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
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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 mmHg 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 multiparous 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.3 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 referred by avilation of 189 normoten-

Selected Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>ABPM</td>
<td>ambulatory BP monitoring</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>HBI</td>
<td>hyperbaric index</td>
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<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
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<tr>
<td>PTE</td>
<td>percentage time of excess</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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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 pre-

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 investigat-

ed.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.29,31

The HBI has been defined as a better determinant of BP excess than the BP load (percentage of values above a constant threshold). 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.
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. After synchronization, BP and HR values were edited according to commonly used criteria for the removal of outliers and measurement errors. 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.

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. A detailed explanation of the mathematical development of nonparametric tolerance intervals for hybrid time series has been provided previously. 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. 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. Since the conventional assessment of hypertension relies on absolute casual values >140 or 90 mm Hg for SBP or DBP, 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.

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

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

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 endpoints 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-specific 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 Hg39 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 measurements43,44 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) 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 pregnancy,28 in keeping with the predictable trends 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 pathophysiologic changes that characterize preeclampsia.45 These results can also be applied to
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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. The test evaluated here is noninvasive, since it basically relies on ABPM during gestation, starting preferably at the time of the first obstetric check-up after the positive confirmation 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.

Figure 2. Date of diagnosis of gestational hypertension or pre-eclampsia 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.

The estimation of these tolerance intervals from 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.

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References


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Ramón C. Hermida, Diana E. Ayala, Artemio Mojón, José R. Fernández, Inés Silva, Rafael Ucieda and Manuel Iglesias

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