

Blood Pressure Excess for the Early Identification of Gestational Hypertension and Preeclampsia

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Abstract—We have examined prospectively whether the combined approach of establishing tolerance intervals for the circadian variability of blood pressure (BP) as a function of gestational age, and then determining the so-called hyperbaric index (area of BP excess above the upper limit of the tolerance interval) by comparison of any patient's BP profile (obtained by ambulatory monitoring) with those intervals provides a high sensitivity test for the early detection of pregnant women who subsequently will develop gestational hypertension or preeclampsia. We analyzed 657 BP series from 92 women with uncomplicated pregnancies and 378 series from 60 women who developed gestational hypertension or preeclampsia. BP was sampled for about 48 hours once every 4 weeks after the first obstetric consultation. Circadian 90% tolerance limits were determined as a function of trimester of gestation from 497 series previously sampled from a reference group of 189 normotensive pregnant women. The hyperbaric index was then determined for each individual BP series in the validation sample. Sensitivity of this test for diagnosing gestational hypertension was 93% for women sampled during the first trimester of gestation and increased up to 99% in the third trimester. The positive and negative predictive values were above 96% in all trimesters. Despite the limitations of ambulatory monitoring, the approach presented here, now validated prospectively, represents a reproducible, noninvasive, and high sensitivity test for the very early identification of subsequent gestational hypertension and preeclampsia, on the average, 23 weeks before the clinical confirmation of the disease. (*Hypertension*. 1998;31[part 1]:83-89.)

Key Words: ■ blood pressure ■ diagnostic test ■ tolerance intervals ■ hyperbaric index ■ human pregnancy ■ normotension ■ hypertension, gestational ■ preeclampsia

In order to predict the occurrence of gestational hypertension or even preeclampsia, several (clinical, biochemical, and biophysical) tests have been designed with various degrees of specificity and sensitivity.¹ Gant et al² proposed the roll-over or supine pressor test for predicting the development of acute hypertension in pregnancy. The results of this test are highly variable among different investigators, and there is poor reproducibility in the same patient.¹ Therefore, although the roll-over test has gained some popularity because of its simplicity, it is of little use clinically as a predictive test. Intravenous infusion of angiotensin II was reported to cause a smaller rise in BP in pregnant women than in nonpregnant women.³ These results were complemented by the finding that the relative refractoriness to the pressor effects of angiotensin II is lost to a marked extent in women who subsequently developed preeclampsia.⁴⁻⁶ As for the roll-over test, sensitivity and specificity of the angiotensin II test varied greatly among different studies. Moreover, this test is too complicated and time consuming to be used as a clinical screening procedure.¹

Because an elevated BP is the hallmark for the diagnosis of gestational hypertension and preeclampsia, the issue of whether

the development of this complication may be predicted on the basis of BP obtained during conventional antenatal visits has been addressed in several retrospective and some prospective studies. Values of MAP in the second trimester have been used in predicting the development of preeclampsia later in pregnancy. Page and Christianson⁷ found that when the average MAP in the second trimester was above 90 mm Hg there was a significant increase in the frequency of preeclampsia. Sensitivity of this MAP-2 test was, however, only 43%, with a positive predictive value of 8.6%. These sensitivity and specificity values vary greatly in different studies.^{1,8-12}

Recent studies have tried to overcome the poor results from isolated BP measurements during the second trimester in detecting preeclampsia by relying on ABPM. By the use of this approach, several authors have found a reduced drop in BP by night in preeclamptic patients,¹³⁻¹⁵ whereas others even report an inversion of the circadian pattern of change in BP associated with preeclampsia.¹⁶⁻¹⁸ Most of these studies have usually being carried out during the second or third trimester of pregnancy. Physiological changes, however, already occur early in human

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Selected Abbreviations and Acronyms

ABPM	= ambulatory BP monitoring
BP	= blood pressure
DBP	= diastolic blood pressure
HBI	= hyperbaric index
HR	= heart rate
MAP	= mean arterial pressure
PTE	= percentage time of excess
SBP	= systolic blood pressure

pregnancy.^{13,19–23} By the use of ABPM, a predictable pattern of BP variation along pregnancy was demonstrated for 189 normotensive pregnant women monitored on several occasions during their gestation. This pattern could not be found in pregnancies complicated with gestational hypertension or preeclampsia.²² These differing patterns of predictable variability have been corroborated prospectively in pregnant women systematically sampled by ABPM throughout gestation.²⁴ Moreover, differences between healthy and complicated pregnancies in the circadian pattern of BP, previously documented for the second trimester of pregnancy,²⁵ can be observed as early as in the first trimester of pregnancy, quite before the actual clinical diagnosis of gestational hypertension or preeclampsia.^{13,19} The use of the 24-hour mean of BP did not provide, however, a proper approach for an individualized early diagnosis of gestational hypertension or preeclampsia.¹³

Against this background, the construction of a time-specified reference limit reflecting the circadian BP variability has been proposed as a substitute for the constant limits now used (140/90 mmHg for SBP and DBP).²⁶ A proper reference limit could be constructed, for instance, as a model-independent 90% tolerance interval determined within a short interval (in which no appreciable changes in population characteristics, namely mean and variance, take place), which is progressively displaced throughout one cycle of the periodicity investigated.^{27,28} Once the threshold (given by the upper limit of the tolerance interval) is available, the so-called HBI, as a measure of the total load exerted on the arterial walls,^{29–31} can be calculated by numerical integration as the total area (within one cycle) of any given patient's BP above the threshold.^{28,29} The HBI has been defined as a better determinant of BP excess than the BP load (percentage of values above a constant threshold³²). The HBI as well as the duration of excess (PTE, defined as the percentage time of the 24 hours with BP from the test subject exceeding the upper limit of the tolerance interval) could then be used as nonparametric endpoints for assessing gestational hypertension.

The retrospective evaluation of this approach on 745 BP series sampled by ABPM from 289 pregnant women indicated that sensitivity of the test based on the maximum HBI for the early detection of gestational hypertension was 97% for women sampled during the first trimester of gestation and increased up to 100% in the third trimester.³³ With the aim to corroborate these results, we examined prospectively whether this new approach provides a high sensitivity test for the early detection of pregnant women who subsequently will develop gestational hypertension or preeclampsia.

Methods

Subjects

In this prospective trial we studied 152 Caucasian pregnant women (96 primipara). Of those women, 92 (63 primipara) had uncomplicated pregnancies. Forty-two women (23 primipara) developed gestational hypertension, diagnosed by conventional BP values >140/90 mm Hg for SBP/DBP without clinical record of hypertension previous to pregnancy. The remaining 18 women (10 primipara) developed preeclampsia, defined here as gestational hypertension and proteinuria, >300 mg/24 hours in urine, with or without edema. All women received obstetric care at the Obstetric Physiopathology (high risk) Unit, Hospital General Clínico Universitario de Galicia, Santiago de Compostela, Spain. Reasons for receiving medical care at this Unit include, among others, family or personal history of either gestational hypertension; preeclampsia; chronic hypertension; cardiovascular, endocrine, bleeding, or metabolic disease; a personal history of previous spontaneous abortion; multiple pregnancy; obesity; and early or late nulliparous pregnancy (<18 or >35 years). The incidence of gestational hypertension and preeclampsia in this Unit is about three times that of the general obstetric population in our setting. Inclusion criteria for this trial were absence of any condition requiring the use of antihypertensive medication, age (18 to 40 years) and gestational age (<20 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, and any other endocrine disease such as hyperthyroidism, as well as the impossibility to tolerate the use of an ambulatory BP monitor. The Ethical Committee of Clinical Research from the Medical School approved the study. All volunteers signed consent forms before entering the study. We also used information sampled from 189 women with uncomplicated pregnancies, volunteers of a previous retrospective trial on the study of BP in pregnancy.³³ Data from this independent reference population were used to determine tolerance intervals for the circadian variability in BP as a function of trimester of gestation.²⁸

BP Assessment

The SBP, MAP, DBP and HR of each subject were automatically monitored every 30 minutes during the day (9 AM to 10 PM) and hourly during the night for 48 hours with an ABPM-630 Colin device at the time of recruitment and then every 4 weeks until delivery. BP series were eliminated from analysis when they showed an irregular schedule during the days of sampling, an odd sampling with spans of >3 without BP measurement, or a night resting span <6 hours or >12 hours. The total number of BP series provided by the women under investigation fulfilling all mentioned requirements set a priori was 1035. Additionally, we also analyzed data from 497 BP profiles previously sampled from the reference population of 189 normotensive pregnant women. All women were living during sampling on their usual diurnal waking (approximately 8 AM to midnight for most subjects), 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 the monitor according to the standards published by the Association for Advancement of Medical Instrumentation³⁴ has been previously established.³⁵ 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 AM and 1 PM. During monitoring, each subject maintained a diary regarding information about their activity cycle, dietary consumption, physical activity, emotional state, and other external or internal stimuli possibly affecting BP.

Obstetric Care

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 members of the

research group in one room of the Unit. Conventional obstetric examinations, usually done on the same day just before starting ABPM, were carried out by different members of the research team in other rooms of the Unit. Diagnosis of gestational hypertension or preeclampsia (as defined above) was done using information from the conventional obstetric examinations and routine analyses of urine. Information from these conventional examinations and information obtained from ABPM were kept in separate files. Comparison of the information from both files for each woman was only done after delivery, when the final pregnancy outcome (either normotension, gestational hypertension, or preeclampsia) was available. Information obtained from ABPM was withheld from the patient as well as from the obstetrician taking conventional care of the patient. This blind approach allowed comparison of the actual time of diagnosis made by conventional practice as compared with the time of diagnosis obtained on the basis of the determination of HBI from data sampled by ABPM.

Statistical Methods

Original oscillometric data from each individual BP series were first synchronized according to the rest-activity cycle of each subject by recalculation of all times of sampling in terms of hours from midsleep. This avoided differences among subjects in actual times of daily activity. The same synchronization was previously applied to data sampled from the reference population. This approach allows a proper comparison of any patient's BP profile with the tolerance limits by reducing the probability of spurious BP excess due to differences in the rest-activity cycle.²⁹ After synchronization, BP and HR values were edited according to commonly used criteria for the removal of outliers and measurement errors.^{36,37} The synchronized data from the reference normotensive pregnant women were used to determine time-specified tolerance intervals, to be used as reference threshold in the calculation of HBI. Those limits were derived separately for each trimester of pregnancy, in keeping with the trends in BP during gestation previously documented.^{22,24}

The method for the determination of tolerance intervals, derived on the basis of bootstrap techniques, does not need to assume normality or symmetry in the data. It is, therefore, highly appropriate to describe

the circadian pattern of BP.²⁷ A detailed explanation of the mathematical development of nonparametric tolerance intervals for hybrid time series has been provided previously.^{27,28} Results will rely on model-independent, smoothed tolerance intervals obtained by taking into account only among-subjects variance and determined for 2-hour time classes with 1-hour overlap between consecutive time classes. Advantages of these smoothed tolerance intervals with respect to any other tolerance or prediction intervals have been already documented.^{27,28} Once the tolerance intervals are obtained, both the PTE and the HBI for any given subject can be obtained by numerical integration. Details of the mathematical procedure for determining these parameters have also been previously described.^{28,29} Since the conventional assessment of hypertension relies on absolute casual values >140 or 90 mm Hg for SBP or DBP,²⁶ results based on the determination of BP excess will be expressed as a function of the maximum HBI, defined as the maximum of three values of HBI, those determined for SBP, MAP, and DBP, respectively, for any given subject. Analysis of the HBI obtained separately for any of the three cardiovascular variables provided lower sensitivity and specificity than results based on the maximum HBI.³³

Results

Fig 1 (top) shows the distributions of the maximum HBI determined from the BP series sampled by ABPM in the validation groups of healthy and complicated pregnant women, represented as a function of trimester of pregnancy. The top graphs of Fig 1 indicate that the range of physiologically acceptable BP excess for normotensive pregnant women did not exceeded 15 mm Hg×hour for any of the three cardiovascular variables in any trimester. Moreover, most of the series analyzed are characterized by having no excess with respect to the upper limit of the tolerance interval. This range of acceptable BP excess is comparable to that obtained before for the reference population providing data used for determin-

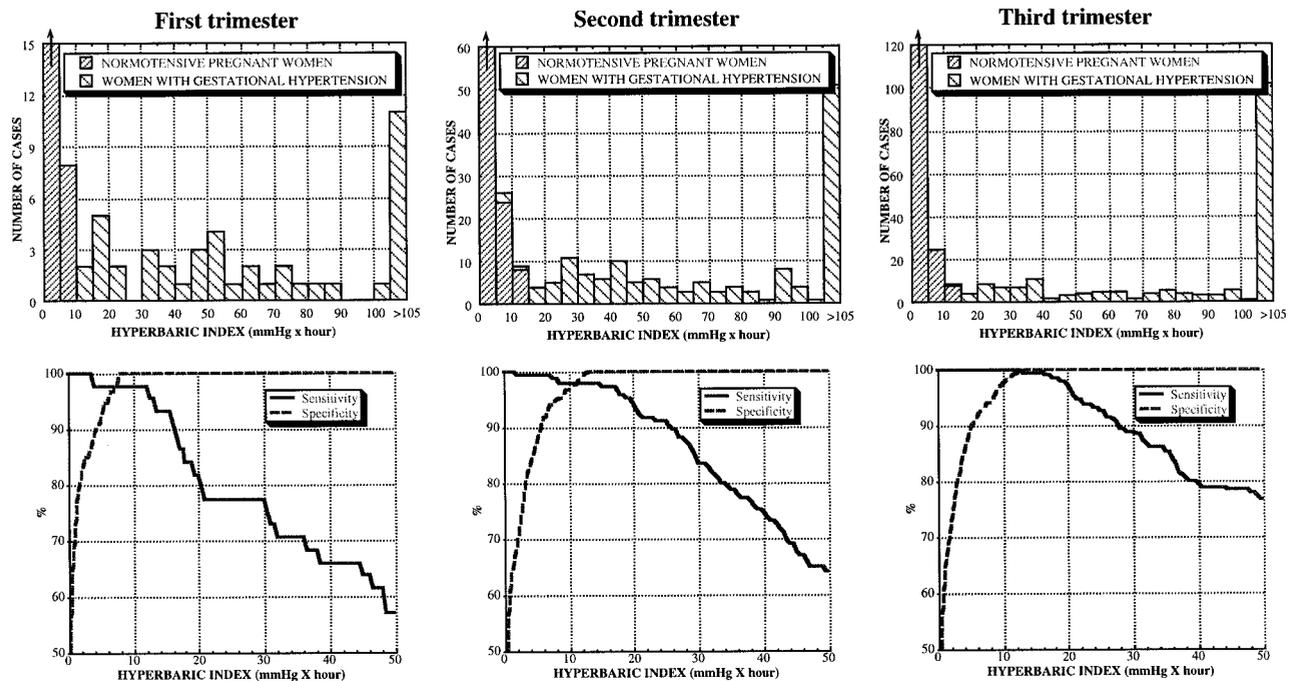


Figure 1. Frequency distribution of maximum HBI* (top) from normotensive pregnant women and women who developed gestational hypertension or preeclampsia sampled in different trimesters of pregnancy. Characteristics of the diagnostic test based on the HBI are shown at the bottom. *Maximum of three values determined from individual 48-hour series of systolic, mean arterial, and diastolic blood pressure, respectively, by comparison with 90% circadian tolerance limits obtained from a reference population of 189 normotensive pregnant women.

ing the tolerance intervals.³³ The graphs on the top of Fig 1 also indicate that for women with diagnosis of gestational hypertension or preeclampsia, most BP series are characterized by a maximum HBI above that threshold value, even in the first trimester of pregnancy. Moreover, many of these series have a maximum HBI >105 mm Hg×hour, a value chosen here only to keep the length of the horizontal axis of the histograms below a reasonable size.

The distributions of the maximum PTE show a slightly larger overlap between normotensive and hypertensive women than the maximum HBI, partly because the PTE is a truncated variable with a maximum possible value of 100. Results indicate that most of the normotensive subjects have a maximum PTE <25% in all trimesters of pregnancy (not shown). On the contrary, most of the women with a pregnancy outcome of gestational hypertension or preeclampsia exceeded 25% in PTE. Most but not all of the complicated pregnancies are characterized by a consistent BP excess above the upper limit of the circadian tolerance interval during at least 50% of the 24 hours. Results also indicate a tendency to increasing values of PTE for complicated pregnancies with advancing gestational age.

Using results from Fig 1 as well as from the clinical files, we determined and compared sensitivity and specificity for diagnosing gestational hypertension and preeclampsia based on conventional clinical practice as well as on the maximum HBI (both approaches being carried out independently by different members of the research team). The Table indicates that no woman who later developed gestational hypertension or preeclampsia was actually properly identified with conventional criteria during the first trimester of gestation. During the second trimester, only 2% of the conventional check-ups done on the day when ABPM started for each BP series in this study

predicted gestational hypertension or preeclampsia. For the third trimester, sensitivity increases up to 25%, a value somehow too high because it includes diagnoses made close to the time of delivery on the basis of urine tests identifying proteinuria. Specificity of conventional practice was always very high, mostly because practically none of the clinically healthy pregnant women nor most of those who will actually develop preeclampsia show casual BP values >140/90 mm Hg for SBP/DBP at any gestational age, as previously documented.^{13,19}

When diagnosis was based on a threshold value of 15 mm Hg×hour for the maximum HBI, results in the Table indicate a sensitivity of 93% for women sampled during the first trimester of gestation. Sensitivity increases with gestational age, mainly because BP also increases steadily in those women who subsequently developed gestational hypertension or preeclampsia.^{22,24} Specificity was also very high, in keeping with the documented characteristics of the calculation of smoothed tolerance intervals.²⁷⁻²⁹ The positive and negative predictive values of the test based on the maximum HBI were >96% in all trimesters of pregnancy. The relative risk increased with gestational age. The values of this parameter were already very high in the first trimester of pregnancy. These results corroborate early retrospective studies on the use of this tolerance-hyperbaric test for diagnosing gestational hypertension and preeclampsia.³³

The characteristics of this test as a function of trimester of gestation are described at the bottom of Fig 1. These graphs represent sensitivity and specificity determined as a function of different threshold values for the maximum HBI. Fig 1 (bottom) indicates that as we increase the threshold value, specificity will increase very rapidly. Sensitivity, on the contrary, will smoothly decrease for higher values of HBI. The slopes for increasing specificity and decreasing sensitivity are

Diagnosis of Gestational Hypertension Based on Conventional Clinical Practice and Maximum Hyperbaric Index in Spanish Pregnant Women

	1st Trimester	2nd Trimester	3rd Trimester	All Trimesters
Conventional practice				
Sensitivity	0	2.07	24.87	13.23
Specificity	100	98.80	98.09	98.63
Positive predictive value	...	50.00	88.68	84.75
Negative predictive value	67.88	63.50	68.44	66.39
Relative risk	...	1.37	2.81	2.52
Maximum HBI				
Sensitivity	93.18	97.24	99.47	97.88
Specificity	100	100	100	100
Positive predictive value	100	100	100	100
Negative predictive value	96.88	98.43	99.68	98.79
Relative risk	32.05	63.69	312.50	82.64
Cases-Normotension	93(70)	250(91)	314(90)	657(92)
Cases-Hypertension	44(35)	145(53)	189(56)	378(60)

HBI indicates hyperbaric index, the area of blood pressure excess (obtained by numeric integration) above a given threshold, here a 95% upper circadian tolerance limit computed separately for each trimester of pregnancy from data previously sampled for about 48 hours by ambulatory noninvasive monitoring on a reference population of 189 normotensive pregnant women. Maximum HBI indicates the maximum of three values, those obtained for systolic, mean arterial, and diastolic blood pressure, respectively, for each individual blood pressure profile. Cases indicates the total number of blood pressure profiles obtained in each trimester of pregnancy from a total number of women (either normotensive or with a final diagnosis of gestational hypertension), given in parentheses. Numbers in parentheses for each trimester do not add up to the grand total of women studied because most subjects were monitored in more than one trimester.

markedly different. Moreover, Fig 1 also indicates that the range for a threshold value of HBI providing both sensitivity and specificity >90% is very high. These results characterize a highly stable diagnostic test.

Discussion

The use of a set of new end points in addition to the BP values themselves and the rhythm characteristics derived therefrom has been advocated to improve sensitivity and specificity in diagnosing hypertension and the evaluation of a given subject's response to treatment.^{29–31} This approach is here extended for the early identification of gestational hypertension and preeclampsia. Apart from the HBI and PTE used here, other parameters have been defined previously. In 1988, the Mayo Clinic suggested the use of a BP load,³² defined as the percentage of BP values exceeding a given threshold (usually 140/90 for SBP/DBP during activity and 120/80 during resting hours), which is somehow similar to the PTE obtained here by reference to time-specified limits. More recently, within the context of ABPM, it was suggested the use of the amount of excess, although determined using arbitrary fixed limits of either 140/90 mm Hg³⁸ or with respect to daytime and nighttime averages.^{39,40} The HBI represents a better determinant of BP load than the above definition used in most papers on ABPM. Advantages of the endpoints used here as compared to the BP load or to parameters derived from the use of fixed limits have been previously documented,^{29,33,41,42} and also corroborated from the results in the Table. Sensitivity, positive predictive value, and relative risk of tests for diagnosing gestational hypertension and preeclampsia relying on casual BP measurements^{13,19} or on other parameters determined from the ABPM series (24-hour mean, nocturnal mean, diurnal mean, circadian rhythm-adjusted mean, or BP load as defined above^{13,33}) were always much lower than the corresponding results obtained for the HBI.

Fig 1 indicates a small overlap between the distributions of maximum HBI obtained for normotensive pregnant women and for women who developed gestational hypertension or preeclampsia. The lack of overlap results in a test for the early identification of gestational hypertension or preeclampsia with high sensitivity and specificity, as indicated in the Table. Sensitivity was already very high (93%) when the pregnant women were sampled by ABPM for about 48 hours before the 14th week of gestation (first trimester), when conventional clinical practice indicated normotension and absence of any clinical symptom or evidence of the disease for all women investigated. The tolerance intervals used as reference threshold for the determination of HBI²⁸ reflect a maximum "tolerable" BP much lower than the constant limits of 140/90 mm Hg now used for diagnosis of gestational hypertension on the basis of casual BP measurements.²⁶ In the first trimester, the upper limit of the tolerance interval does not exceed 125/75 mm Hg for SBP/DBP during activity nor 105/65 mm Hg during the resting hours. Those upper limits are similar for the third trimester but even lower during the second trimester of pregnancy,²⁸ in keeping with the predictable trends characterizing healthy pregnancies previously documented.^{22,24}

As pointed out by Dekker and Sibai,¹ the general impression is that a pregnant women with a DBP <70 mm Hg or a MAP

<80 mm Hg in the second trimester runs a small risk of having preeclampsia later in pregnancy. It is also generally accepted that BP values >140/90 mm Hg are associated with an increased risk of developing gestational hypertension or preeclampsia. The question is what happens with pregnant women with BP values in the rather extensive area between, for example, 70 and 90 mm Hg for DBP or between 120 and 140 mm Hg for SBP during the second trimester of pregnancy. The answer to this question cannot be obtained if one relies on casual BP measurements.^{13,19} Results from the Table indicate a very poor sensitivity of diagnosis based on conventional clinical practice, including the conventional measurement of BP during office hours. Answer to the question cannot rely either on the calculation of the average value of BP, the most common approach when analyzing ambulatorily monitored BP.¹³ Results shown in the Table and Fig 1 indicate that BP elevations above the upper limit of the time-specified tolerance interval exceeding an acceptable physiological amount of excess are consistently associated with a subsequent development of gestational hypertension or even preeclampsia. Results from the Table also indicate that once a given amount of excess allowing early diagnosis is obtained for any given woman, the diagnosis can be maintained on the basis of subsequent evaluations of maximum HBI determined from BP sampled by ABPM at a later gestational age. Moreover, values of maximum HBI below the critical threshold from normotensive pregnant women are consistently associated with uncomplicated pregnancies, specially when such a low HBI is corroborated by a second BP profile of ABPM obtained during the first half of gestation.

To evaluate how early the test can be carried with high sensitivity, we compared the actual date of diagnosis of gestational hypertension or preeclampsia obtained from the conventional clinical reports with the date of diagnosis based on a maximum HBI exceeding the critical threshold of 15 mm Hg×hour (Fig 2, top). Fig 2 (top) indicates that all women who subsequently developed gestational hypertension or preeclampsia included in the protocol during the first or early second trimesters were actually positively identified with the test before the beginning of the third trimester, although evidence of the disease was not clinically obtained until much later in pregnancy or even delivery (when a prelabor test of urine confirmed proteinuria). For a further comparison of time of diagnosis, the bottom graph of Fig 2 represents the time delay (in weeks) between the date of diagnosis based on the maximum HBI and the date of confirmed diagnosis from the medical records. Results from Fig 2 indicate that the average time of early diagnosis was about 23 weeks, more than half of the total expected duration of pregnancy. The determination of the maximum HBI provides, therefore, a high sensitivity tool for a very early identification of those pregnant women that, in the absence of any other clinical evidence, will subsequently develop gestational hypertension or preeclampsia. Results from the Table indicate that the identification could be obtained for most women before the 14th week of pregnancy, providing valuable time for preventive intervention and possible correction of the pathophysiological changes that characterize preeclampsia.⁴³ These results can also be applied to

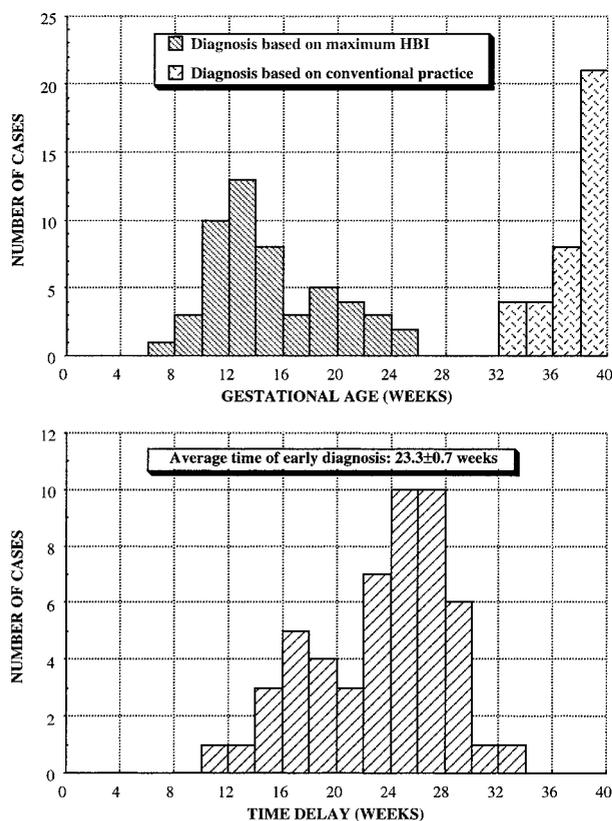


Figure 2. Date of diagnosis of gestational hypertension or preeclampsia based on conventional clinical practice or from the maximum HBI* in women sampled every 4 weeks starting at the first or second trimesters of pregnancy (top). The time delay between the diagnosis based on the maximum HBI and the clinical confirmation of disease is shown on the bottom. *HBI is the area of blood pressure (BP) excess (obtained by numerical integration) above a given threshold, here a 95% upper circadian tolerance limit determined separately for each trimester of pregnancy from data sampled by ambulatory noninvasive monitoring on a reference population of 189 normotensive pregnant women. Maximum HBI is the highest of three values obtained from 48-hour profiles of systolic, mean arterial, and diastolic BP, respectively.

determine the clinical parameters associated to altered ABPM, an issue that deserves future investigation.

The ideal predictive test should be easy to perform early in pregnancy and to be reproducible and noninvasive, with high sensitivity and a high positive predictive value.¹ The test evaluated here is noninvasive, since it basically relies on ABPM for 48 hours (instead of the most common span of 24 hours used in pregnancy⁴⁴). Advantages of sampling over 48 hours have already been established.^{29,36} The test's sampling requirements are not very demanding. Results in Fig 1 and the Table were obtained with BP series sampled mostly at half-hour to 1-hour intervals, without apparent loss in sensitivity or specificity. Even when 15-minute sampling has been advocated before,⁴⁴ a larger sampling interval increases compliance and patient acceptability. Moreover, a minimum number of BP measurements is guaranteed by sampling over 2 days instead of only 1 day. Sampling requirements for estimating stable tolerance intervals are also low, as described previously.^{27,28} The estimation of these tolerance intervals from a reference popu-

lation and the calculation of indices of BP excess or deficit are features included into the software system for early diagnosis of gestational hypertension.^{28,29} All calculations are masked to the obstetrician, who can obtain a complete report for any given pregnant woman in a very short time (less than 2 seconds in any Power Macintosh). The computer-based medical system that incorporates all the statistical methods needed for the implementation of the tolerance-hyperbaric test²⁹ represents a tool for a new interpretation of serial BP values and for a refined diagnosis, incorporating automatic monitors that may become cost effective. As an indication of reproducibility, results from the Table corroborate prospectively those obtained from previous retrospective studies.³³ Finally, the diagnostic test provides both a high sensitivity and high positive predictive value, as concluded from the results in the Table, as early as in the first trimester of pregnancy. In summary, the method here described represents a reproducible, noninvasive, and high sensitivity test for the very early identification of women who subsequently will develop gestational hypertension and preeclampsia.

Limitations of this approach stem from the fact that instrumentation for ABPM, although advanced, is not perfect and still quite expensive. Improved methods for removal of outliers and identification of measurement errors are still needed. The statistical methods for establishing nonparametric tolerance intervals and determining the HBI are certainly not as simple as obtaining the average of values sampled by ABPM. Tolerability of ABPM has also been discussed as a possible limitation of the technique in pregnancy. Although compliance is usually very high,^{22,44} patient acceptability tends to be lower.^{22,44} ABPM induces modest sleep disturbances.⁴⁵ However, many pregnant women report that their sleep is altered by ABPM.⁴⁴ These disadvantages may still preclude the use of ABPM for routine screening in pregnancy, although the technique could be cost-effective for evaluating high risk women. In them, ABPM during gestation, starting preferably at the time of the first obstetric check-up after the positive confirmation of pregnancy, provides sensitive end points for use in early risk assessment and as a guide for establishing preventive interventions.⁴³

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