

Time-Qualified Reference Values for Ambulatory Blood Pressure Monitoring in Pregnancy

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Abstract—To recognize the highly statistically significant circadian variability of blood pressure in pregnancy is to admit that the diagnosis of gestational hypertension or preeclampsia should be based not just on whether a casual blood pressure value is too high or too low, but rather on more pertinent questions: How long is blood pressure elevated above a given time-varying threshold? What is the excess blood pressure? When does most of the excess occur? Answers to these questions may be obtained by establishing (1) an adequate reference threshold for blood pressure and (2) a proper measurement of blood pressure elevation. Accordingly, we derived time-specified reference standards for blood pressure as a function of gestational age. We analyzed 1408 blood pressure 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 women with uncomplicated pregnancies. Data from each blood pressure series were synchronized according to the rest-activity cycle of each individual to avoid differences among women in actual times of daily activity. Data were then used to compute 90% circadian tolerance intervals for each trimester of pregnancy, in keeping with the trends in blood pressure along gestation previously documented. The method, derived on the basis of bootstrap techniques, does not need to assume normality or symmetry in the data, and therefore, it is highly appropriate to describe the circadian pattern of blood pressure variability. Results not only reflect expected changes in the tolerance limits as a function of gestational age, but also upper limits markedly below the thresholds currently used for diagnosing hypertension in pregnancy. The use of these time-qualified tolerance limits for the computation of a hyperbaric index as a measure of BP excess has already been shown to provide high sensitivity and specificity in the early identification of gestational hypertension and preeclampsia. (*Hypertension*. 2001;38[part 2]:746-752.)

Key Words: blood pressure ■ heart rate ■ pregnancy ■ circadian ■ blood pressure monitoring, ambulatory

The construction of time-specified reference limits requires systematic sampling in clinical health, in particular for those variables that are characterized by circadian rhythms of large amplitude, as is the case for blood pressure (BP). To date, BP determined casually in the examiner's office has been commonly used to diagnose hypertension and evaluate treatment efficacy.¹ These conventional time-unspecified single measurements may be misleading because BP and heart rate (HR) vary according to a spectrum of rhythms with several frequencies (the circadian in particular) and because measurements may be influenced by a host of internal factors, such as autonomic nervous system tone, vasoactive hormones, and hematologic and renal variables, plus a variety of external factors, including ambient temperature/humidity, physical activity, emotional state, alcohol/caffeine consumption, meal composition, ethnicity, gender, and sleep/wake routine.²⁻⁷ Self-measurement, if performed systematically, offers an alternative, but it interferes with daytime activities and is not feasible during sleep. The development of automatic instrumentation for indirect non-invasive ambulatory BP monitoring (ABPM) makes it possi-

ble to follow the time course of BP variation over ≥ 24 hours in large groups of individuals. The use of such monitors has provided a method for BP assessment in pregnancy that may compensate for some of the limitations of office values and self-measurements.^{8,9}

By the use of ABPM, predictable patterns of BP changes along gestation have been identified for both clinically healthy and hypertensive pregnant women.¹⁰ In normotensive 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.¹⁰ Despite these differing patterns of BP predictable variation, diagnosis of hypertension in pregnancy still relies mostly on constant thresholds for BP not specified as a function of gestational age.^{11,12} Moreover, differences between healthy and complicated pregnancies in the circadian pattern of BP can be observed by ABPM as early as in the first trimester of pregnancy, before the actual clinical diagnosis of gestational

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hypertension or preeclampsia takes place for the women investigated.¹³ The circadian pattern with large amplitude that characterizes BP of healthy pregnant women at all gestational ages¹³ suggests that the current static BP threshold values currently used for the diagnosis of hypertension in pregnancy should be replaced by a time-qualified reference limit that reflects the mostly predictable BP variability along the 24 hours of the day.⁶

Time-specified reference limits can be constructed in different ways. They can be model dependent¹⁴ or model independent,^{5,6} and they can be computed as prediction^{15,16} or tolerance intervals.^{5,17,18} When samples from a reference group of subjects are available, one may thus construct a prediction interval expected to include any single future observation from the reference population with a specified confidence.^{15,16} Alternatively, the reference interval may consist of a somewhat broader tolerance interval that will include at least a specified proportion of the population with a stated confidence.^{5,17,18} The latter kind of reference interval is commonly used in industry and has been recommended for clinical measurements.^{5,6} In the case of hybrid data (time series of data collected from a group of subjects), such a tolerance interval could be very difficult to determine by following a parametric approach similar to the procedure used for the computation of prediction intervals,^{15,16} especially when consideration of both within-individual and between-individuals variances is required. Moreover, the parametric construction of prediction intervals is restricted by the assumption of the hypotheses of normality and symmetry of values. These 2 conditions are very difficult to meet for most clinical data, which are usually characterized by short, sparse, noisy, and nonequidistant time series. Accordingly, we have developed a nonparametric method for the computation of tolerance intervals.^{5,17,18} Because the method is based on bootstrap techniques,^{19,20} it does not need to make any distributional assumption, such as normality or symmetry in the data, 2 basic assumptions usually violated when analyzing BP. We have used this method to establish time-qualified tolerance limits as a function of gestational age and rest-activity cycle for BP and HR, using data obtained from normotensive pregnant women who were systematically studied by 48-hour ABPM from the first obstetric visit to the hospital until delivery.

Methods

Subjects

We studied 235 (126 nulliparous) untreated white pregnant women with uncomplicated pregnancies, who fulfilled all required criteria for this trial (see below). They were 30.5 ± 5.6 (mean \pm 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 carried out 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 of 18 to 40 years, gestational age <16 weeks at the time of inclusion, casual BP measurements <140/90 mm Hg for systolic (SBP)/diastolic BP (DBP) for the duration of pregnancy, diurnal mean for all ABPM profiles consistently <135/85 mm Hg for SBP/DBP, 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,^{21,22} previously calculated from an independent reference population of 189 normotensive pregnant women¹⁸) consistently below the previously established threshold for diagnosing hypertension in pregnancy²¹ 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 anti-inflammatory medication, diabetes or any other endocrine disease such as hyperthyroidism, and intolerance to the use of an ABPM device.

Apart from the 235 women providing all required information, 23 subjects who provided <4 profiles of ABPM (5 spontaneous abortions and 18 who withdrew from the trial) were eliminated from the study. For this study on reference norms, we did not use either information on 128 women who developed hypertension in pregnancy and were studied following the same protocol as the normotensive volunteers. 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 BP and HR 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 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 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 BP series provided by the 235 women under investigation fulfilling all mentioned requirements set a priori was 1408.

During sampling, all women were living on their usual diurnal waking (\approx 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.²³ 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 and awakening in the morning and of meals, exercise, and unusual physical activity, plus events and mood/emotional states that might affect BP.

Statistical Methods

Each individual's clock-hour BP and HR 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.⁶ BP values were then edited according to commonly used criteria for the removal of outliers and measurement errors.²⁴ The remaining synchronized data from the reference normotensive population of pregnant women were used to compute time-specified tolerance intervals. Those limits were derived separately for each trimester of pregnancy, in keeping with the trends in BP during gestation previously documented.¹⁰ The procedure for the computation of model-independent tolerance limits starts with the analyst setting the

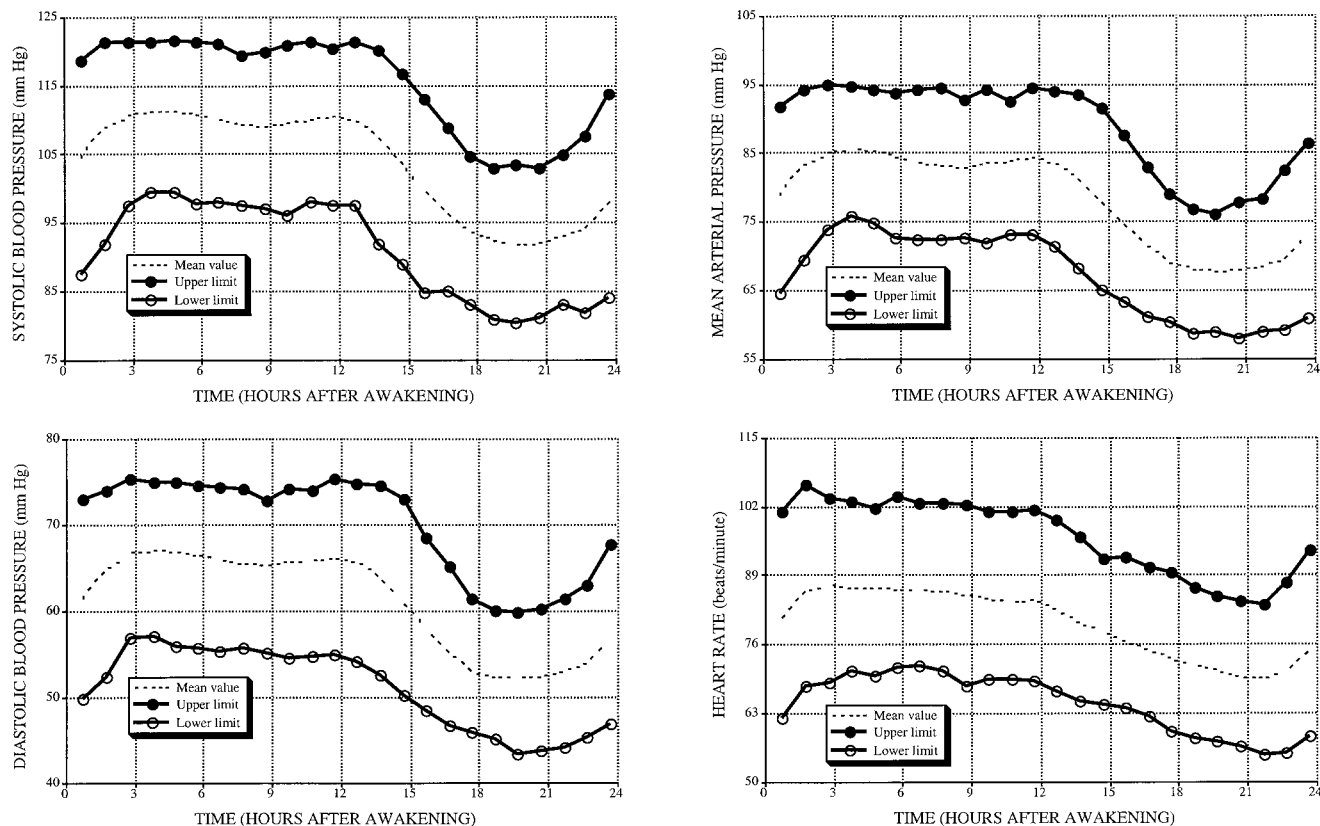


Figure 1. Circadian 90% tolerance intervals for BP and HR from normotensive pregnant women who were assessed by 48-hour ambulatory monitoring in the first trimester of pregnancy.

size of the time span for which the limits are to be computed (that in which no appreciable changes in population characteristics, ie, mean and variance, take place) and the distance between consecutive time classes (this allows computation of smoothed limits by overlapping time intervals, as well as dealing with nonequidistant sampling). In so doing, one needs to take into account the existence of periodicities in the studied variable. If, for instance, a 24-hour period is assumed to characterize BP variability, data that are separated in time by a multiple of 24 hours should be included in the same time class.

In dealing with hybrid time series, 2 kinds of variability in the data can be computed: among individuals (arising from the differences among the individuals in the population) and within individuals (arising from the differences among data sampled on the same individual). To characterize all isolated values sampled from any given individual, one must take both these variances into account. With respect to the population, however, the most important variability is that given by the between-individuals variance. In such cases, the within-individual variance can be eliminated by averaging all data sampled from the same individual in each time class; the hybrid database will now be characterized by a smoothed sample in which each time series has, at the most, only 1 datum in each time interval (the average of the original values for the individual in that time interval).^{5,17,18} A detailed explanation of the mathematical development of nonparametric tolerance intervals for hybrid time series has been provided previously.^{5,17,18}

From a practical point of view, it is important to consider the actual time when the tolerance interval calculated for any given time class is going to be represented. One simple approach could be to associate the tolerance interval to the middle point of the time class. This approach, however, does not take into account the actual sampling times of all values used in the computation of the tolerance interval. To avoid such limitations, a better approach first calculates the mean of all sampling times of data provided for any given individual in the time class of interest. This mean time would then be

associated to the datum of the smoothed sample characterizing the individual in that time class (average of original values for the individual in the time class). Next, the time to be associated with the tolerance interval is calculated by averaging the mean time across all individuals providing data in the time class of interest. The tolerance interval can then be represented along the time scale by connecting the values obtained for each time class (linear interpolation).⁵

Results

For the normotensive pregnant women participating in this trial, no statistically significant difference was found by analysis of variance in BP as a function of parity or maternal age for any trimester of pregnancy.²⁵ Data from the whole database were therefore pooled for subsequent analysis and only divided according to trimester of gestation. The tolerance intervals were calculated for SBP, mean arterial BP (MAP), DBP, and HR, taking into account between-individuals variability and using 2-hour time classes with 1-hour overlap between consecutive time classes. Allowing a certain degree of overlap between consecutive time classes provides a further smoothing of the tolerance intervals. These double-smoothed intervals are less dependent of extreme values and outliers than the limits computed for nonoverlapped time classes and limits calculated by taking into account between-individuals as well as within-individual variances. Diagnoses based on these smoothed intervals have a higher sensitivity because they contain a lower proportion of false-negatives than the diagnoses based on other (wider) tolerance intervals, as previously documented.^{5,6,18}

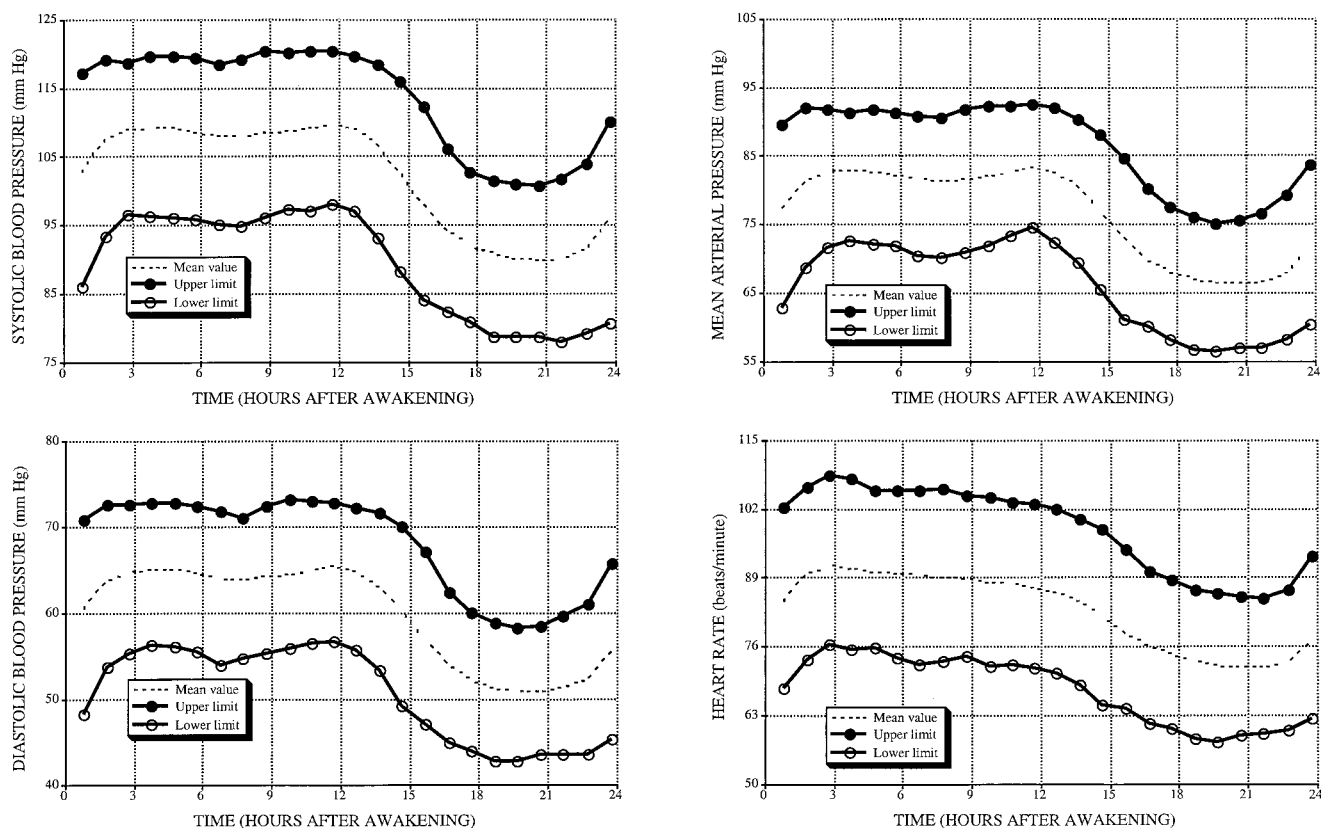


Figure 2. Circadian 90% tolerance intervals for BP and HR from normotensive pregnant women who were assessed by 48-hour ambulatory monitoring in the second trimester of pregnancy.

Figures 1 to 3 represent the tolerance intervals (derived to cover 90% of the population of normotensive pregnant women with a 90% confidence in each time class) calculated following the specifications given above for the 4 circulatory variables in each trimester of pregnancy. The graphs represent in each case the upper and lower limits of the tolerance interval (in hours after awakening from nocturnal sleep), as well as the mean value of BP and HR for the women studied by 48-hour ABPM in each trimester of their gestation. The upper limit of the tolerance interval in all 3 trimesters of pregnancy is not only markedly $<140/90$ mm Hg but also below the thresholds of $135/85$ mm Hg previously recommended for the diurnal mean of BP determined by ABPM in the diagnosis of hypertension.²⁶ The values for the upper limit of the tolerance intervals represented in Figures 1 to 3 are also lower than values obtained following the same mathematical approach for clinically healthy normotensive nonpregnant women studied by 48-hour ABPM.^{5,6} The tolerance limits also reflect the circadian variability in BP previously documented for normotensive pregnant women in each trimester of pregnancy.¹³

Results from Figures 1 to 3 further corroborate the previously documented predictable trend of BP variation throughout pregnancy.¹⁰ The limits represented in Figure 2 for women sampled in the second trimester of pregnancy are lower than limits calculated from data obtained on the same women during the first (Figure 1) and third (Figure 3) trimesters of pregnancy. For HR, results have indicated a

predictable pattern of increasing values until the end of the second trimester (27 weeks of gestation) and a slightly decreasing HR thereafter. This decrease 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.¹⁰ In keeping with these results, the upper limit of the tolerance interval for HR is lower in the first than in the second or third trimesters of pregnancy.

Discussion

The accumulation of databases collected under standardized conditions on healthy individuals makes it possible to determine reference intervals for BP measurements as a function of factors presumably affecting BP, such as circadian stage or gestational age. By the use of these time-qualified reference limits (Figures 1 to 3), many false-positive and also false-negative diagnoses can be eliminated compared with diagnoses made relying on just time-unspecified casual BP measurements.^{21,22} Once the tolerance interval from a proper reference population is available, the hyperbaric index, as a proper determinant of BP excess, can be calculated by numerical integration as the total area (within 1 cycle) of the given patient's BP above the threshold provided by the upper limit of the tolerance interval.^{21,22} The problem amounts to a summation of trapezoidal areas delineated by the upper limit of the tolerance interval and the straight lines connecting successive data points from the patient (or average values for each time span, if using limits calculated by taking into

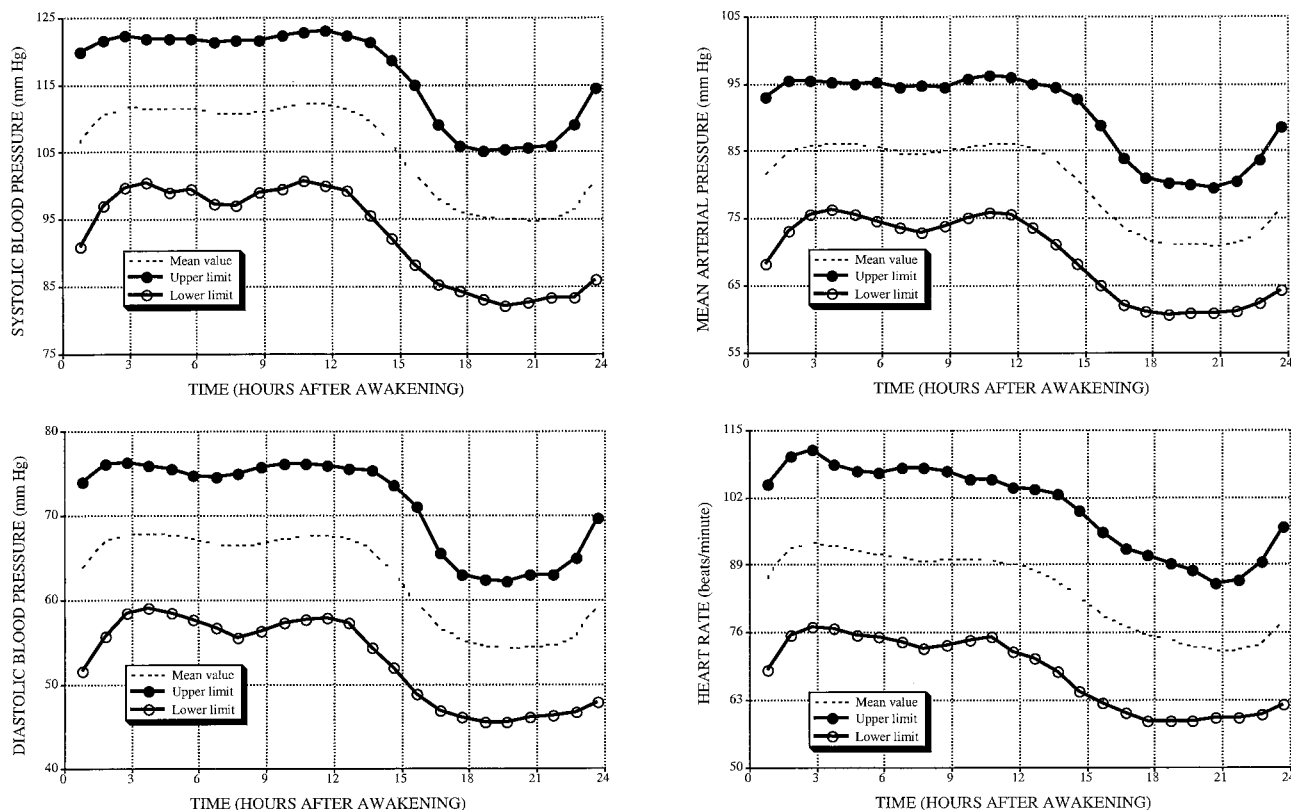


Figure 3. Circadian 90% tolerance intervals for BP and HR from normotensive pregnant women who were assessed by 48-hour ambulatory monitoring in the third trimester of pregnancy.

account only the variance between individuals, as it is the case herein for Figures 1 to 3).^{18,27} Because only the area of pressures above the critical upper limit is of interest, whenever consecutive data points lie on opposite sides of the threshold, it is necessary to calculate the time at which BP exceeds the limit. This can easily be done by linear interpolation.^{18,27} All these features are incorporated in a computer-based medical system for the computation of BP excess in the diagnosis of hypertension, as previously described.²⁷

The combination of tolerance intervals as time-varying reference threshold for BP with the hyperbaric index as a measure of BP excess has led to define the so-called tolerance-hyperbaric test.^{21,22} This test, and therefore the hyperbaric index as measure of BP excess, has already been shown to provide a much higher sensitivity and specificity in the diagnosis of hypertension²² as well as in the early identification of hypertensive complications in pregnancy²¹ compared with those of the 24-hour mean value²⁸ or the BP load,^{6,10,29} parameters also calculated from the BP series obtained by ABPM. For the women investigated in this study, sensitivity of the tolerance-hyperbaric test was 94% for women sampled in the first trimester of gestation and increased up to 99% in the third trimester. The positive and negative predictive values were >97% in all trimesters. Even more relevant from the clinical point of view is that results also indicate that normotensive women were characterized by highly significant reductions of 60% in the incidence of preterm delivery, 70% in the incidence of intrauterine growth retardation, and 50% in the incidence of delivery by cesarean

section, compared with the incidence in all those perinatal parameters for women with a hyperbaric index consistently above the threshold for diagnosis of gestational hypertension²¹ from all ABPM profiles obtained after 20 weeks of gestation.³⁰ On the other hand, normotensive women gave birth to children on average 250 g heavier than those from women identified as hypertensive according to the tolerance hyperbaric test.³⁰ These results further corroborate the prognostic value of this test and the potential clinical use of the reference limits represented in Figures 1 to 3 for the diagnosis of hypertension in pregnancy.

It should be emphasized that using the tolerance intervals represented in Figures 1 to 3 as a reference threshold necessarily implies that all patients to be tested should be monitored following a similar sampling scheme than that applied to obtain data from the reference population (eg, every 20 minutes during the day and every 30 minutes during the night for 48 consecutive hours). Moreover, if a smoothed tolerance interval is to be used as reference standard, calculated, for instance, for 2-hourly time classes with 1-hour overlap between consecutive time classes, a similar smoothing procedure should be applied to the time series obtained from the test patient. Using a smoothed tolerance interval (where the within-individual variance is not longer taken into account) as reference for all single BP measurements would lead to a higher proportion of false-positive diagnoses.⁵

The limits represented on Figures 1 to 3 could be somehow compared with reference thresholds for ABPM in pregnancy presented previously.³¹⁻³³ Ferguson et al,³² in a study on

women sampled by ABPM at 3 different states of gestation, also found BP measurements in pregnancy to be lower than values obtained from nonpregnant women; their limits were also higher at the end on pregnancy compared with those obtained for early stages of gestation on the same women. Brown et al³³ found increasing reference standards with gestational age from data sampled on women studied at ≥ 1 of 4 stages of gestation; those stages, however, had different length in terms of gestational weeks and were not defined as a function of trimester of gestation. Moreover, results from all those studies were presented in terms of confidence limits instead of prediction or tolerance intervals. Although these will define limits to include any given subject from the reference population or a specified proportion of the whole population, respectively, confidence intervals are calculated to include the average value of the subjects used as a reference sample with a stated confidence. Limitations of confidence compared with tolerance or even prediction intervals in clinical applications are important and have been extensively documented before.^{5,14,17,18}

The use of tolerance intervals as the correct threshold for the circadian variability of BP is preferred and proposed here as a substitute to the prediction limits used previously.^{15,16} This is primarily because the practical use of prediction limits is restricted by the assumptions of normality and symmetry,¹⁵ usually violated when BP, HR, and most other variables of clinical interest are analyzed. The nonparametric procedure for the computation of tolerance intervals does not need to make such assumptions.⁵ Moreover, the tolerance intervals may be easily computed for the case in which only between-individuals variability is taken into account. These smoothed limits are narrower than the prediction limits, providing, in general, a smaller proportion of false-negative diagnoses.^{6,27} On the other hand, the smoothed tolerance intervals do not provide a significantly larger number of false-positives, as the smoothed time series computed for the test subject, to be compared against the tolerance intervals, is not influenced by outliers and extreme values to the same extent as are the original time series used for comparison against the prediction intervals.⁵ In any event, the issue of sensitivity and specificity should be more particularly discussed in terms of the measure of BP excess or deficit to be used in conjunction with the reference intervals.^{21,22,27} Finally, the improved sensitivity that is the basic concern in most clinical applications (reducing the number of false-negatives, even at the cost of getting more false-positives), could be achieved easily by decreasing the percentage of the population assumed to be covered within the tolerance intervals.

Sampling requirements also deserve some comments. The prediction intervals should not be considered generally applicable when constructed on the basis of a small sample size.¹⁵ When relatively small sample sizes are under consideration, use of nonparametric tolerance intervals is indicated.⁵ It has been shown^{5,6} that the tolerance intervals computed according to the nonparametric approach used here are stable, with no relevant changes of width at any given time class, and provide the expected coverage of the population (say 90%), with sample sizes of ≈ 50 time series of BP obtained with a sampling scheme similar to that used here (20- to 30-minute

intervals for 48 hours), a number much lower than that needed for computation of a stable prediction interval.^{5,15,16} The sample sizes used in the computation of the tolerance intervals provided in Figures 1 to 3 warrant their stability and their use as a proper reference, at least for Spanish pregnant women. Possible extrapolation to other ethnic groups deserves further investigation. Further advantages of smoothed tolerance intervals with respect to any other tolerance or prediction intervals have been previously documented.^{5,6}

The combination of hardware for ABPM with the software needed for the establishment of time-qualified tolerance limits and the assessment of the extent and timing of BP elevation²⁷ may serve to help in prognosis and diagnosis with a better assessment of health status,^{21,22} to initiate treatment if needed, to time treatment when it is most desirable and least harmful in terms of undesired effects,³⁴ and to gauge the subject's response to treatment.²⁷

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