<td>3.83</td>
<td>9.38</td>
<td>25.00</td>
<td>&lt;0.001</td>
<td>0.011</td>
</tr>
<tr>
<td>Newborn’s Apgar score at 1 min</td>
<td>8.81±0.97</td>
<td>8.79±0.91</td>
<td>8.18±2.20</td>
<td>0.014</td>
<td>0.022</td>
</tr>
<tr>
<td>5 min</td>
<td>9.88±0.44</td>
<td>9.81±0.54</td>
<td>9.24±2.02</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>10 min</td>
<td>9.98±0.19</td>
<td>9.96±0.19</td>
<td>9.58±1.77</td>
<td>0.002</td>
<td>0.025</td>
</tr>
</tbody>
</table>

NT indicates normotension; GH, gestational hypertension; and PE, preeclampsia. All values are mean±SD when appropriate.

*Values provided correspond to the average of 3 to 6 conventional BP measurements obtained by a midwife for each woman at the time of her first and last (before delivery) visits to the hospital.
BP Assessment

In this trial, the SBP, DBP, and heart rate (HR) of each woman were scheduled to be measured by ABPM every 20 minutes during the day (7:00 AM to 11:00 PM), every 30 minutes during the night for 48 consecutive hours with an Spacelabs 90207 device at the time of recruitment (usually within the first trimester of pregnancy), and then every 4 weeks until delivery. BP series were eliminated from analysis (a total of 79) 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 hours or ≥12 hours. The total number of valid BP series provided by the 403 women under investigation fulfilling all mentioned requirements set a priori was 2430. During sampling, all women were maintaining 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.21,22 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 time of going to bed at night, awakening in the morning, eating meals, exercising, and participating in unusual physical activity, plus events and mood/emotional states that might affect BP.

Statistical Analysis

Original oscillometric data from each BP series were edited according to commonly used criteria for the removal of outliers and measurement errors.23 The remaining data were analyzed by the use of Chronolab,24 a software package for biological signal processing by linear and nonlinear least-squares estimation. Each BP series was analyzed by the least-squares fit of a multiple-component cosine curve with periods of 24 and 12 hours to determine the 24-hour rhythm-adjusted mean or midline estimating statistic of rhythm (MESOR), defined as the average value of the rhythmic function fitted to the data, and the amplitudes of both components.25 This model has been shown to describe sufficiently well the circadian pattern of BP variability in healthy and complicated pregnancies,18 despite the fact that other ultradian rhythms can be demonstrated to be statistically significant in some but not all pregnant women studied by 48-hour ABPM. Because the data were obtained at an unequidistant 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 because of the denser sampling during activity). The estimates of the 24-hour mean thus obtained for all BP series were used to establish their pattern of variation along gestational age for groups of uncomplicated and complicated pregnant women by polynomial regression analysis.26 Additionally, the demographic characteristics included in the Table were compared between groups of pregnant women by ANOVA (quantitative variables) or nonparametric $\chi^2$ testing (incidence of complications).

Results

The baseline characteristics of the 3 groups of pregnant women investigated differed in maternal weight ($P<0.001$) but not in age ($P=0.077$) or height ($P=0.348$). Maternal weight was characterized by a continuous linear increase along gestation for the 3 groups of women investigated. There was no significant difference between women who developed gestational hypertension and those who developed preeclampsia in maternal weight at the time of inclusion ($P=0.811$; the Table) or in their linear pattern of increasing weight throughout pregnancy ($P>0.387$). Weight was statistically significantly higher in women with complicated pregnancies compared with normotensive women at all times during gestation, in keeping with results previously reported.27 Comparison of the linear models obtained for these 2 groups of women indicates, however, that the slopes of increasing weight with gestational age are similar ($P=0.497$).

Comparison of the average of 3 to 6 serial casual BP measurements taken by a trained midwife at the time of the first visit to the hospital indicates statistically significant differences between women with healthy and complicated pregnancies ($P<0.001$ for both SBP and DBP) but similar BP values for women who later developed gestational hypertension compared with those who developed preeclampsia ($P=0.735$ and $P=0.512$ for SBP and DBP, respectively), in keeping with the previously documented similarity of circadian characteristics of ABPM among those 2 groups of women during the first half of pregnancy.18 The Table also indicates statistically significant differences between the 3 groups of women in casual BP measurements taken at the last obstetric visit (shortly before delivery; $P<0.001$ for both SBP and DBP), gestational age at delivery ($P<0.001$, mostly because of the earlier mean delivery time of women who develop preeclampsia), newborn weight ($P<0.001$), and Apgar scores at 1, 5, and 10 minutes after birth ($P=0.014$, $P=0.001$, and $P=0.002$, respectively). The nonparametric comparison by $\chi^2$ test in percentage of complications further indicates statistically significant differences between the 3 groups of women in preterm delivery and intrauterine growth retardation ($P<0.001$ in both cases). Differences in the incidence of these 2 complications are also significant when normotensive women are compared with those who developed gestational hypertension ($P=0.031$ and $P<0.001$, respectively). Finally, the incidence of delivery by cesarean section was double for complicated compared with uncomplicated pregnancies. There are statistically significant differences between women with gestational hypertension and those with preeclampsia in casual BP at the last obstetric visit ($P<0.001$), incidence of intrauterine growth retardation ($P<0.001$) and preterm delivery ($P=0.011$), and newborns’ Apgar scores ($P<0.025$).

For the normotensive pregnant women, no difference was found by ANOVA in BP as a function of parity or maternal age for any trimester of pregnancy.28 Data from the whole database were therefore pooled for subsequent analysis and only divided according to pregnancy outcome. Polynomial regression analysis of 24-hour means of BP obtained in 1408 series sampled on clinically healthy pregnant women revealed a predictable pattern of variation with gestational age. The predictable variability in the circadian MESOR of BP can be approximated by a second-order polynomial model on gestational age ($P<0.001$ for SBP and DBP). Results indicate a steady linear decrease in SBP and DBP (Figures 1 and 2) up to the 20th week of pregnancy, followed by an increase in BP up to the day of delivery. Extrapolation of the second-order model represented in Figures 1 and 2 (top) indicates that for normotensive pregnant women, BP values obtained by 48-hour ABPM at the end of gestation are similar to those that
could be found at the beginning of pregnancy for the same women. The predictable variability of BP along pregnancy in normotensive women further indicates a 7% increase in SBP (9% for DBP) between the middle of gestation and delivery. This pattern of variation is not found in pregnancies complicated with gestational hypertension or preeclampsia. In this case, the 24-hour mean of BP is stable until the 22nd week of pregnancy (linear correlation coefficient $r=0.074$, $P=0.320$ for SBP, Figure 1, bottom, and $r=0.098$, $P=0.104$ for DBP, Figure 2, bottom). Between 23 weeks of gestation and delivery, complicated pregnancies are characterized by a statistically significant increase in BP with gestational age (linear correlation coefficient $r=0.433$, $P<0.001$ for SBP, and $r=0.453$, $P<0.001$ for DBP). Results in Figures 1 and 2 further indicate that during the first half of pregnancy, SBP is slightly elevated in women who developed preeclampsia compared with those who developed gestational hypertension ($P=0.007$), but DBP is similar among those 2 groups of pregnant women ($P=0.184$). During the second half of gestation, the linear trend of increasing BP for women who developed preeclampsia has a significantly higher slope than the trend for women with gestational hypertension ($P<0.001$ for SBP and DBP). The predictable changes in BP shown in Figure 1 (bottom) indicate an 8% and 10% increase during the second half of gestation for SBP in women with gestational hypertension and preeclampsia, respectively, whereas the increase in DBP for those 2 groups of women between 22 weeks of gestation and delivery was 12% and 15% (Figure 2).

HR shows a predictable pattern of increasing values until the end of the second trimester (27 weeks of gestation) and a slightly decreasing HR thereafter for all 3 groups of women investigated (Figure 3). This decrease, as shown in Figure 3, is more prominent just at the end of pregnancy. HR is, however, stable and without statistically significant changes between 28 and 36 weeks of pregnancy. This predictable pattern of variation can be approximated by a second-order polynomial model on gestational age. There is no statistically significant difference in HR between women who developed gestational hypertension or preeclampsia at any stage of pregnancy. The second-order model of predictable variability in HR is equivalent for these 2 groups of complicated pregnancies ($P=0.156$ and $P=0.177$ for the comparison of first- and second-order polynomial coefficients). Although the general waveform of predictable variability through gestation is also similar for normotensive pregnant women (Figure 3, top), healthy pregnancies are characterized by a significantly lower HR in all trimesters of gestation (differences of 2.36, 2.46, and 2.57 bpm in the 24-hour mean of HR for the first, second, and third trimesters, respectively; all $P<0.002$).

**Figure 1.** Variation of 24-hour mean of systolic ABPM along gestational age in normotensive pregnant women (top; 1408 series from 235 subjects) and women with gestational hypertension or preeclampsia (bottom; 800 series from 128 subjects or 222 series from 40 subjects, respectively).

**Figure 2.** Variation of 24-hour mean of diastolic ABPM along gestational age in normotensive pregnant women (top; 1408 series from 235 subjects) and women with gestational hypertension or preeclampsia (bottom; 800 series from 128 subjects or 222 series from 40 subjects, respectively).
of variation seen in these variables even within a single day. Recommended tests for detecting gestational hypertension based on increases of ≥15 mm Hg in casual measurements of DBP from early values should no longer be considered valid, because those differences can be found in the course of a healthy pregnancy (as indicated in Figures 1 and 2), not just for casual measurements but for the more stable and less variable daily mean.

It is important to note that as represented in Figures 1 and 2, the daily BP mean is already highly statistically significantly different between complicated and uncomplicated pregnancies in the first trimester of gestation, in keeping with results recently reported. By the 14th week of gestation, the predictable trend of BP for women with gestational hypertension and preeclampsia reaches 115/67 mm Hg for SBP/DBP, whereas the second-order model of variation found for healthy pregnant women situates the level of mean BP at 103/60 mm Hg at the end of the first trimester of pregnancy. Differences in the 24-hour mean of BP between complicated and uncomplicated pregnancies can be observed, therefore, quite before the actual clinical diagnosis of gestational hypertension or preeclampsia usually takes place.

Although BP increases linearly during the second half of gestation for complicated pregnancies, Figures 1 and 2 (bottom) indicate that the average BP values obtained in this study for women who developed gestational hypertension or even preeclampsia are well within the normal ranges of BP variability until the very late stages of pregnancy. Only 13 of 1022 BP profiles sampled from women with complicated pregnancies have a 24-hour mean value >135 mm Hg for SBP, and only 8 profiles showed a daily mean >85 mm Hg for DBP. Reference BP thresholds for diagnosing hypertension in pregnancy should then be revised to allow proper early identification of those women more prone to developing complications in pregnancy. This study of women systematically sampled by 48-hour ABPM throughout gestation confirms the predictable pregnancy-associated variability in BP and provides proper information for the establishment of gestational age–dependent reference limits for BP, taking into account the trends in BP throughout pregnancy demonstrated here, to be used in the early diagnosis of hypertensive complications in pregnancy.

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References


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