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Ambulatory Blood Pressure Monitoring for the Early Identification of Hypertension in Pregnancy

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Gestational hypertension and preeclampsia are major contributors to perinatal morbidity and mortality. The diagnosis of gestational hypertension still relies on conventional clinic blood pressure (BP) measurements and thresholds of ≥140/90 mm Hg for systolic (SBP)/diastolic (DBP) BP. However, the correlation between BP level and target organ damage, cardiovascular disease risk, and long-term prognosis is greater for ambulatory BP monitoring (ABPM) than clinic BP measurement. Accordingly, ABPM has been suggested as the logical approach to overcoming the low sensitivity and specificity of clinic BP measurements in pregnancy. With the use of ABPM, differing predictable BP patterns throughout gestation have been identified for clinically healthy and hypertensive pregnant women. In normotensive pregnancies, BP steadily decreases up to the middle of gestation and then increases up to the day of delivery. In contrast, women who develop gestational hypertension or preeclampsia show stable BP during the first half of pregnancy and a continuous linear BP increase thereafter until delivery. Epidemiologic studies have also consistently reported sex differences in the 24-h patterns of ambulatory BP and heart rate. Typically, men exhibit a lower heart rate and higher BP than women, the differences being larger for SBP than DBP. Additionally, as early as in the first trimester of gestation, statistically significant increased 24-h SBP and DBP means characterize women complicated with gestational hypertension or preeclampsia compared with women with uncomplicated pregnancies. However, the normally lower BP in nongravid women as compared with men, additional decrease in BP during the second trimester of gestation in normotensive but not in hypertensive pregnant women, and significant differences in the 24-h BP pattern between healthy and complicated pregnancies at all gestational ages have not been taken into consideration when establishing reference BP thresholds for the diagnosis of hypertension in pregnancy. Several studies reported that use of the 24-h BP mean is not a proper test for an individualized early diagnosis of hypertension in pregnancy defined on the basis of *cuff* BP measurements, thus concluding that from such an awkward approach ABPM is not useful in pregnancy. The 24-h BP pattern that characterizes healthy pregnant women at all gestational ages suggests the use for diagnosis of a time-specified reference limit reflecting that mostly predictable BP variability. Once the time-varying threshold, given, for instance, by the upper limit of a tolerance interval, is available, the hyperbaric index (HBI), as a determinant of BP excess, can be calculated as the total area of any given subject's BP above the threshold. This tolerance-hyperbaric test, where diagnosis of gestational hypertension is based on the HBI calculated with reference to a time-specified tolerance limit, has been shown to provide high sensitivity and specificity for the early identification of subsequent hypertension in pregnancy, as well as a valuable approach for prediction of pregnancy outcome. ABPM during gestation, starting preferably at the time of the first obstetric check-up following positive confirmation of pregnancy, provides sensitive endpoints for use in early risk assessment and guide for establishing prophylactic or therapeutic intervention, and should thus be regarded as the required standard for the diagnosis of hypertension in pregnancy. (Author correspondence: rhermida@uvigo.es)

Keywords: Ambulatory blood pressure monitoring, Circadian rhythm, Gestational hypertension, Preeclampsia, Pregnancy

INTRODUCTION

Gestational hypertension and preeclampsia are major contributors to perinatal morbidity and mortality. Hypertension complicates ~10% of all pregnancies, increasing the risk of oxidative stress, platelet dysfunction, and endothelial damage (Higashi et al., 2002; Portaluppi et al., 2004; Varani et al., 1999a, 1999b, 2000). Moreover, hypertension in pregnancy is associated with increased risk of adverse fetal, neonatal, and maternal outcomes, including preterm birth, intrauterine growth restriction, perinatal death, acute renal or hepatic failure, antepartum hemorrhage, postpartum hemorrhage, and maternal death (Duley, 2009; Roberts et al., 2011;

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Steegers et al., 2010). Hypertensive complications in pregnancy range from hypertension alone (gestational nonproteinuric hypertension) through proteinuria and multiorgan dysfunction (preeclampsia) to seizures (eclampsia) (Brown et al., 2001c). Reported population rates of gestational hypertension vary substantially, ranging from 4% to 10%, including preeclampsia rates of 2% to 5% (Hernández-Díaz et al., 2009; Klemmensen et al., 2007; Lawler et al., 2007; Roberts et al., 2005; Ros et al., 1998; Walker et al., 2009; Wallis et al., 2008), although these values might well underestimate the real prevalence of hypertension in pregnancy (Hermida & Ayala, 2002). At least part of this variation is likely due to under-ascertainment and/or misclassification of gestational hypertension and preeclampsia (Hermida & Ayala, 2002; Hermida et al., 2003a; Roberts et al., 2008).

Many of the physiologic changes of preeclampsia are essentially a reversal of those that accompany a healthy pregnancy, i.e., absence of plasma volume increase, blood pressure (BP) elevation, peripheral vascular resistance increase, and aldosterone insufficiency (Dekker & Sibai, 1993). Although the exact cause of preeclampsia is unknown, several mechanisms have been suggested, including enhanced sensitivity to vasopressors, abnormal maternal immunologic reaction, and imbalance in the production of vasoactive prostaglandins (thromboxane A_2 and prostacyclin), resulting in vasoconstriction of small arteries, platelet activation, and uteroplacental insufficiency (Dekker & Sibai, 1993; Friedman, 1988; Page, 2002; Redman & Sargent, 2003; Sibai et al., 2003; Walsh, 1985). Although preeclampsia is a severe complication of pregnancy, any form of gestational hypertension is associated with increased risk of adverse maternal and fetal outcomes (Buchbinder et al., 2002; Roberts et al., 2005). It also appears that history of either gestational hypertension or preeclampsia in a prior pregnancy places the pregnant woman and her offspring at high risk for future, typically within 7 to 12 yrs, development of hypertension (Svensson et al., 1983).

Risk factors for gestational hypertension and preeclampsia have been well documented (Cnattingius et al., 2004; Duckitt & Harrington, 2005; Hernández-Díaz et al., 2009; Roberts et al., 2005; Saftlas et al., 2003; Steegers et al., 2010). Factors that increase risk include nulliparity, advanced maternal age, multiple births, diabetes, chronic hypertension, obesity, previous preeclampsia, family history of preeclampsia, different father and/or ≥10 yrs since last pregnancy, renal disease, and presence of antiphospholipid antibodies (Cnattingius et al., 2004; Duckitt & Harrington, 2005; Hernández-Díaz et al., 2009; Roberts et al., 2005; Saftlas et al., 2003; Skjaerven et al., 2002; Steegers et al., 2010). Decreased risk of pregnancy hypertension and preeclampsia has been associated with placenta previa, summer births, low-dose aspirin (particularly when ingested regularly at bedtime commencing early in pregnancy) and calcium supplementation in high-risk women, treatment of gestational diabetes, and use of BP-lowering medications (Askie et al., 2007; Ayala et al., 2012a; Crowther et al., 2005; Duckitt & Harrington, 2005; Hermida et al., 1997a, 1999, 2003b; Hofmeyr et al., 2006; Steegers et al., 2010). As the majority of cases of gestational hypertension and preeclampsia are diagnosed at term, increasing rates of early elective delivery result in underestimation of their prevalence (Koopmans et al., 2009; MacDorman et al., 2010; Mealing et al., 2009).

Several clinical, biochemical, and biophysical tests have been designed to predict the occurrence of gestational hypertension or preeclampsia with various degrees of specificity and sensitivity (Cnossen et al., 2008a, 2008b, 2009; Dekker & Sibai, 1991; Meads et al., 2008). Because an elevated BP after 20 wks of gestation in a previously normotensive woman is common to the definition of both gestational hypertension and preeclampsia (Brown et al., 2001c; Davey & MacGillivray, 1988; Lindheimer et al., 2008), the issue of whether the development of these complications may be predicted on the basis of clinic BP measured during conventional antenatal visits has been addressed in several retrospective and some prospective studies (Chesley & Sibai, 1988; Gallery et al., 1977; Miller et al., 2007; Moutquin et al., 1985; Nijdam et al., 2010; O'Brien, 1990; Öney & Kaulhausen, 1983; Page & Christianson, 1976; Peek et al., 1996; Poon et al., 2008, 2009; Reiss et al., 1987; Villar & Sibai, 1989). Office BP values, however, have several shortcomings; they provide a measurement that represents only a fraction of the 24-h BP profile, usually under circumstances that may have pressor effect, and the technique is fraught with potential errors, including instrument defects and examiner technique (Halberg et al., 1990; Patterson, 1984; Sassano et al., 1987; Wilcox, 1961). In addition, maternal posture can significantly affect clinic BP measurements in pregnant women (Sibai, 1988). Therefore, office BP readings are neither diagnostic nor sufficiently predictive of the development of hypertension in pregnancy (Hermida & Ayala, 1997, 2002, 2004, 2010; Hermida et al., 1997e, 1998, 2003a, 2004a; Peek et al., 1996). The reported sensitivity and specificity of clinic BP measurements vary greatly between studies, with sensitivity being as low as 9% (Ayala et al., 1997a) and positive predictive value being as low as 8% (Page & Christianson, 1976). Nonetheless, the diagnosis of gestational hypertension still relies on conventional clinic BP measurements and the use of constant threshold values, i.e., 140/90 mm Hg for systolic (SBP)/diastolic (DBP) BP after 20 wks of gestation in a previously normotensive woman (Brown et al., 2001c; Davey & MacGillivray, 1988; Lindheimer et al., 2008). This reference threshold, equivalent to the one used for the diagnosis of essential hypertension based on clinic BP measurements (Chobanian et al., 2003; Mancia et al., 2007; Pickering et al., 2005), is applied independently of gestational age at the time of BP measurement. However, an increasing number of studies (Ayala et al., 2012a; Clement et al., 2003; Eguchi et al., 2008;

Hermida et al., 2010, 2011a, 2011b, 2011c, 2012a, 2012c, 2012d; Perloff et al., 1983; Salles et al., 2008; Verdecchia et al., 1994) clearly document that the correlation between BP level and target organ damage, cardiovascular disease risk, and long-term prognosis is much stronger for ambulatory BP monitoring (ABPM) than clinic BP measurement. This is not a surprising finding when one considers that the physiologic time-dependent structure and control of BP, especially the circadian one (Portaluppi & Smolensky, 2007; Portaluppi et al., 1996, 2012; Smolensky et al., 2007, 2012), appears to be altered in many hypertensive conditions (Portaluppi et al., 1990, 1992, 1994; Trasforini et al., 1991) and closely related to the risk of target organ damage (Gallerani et al., 1997; Hermida et al., 2010; Manfredini et al., 1996; Pinotti et al., 2005; Portaluppi & Hermida, 2007; Portaluppi & Smolensky, 2010; Smolensky et al., 2010). Therefore, ABPM has been suggested by some researchers (Hermida & Ayala, 2002; Hermida et al., 1997b, 1997c, 1997d, 1997e, 1998, 2003a; Shennan & Halligan, 1998) to be a logical approach to overcoming many of the shortcomings and uncertainties associated with clinical BP measurement in pregnancy. Indeed, during the past two decades multiple studies have evaluated the potential prognostic value of ABPM for the early detection of hypertension in pregnancy (Bellomo et al., 1995, 1999; Brown et al., 2011a; Churchill et al., 1997; Cugini et al., 1992; Halligan et al., 1993; Higgins et al., 1997; Kyle et al., 1993; Margulies et al., 1987; Penny et al., 1998; Shennan & Halligan, 1998; Tranquilli et al., 2004; Waugh et al., 2000). However, similar to the deficiency of studies based on clinic BP measurements, almost all investigators reporting on the potential prognostic value of ABPM failed to take into account the potential role of gestational age at the time of measurement on their findings (Bellomo et al., 1995, 1999; Churchill et al., 1997; Kyle et al., 1993; Margulies et al., 1987), thus disregarding the predictable changes in BP that occur throughout gestation.

PREDICTABLE BP TRENDS DURING GESTATION IN HEALTHY AND COMPLICATED PREGNANCIES

In a study based on clinic BP measurements, MacGillivray et al. (1969) showed that BP declined in the second trimester of pregnancy and rose again thereafter in the third trimester. By the systematic use of ABPM during gestation, we (Ayala & Hermida, 1993, 1995) previously quantified predictable BP changes in two consecutive pregnancies of a clinically healthy woman. She (D.E.A.) wore always the same ambulatory BP device for 48 consecutive hours on several occasions for a total of 76 d of monitoring in each of two consecutive pregnancies. Results of polynomial regression analysis revealed that in both pregnancies the predictable variability of the 48-h BP mean (average of all valid readings obtained during the 48-h ABPM span) can be approximated by a second-order polynomial model on gestational age; a steady decrease in BP (Figure 1, top) up to the 22nd wk of gestation was followed by an increase in BP up to the day of delivery, with final BP values similar to those found early in pregnancy (Ayala & Hermida, 1993). This predictable model was highly statistically significant for both SBP and DBP (multiple correlation coefficient being .871 for SBP and .867 for DBP for the composite of both pregnancies, $p < .001$ in both cases). Moreover, the models representing BP variability throughout gestation were similar for both pregnancies, except for a consistent decrease of BP during the second pregnancy as compared with the first, maybe due to the intake of 625 mg/d of calcium during the second pregnancy (Ayala & Hermida, 1993; Hofmeyr et al., 2006). Indeed, data obtained from systematic ABPM in normotensive pregnant women indicated lack of differences in BP according to parity (Ayala & Hermida, 2001; Hermida & Ayala, 2005b; Hermida et al., 2004b). She (D.E.A.) also wore the same ABPM device 2 out of each 6 d for a span of 9.6 mo starting 1 yr after delivery of the second pregnancy. Analysis of these data revealed that the second-order pattern of variation in the 48-h BP mean characterizing the two uncomplicated pregnancies could be found for data sampled during nonpregnancy

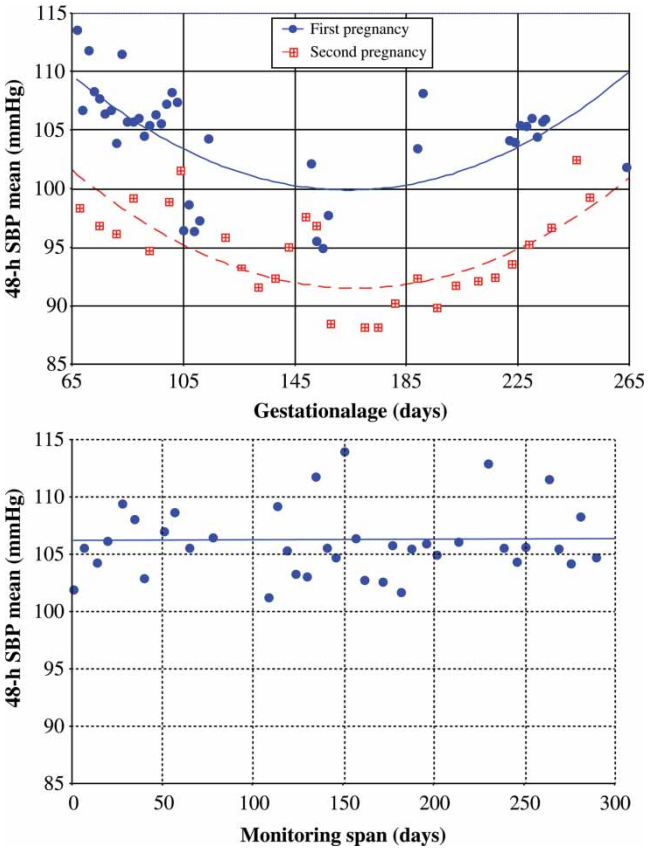

FIGURE 1. Variation of 48-h SBP mean throughout gestation in two consecutive pregnancies of a healthy woman (top) and along a 9.6-mo monitoring span during nonpregnancy in the same woman (bottom). The lines represent in each case the best-fitted waveform model obtained by linear polynomial regression analysis. Updated from Ayala and Hermida (1993).

in the same woman and over an equivalent span of time to what could have been her third pregnancy. The graph at the bottom of Figure 1 for SBP indicates the lack of predictable variability in BP during nonpregnancy as compared with the patterns found for two consecutive healthy pregnancies of the same woman.

These findings from the study of only one, extensively documented, unique case were further corroborated in several retrospective and prospective investigations (Ayala et al., 1997b; Hermida et al., 1997b). In the attempt to corroborate and extend conclusions from these previous reports, we analyzed data obtained from a prospective study on 403 (207 nullipara) untreated Spanish pregnant women. Among them, 235 were normotensive, 128 developed gestational hypertension, and 40 developed preeclampsia. Gestational hypertension was defined as a hyperbaric index (HBI)—total area of BP excess summed over the 24-h period above the upper limit of the time-varying tolerance interval calculated as a function of gestational age (Hermida et al., 2001b)—consistently above the threshold for diagnosis of hypertension in pregnancy (Hermida & Ayala, 2002; Hermida et al., 1997e, 1998, 2003a, 2004a) after the 20th wk of gestation for further corroboration. Preeclampsia was defined as gestational hypertension (following the criteria given above) and proteinuria, ≥300 mg/24-h urine, diagnosed after the 20th wk of gestation in a previously normotensive woman.

A full description of this prospective study on the systematic ABPM evaluation in pregnancy has been provided elsewhere (Hermida & Ayala, 2002; Hermida et al., 2001a, 2003c, 2004a, 2004c). In summary, inclusion criteria were absence of any condition requiring use of BP-lowering medication, maternal age 18 to 40 yrs, and gestational age <16 wks at the time of inclusion. Exclusion criteria were multiple pregnancies, chronic hypertension, chronic liver disease, renal disease, any disease requiring use of anti-inflammatory medication, diabetes or any other endocrine disease such as hyperthyroidism, and intolerance to the use of an ABPM device. The study was approved by the state Ethics Committee of Clinical Research, and respected the criteria set forth for ethical medical research as outlined in the Helsinki Declaration and instructions to authors for the journal (Portaluppi et al., 2010). All women gave written informed consent.

The SBP and DBP of each pregnant woman were automatically assessed every 20 min between 07:00 and 23:00 h and every 30 min during the night for 48 consecutive hours with a properly calibrated and validated SpaceLabs 90207 device (SpaceLabs, Issaquah, WA, USA) at the time of recruitment (usually within the first trimester of pregnancy), and then every 4 wks thereafter until delivery. A 48-h, instead of the most common 24-h, monitoring was chosen to improve the reproducibility of results, since reproducibility of ABPM characteristics, including mean BP values and the HBI, is highly dependent on duration of monitoring, as previously demonstrated (Hermida & Ayala, 2003; Hermida et al., 2002b, 2007a, 2012b). No one was hospitalized during monitoring. The BP cuff was worn on the nondominant arm with proper cuff size determined by upper arm circumference measurement before commencing ABPM. During the two consecutive days of ABPM, women were instructed to adhere to their usual activities with minimal restrictions, but to maintain a similar activity-rest schedule and avoid daytime napping and use of over-the-counter or any other medication for the duration of the trial. They kept a diary listing the time of retiring to bed at night, awakening in the morning, consumption of meals, participation in exercise, and episodes of atypical physical activity, mood/emotional states, and other events that might affect BP. This individualized information was utilized to edit the ABPM data and to determine the commencement and termination of daytime activity and nighttime sleep spans so as to accurately derive the awake and asleep BP means of each women. BP series were considered invalid for analysis if ≥30% of the measurements were missing, if data were lacking for an interval of >2 h, if data were obtained while patients had an irregular rest-activity schedule during the two days of monitoring, or if the nighttime sleep period was <6 or >12 h during ABPM. All women provided at least four valid ABPM profiles. The total number of BP profiles provided by the 403 women under investigation was 2430. Demographic characteristics of the women investigated are included in Table 1. Gestational age and fetal growth were determined by monthly echography assessments. To avoid examiner bias, the same midwife obtained 3 to 6 conventional clinic BP measurements at each obstetric visit, after the woman had rested in a seated position for ≥10 min.

Each individual's clock-hour BP values were first referenced to hours after awakening from nighttime sleep, based on information obtained from the woman's diary. This transformation avoided introduction of bias due to slight differences among individuals in their sleep-activity routine (Hermida et al., 2002c). ABPM profiles were edited according to conventional criteria to correct for measurement errors and outliers; SBP readings >250 or <70 mm Hg, DBP >150 or <40 mm Hg, and pulse pressure (difference between SBP and DBP) >150 or <20 mm Hg were automatically eliminated. The 48-h BP mean values derived from the 2430 BP series were used to establish their pattern of variation along gestational age for groups of normotensive and hypertensive pregnant women by polynomial regression analysis. Additionally, the demographic characteristics included in Table 1 were compared between groups of pregnant women by analysis of variance (ANOVA) (continuous variables) or nonparametric chi-square testing (incidence of complications).

Polynomial regression analysis of the 48-h BP means representing the 1408 profiles from clinically healthy normotensive pregnant women revealed a predictable pattern of variation with gestational age. A

TABLE 1. Demographic characteristics of women investigated

Variable	NT	GH	PE	*p* value for comparison of: 3 groups	GH vs. PE
Women, n	245	140	49		
ABPM profiles, n	1420	847	256		
Age, yrs	30.2 ± 5.4	30.0 ± 5.1	31.5 ± 5.4	.276	.156
Weight, kg	63.2 ± 9.7	73.7 ± 17.6	76.1 ± 14.9	<.001	.416
Height, cm	162.1 ± 5.5	162.6 ± 6.8	162.0 ± 5.9	.607	.617
BMI, kg/m^2	24.1 ± 3.6	27.8 ± 6.2	29.0 ± 6.5	<.001	.311
SBP at first visit, mm Hg*	119 ± 10	125 ± 11	125 ± 10	<.001	.924
DBP at first visit, mm Hg*	65 ± 7	70 ± 9	68 ± 10	<.001	.578
PP at first visit, mm Hg*	54 ± 8	55 ± 9	57 ± 7	.053	.474
SBP at last visit, mm Hg*	119 ± 12	134 ± 11	144 ± 16	<.001	<.001
DBP at last visit, mm Hg*	68 ± 10	78 ± 12	86 ± 10	<.001	<.001
PP at last visit, mm Hg*	51 ± 9	56 ± 10	58 ± 10	<.001	.357
Gestational age at delivery, wks	39.4 ± 1.0	39.1 ± 1.4	38.1 ± 3.0	<.001	<.001
Newborn weight, g	3335 ± 448	3133 ± 557	3068 ± 870	<.001	.497
Delivery by cesarean section, %	18.4	36.4	34.7	<.001	.828
Intrauterine growth retardation, %	4.9	17.1	26.5	<.001	.154
Preterm delivery (<37 wks), %	2.7	10.7	22.5	<.001	.040
Newborn's Apgar score† at:					
1 min	8.8 ± 1.0	8.7 ± 1.1	8.2 ± 2.5	.009	.025
5 min	9.9 ± .3	9.8 ± .6	9.1 ± 2.5	<.001	.006
10 min	10 ± .1	9.9 ± .4	9.4 ± 2.3	<.001	.014

Values are shown as mean ± SD. NT = normotension; GH = gestational hypertension; PE = preeclampsia; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure (difference between SBP and DBP).

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

†The Apgar score is determined by evaluating the newborn with five criteria on a scale from 1 to 2, i.e., appearance, pulse, grimace, activity, and respiration.

second-order polynomial model on gestational age approximated this predictable BP variability ($p < .001$). SBP (Figure 2, top) and DBP (Figure 3, top) both showed a steady linear decrease up to the 20th wk of gestation, followed by an increase in BP up to the day of delivery. The top graphs of Figures 2 and 3 show that, for normotensive pregnant women, BP values obtained by 48-h ABPM at the end of gestation were similar to those found at the beginning of pregnancy for the same women. The same graphs in Figures 2 and 3 also reveal that the predictable BP variability during pregnancy in normotensive women entailed an average increase of 7% in SBP and 9% in DBP between the middle of gestation and delivery.

This pattern of variation was not found in hypertensive pregnancies. In this case, the 48-h BP mean was stable until the 22nd wk of pregnancy (bottom graphs of Figures 2 and 3). Between 23 wks of gestation and delivery, complicated pregnancies were characterized by statistically significant BP increase with gestational age (linear correlation coefficient $r = .433$, $p < .001$ for SBP; $r = .453$, $p < .001$ for DBP). The predictable changes in BP shown on the bottom graphs of Figures 2 and 3 indicate greater average increase in SBP by 9% and DBP by 13%, during the second half of gestation in women who developed hypertension in pregnancy.

The 48-h BP mean was already significantly different between normotensive and hypertensive pregnant women in the first trimester of gestation. By the 14th wk of gestation, the predictable trend of BP for hypertensive women reached 115/67 mm Hg for SBP/DBP, whereas the second-order model of variation found the 48-h BP mean to be 103/60 mm Hg at the end of the first trimester of pregnancy for healthy pregnant women. Differences in the 48-h BP mean between healthy and complicated pregnancies can be observed, therefore, quite before the actual clinical diagnosis of gestational hypertension or preeclampsia is made, usually well within the third trimester of gestation. The results of this study on women systematically sampled by 48-h ABPM throughout gestation confirms the predictable pregnancy-associated variability in BP and provides proper information to establish circadian and gestational-age-dependent reference limits for BP (Hermida et al., 2001b), taking into account the trends in BP throughout pregnancy shown in Figures 2 and 3, for use in the early identification of hypertensive complications in pregnancy (Hermida & Ayala, 2002; Hermida et al., 1997e, 1998, 2003a, 2004a).

24-h BP PATTERNS IN NORMOTENSIVE AND HYPERTENSIVE PREGNANT WOMEN

BP exhibits predictable 24-h variation as a result of both cyclic day-night alterations in behavior (e.g., physical activity, mental stress, and posture), environmental

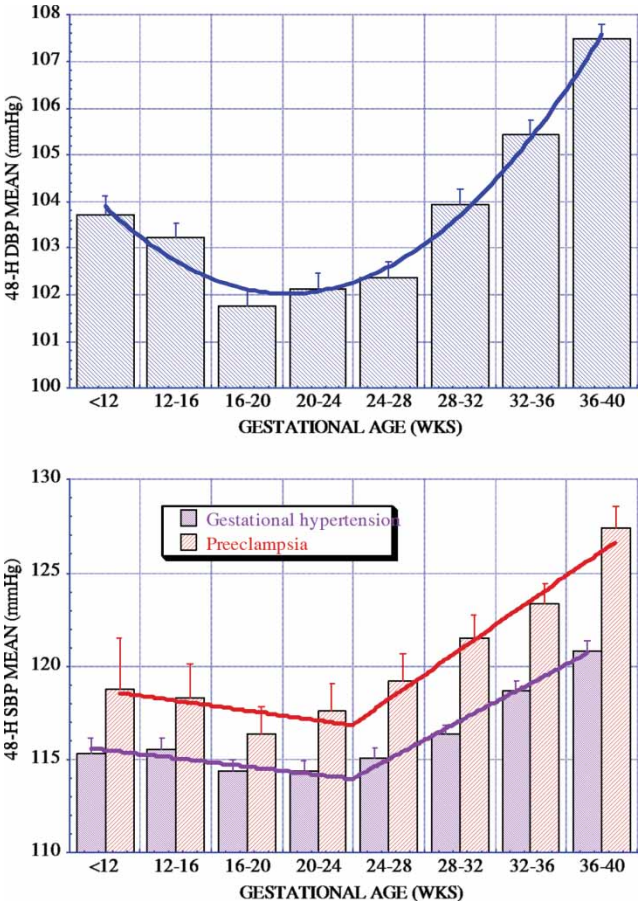

FIGURE 2. Variation of 48-h SBP mean throughout gestation in normotensive pregnancies (top: 1408 ABPM profiles of 48-h duration obtained from 235 women), women who developed gestational hypertension (bottom: 800 ABPM profiles from 128 women), and women who developed preeclampsia (bottom: 222 ABPM profiles from 40 women). Updated from Hermida et al. (2001a).

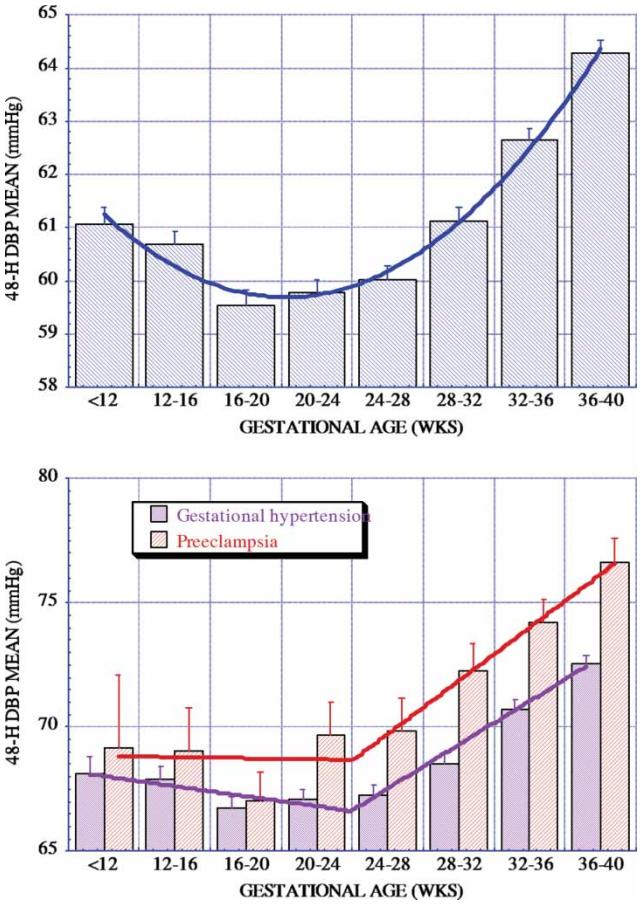

FIGURE 3. Variation of 48-h DBP mean throughout gestation in normotensive pregnancies (top: 1408 ABPM profiles of 48-h duration obtained from 235 women), women who developed gestational hypertension (bottom: 800 ABPM profiles from 128 women), and women who developed preeclampsia (bottom: 222 ABPM profiles from 40 women). Updated from Hermida et al. (2001a).

phenomena (e.g., ambient temperature, noise, etc.), and endogenous circadian (~24-h) rhythms in neural, endocrine, endothelial, and hemodynamic variables (e.g., plasma noradrenaline and adrenaline [autonomic nervous system] and renin, angiotensin, and aldosterone [renin-angiotensin-aldosterone system]) (Fabbian et al., 2012; Hermida et al., 2002a, 2007b; Portaluppi & Smolensky, 2007, 2010; Portaluppi et al., 1996, 2012; Smolensky et al., 2007, 2012).

Such 24-h BP variability also characterizes clinically healthy pregnant women as well as women who develop gestational hypertension or preeclampsia (Ayala & Hermida, 2001; Ayala et al., 1997a; Benedetto et al., 1996; Hermida & Ayala, 2005b; Hermida et al., 1997c, 2000a, 2003a, 2003c; Miyamoto et al., 1998). Changes in the circadian pattern of BP could be used either to predict preeclampsia or to assess its severity (Hermida & Ayala, 2002, 2004; Hermida et al., 1997c, 1997e, 1998, 2003a, 2004a; Miyamoto et al., 1998). However, few studies have reported on the normal 24-h BP pattern determined by ABPM in uncomplicated pregnancies (Contard et al., 1993; Halligan et al., 1993; Margulies et al., 1987), most of them without comparison with the circadian BP pattern in complicated pregnancies, an issue only occasionally addressed (Ayala et al., 1997a; Benedetto et al., 1996; Hermida et al., 1997c, 2000a, 2003a, 2003c; Kyle et al., 1993). By the use of ABPM, several authors have found reduced decline in BP by night in women with preeclampsia (Benedetto et al., 1996; Hermida et al., 1997c, 2000a, 2003a, 2003c), whereas others even reported a reversed circadian BP pattern towards higher nighttime than daytime BP mean associated with preeclampsia (Beilin et al., 1982; Miyamoto et al., 1998; Redman et al., 1976). Most of the latter studies have usually been carried out during the last stages of pregnancy. Limitations of these studies derive also from the inability to properly describe the nonsinusoidal waveform of circadian BP variability (Hermida et al., 1997c, 2000a, 2003c).

Normal values for 24-h ABPM have been determined from several trials, including two of the most extensive studies done thus far in pregnancy, the first involving a primigravid population of 98 women sampled at five different gestational ages (Halligan et al., 1993), and the

second involving the 235 normotensive pregnant women described above, who were systematically sampled every 4 wks from early in the first trimester of pregnancy until delivery (Hermida et al., 2001b, 2003c). Our study also provided comparison of the 24-h BP pattern between healthy and complicated pregnancies. The circadian BP pattern was objectively assessed by population multiple-component analysis (Fernández & Hermida, 1998), a method applicable to nonsinusoidal-shaped hybrid time-series data, i.e., time series of data collected from a group of subjects, consisting of values distributed at equal or unequal intervals. The method produces estimates of the 24-h rhythm-adjusted time-series mean or MESOR (midline estimating statistic of rhythm, i.e., average value of the rhythmic function fitted to the data), as well as the amplitude (one-half the extent of the temporal variability explainable by rhythmicity) and acrophase (crest time expressed as a lag in time from a designated reference, here the time of awakening from nocturnal sleep) for every fitted component of a given period (here 24 and 12 h for SBP and DBP, as currently recommended; Hermida et al., 2002a). When the waveform shape of the rhythm is best approximated by a complex model composed of two or more cosine curves that are harmonics of the fundamental period (here 24 h), the method of multiple components provides three additional summary parameters: overall amplitude (one-half the difference between the maximum and minimum values of the best fitted curve), and orthophase and bathyphase, i.e., peak and trough times, respectively, expressed as a lag relative to the time of awakening from nighttime sleep (Fernández & Hermida, 1998). Population-based parameters of MESOR, overall amplitude, and orthophase of the circadian rhythms in SBP and DBP, obtained for each group of women categorized according to the trimester of gestation and presence or absence of hypertension in pregnancy, were compared using a specially developed nonparametric test (Fernández et al., 2004). Hourly BP means were compared between groups by t test corrected for multiple testing. In so doing, the level of significance was established at $p \leq .002$, after dividing the usual level of .05 by the number of tests done (24; one for each hourly mean).

Figures 4 to 6 show the circadian rhythm of SBP (left) and DBP (right) assessed by 48-h ABPM in each trimester of pregnancy for clinically healthy women and those who developed gestational hypertension or preeclampsia. Dark shading along the lower horizontal axis of graphs denotes the average hours of nighttime sleep across the subject samples. BP data were pooled over an idealized single 24-h span to simplify graphic presentations. These graphs represent circadian population chronograms, i.e., displays of data as a function of time, with hourly means and standard errors of the data computed as follows. First, hourly means were calculated from each individual series, after stacking all data sampled during the 48-h monitoring along a common idealized 24-h span. Second, the average of those individual means at each time interval was derived across the total number of women for each group. The nonsinusoidal curve shown for each group corresponds to the best-fitted waveform model obtained by population multiple-components analysis applied to all the original BP values (not just to hourly means). Differences or

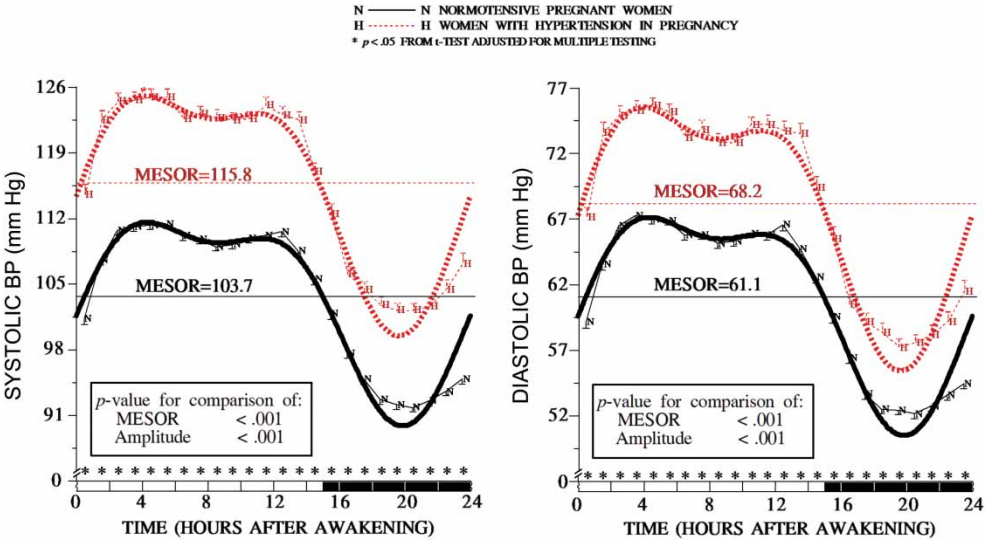

FIGURE 4. Circadian pattern of SBP (left) and DBP (right) in mm Hg of normotensive pregnancies (continuous line) and women who developed gestational hypertension or preeclampsia (dashed line) sampled by 48-h ABPM in the first trimester of pregnancy (<14 wks of gestation). Each graph shows hourly means and standard errors of data for each group of women. Dark shading along lower horizontal axis of graphs denotes average hours of nighttime sleep across the sample. Nonsinusoidal-shaped curves correspond to best-fitted waveform models derived by population multiple-component analysis. MESOR (midline estimating statistic of rhythm) is the 24-h average value of the rhythmic function fitted to the data. Amplitude is one-half the difference between maximum and minimum values of the best-fitted curve. Updated from Hermida et al. (2003c).

similarities of rhythm characteristics, as well as the general waveform of circadian BP variability, can be readily seen from these graphic representations.

A statistically significant increased circadian MESOR of SBP and DBP was documented in pregnancies complicated with gestational hypertension or preeclampsia compared with uncomplicated pregnancies in all three trimesters ($p < .001$ for both SBP and DBP). There was also statistically significant difference in the circadian amplitude of SBP and DBP between healthy and complicated pregnancies in all trimesters of gestation ($p < .001$ for both variables in all trimesters). The elevation of SBP and DBP during the first trimester of pregnancy in women with a later diagnosis of gestational hypertension or preeclampsia as compared with clinically healthy pregnant women is depicted in Figure 4. No differences (always $p > .108$) were detected for the first trimester of pregnancy in the circadian MESOR and amplitude between women who later developed gestational hypertension and preeclampsia. Figure 5 represents the circadian pattern of SBP (left) and DBP (right) of women sampled during the second trimester of pregnancy. Differences between normotensive and hypertensive women were statistically significant at all circadian times after correcting for multiple testing. The circadian MESOR of SBP and DBP of normotensive pregnant women was statistically lower in the second as compared with the first trimester ($p < .001$) in keeping with the documented trends of BP variation with increasing gestational age (Figures 2 and 3). In the second trimester of pregnancy, there was statistically significant difference in the circadian MESOR of SBP ($p = .002$) and DBP ($p = .038$) between the two groups of women who subsequently developed gestational hypertension and preeclampsia (Hermida et al., 2003c).

Figure 6, comparing SBP and DBP between healthy and complicated pregnancies sampled in the third trimester of gestation, indicates larger between-group differences than those shown in Figures 4 and 5 for the first and second trimesters of pregnancy, respectively. As compared with the second trimester, BP slightly increased in normotensive pregnant women, reaching a circadian MESOR comparable to that obtained in the first trimester for the same women (Figure 4). In women with gestational hypertension or preeclampsia, BP increased greatly from the second to the third trimester. The trend of increasing BP with gestational age during the second half of pregnancy is greater for women who developed preeclampsia than those who developed gestational hypertension without proteinuria (Figures 2 and 3). In the third trimester, the difference in circadian MESOR between the gestational hypertension and preeclampsia groups of women was statistically significant for both SBP and DBP ($p < .001$).

Our results indicate statistically significant differences in BP between healthy and complicated pregnancies as early as in the first trimester of pregnancy; nonetheless, at this stage of gestation, both SBP and DBP for women with a later diagnosis of gestational hypertension and preeclampsia were still well within the accepted normal physiologic BP range (Hermida et al., 2003c). Despite this available information, the diagnosis of hypertension in pregnancy based on ABPM has frequently relied on reference thresholds established for the diagnosis of essential hypertension of both women and men (Penny

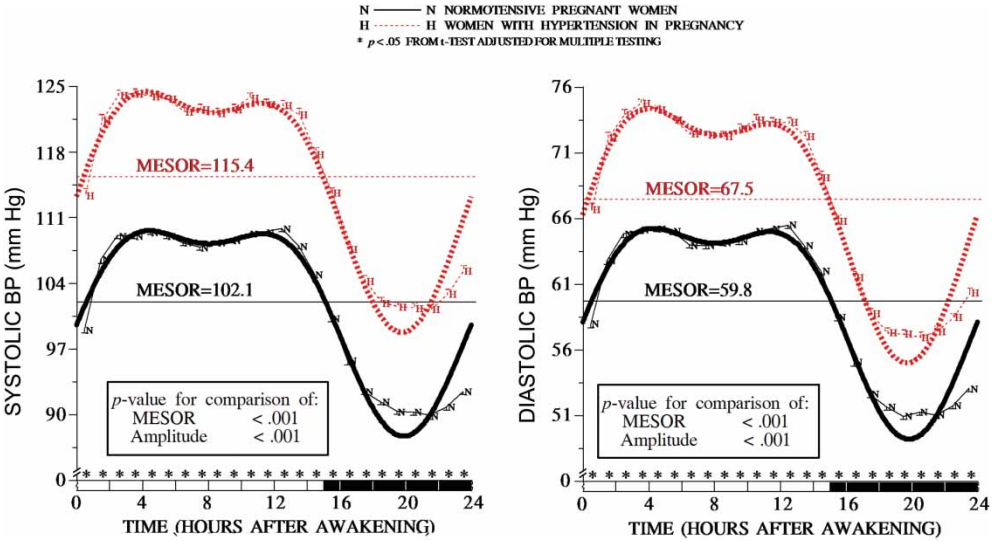

FIGURE 5. Circadian pattern of SBP (left) and DBP (right) in mm Hg of normotensive pregnancies (continuous line) and women who developed gestational hypertension or preeclampsia (dashed line) sampled by 48-h ABPM in the second trimester of pregnancy (14 to 27 wks of gestation). Each graph shows hourly means and standard errors of data for each group of women. Dark shading along lower horizontal axis of graphs denotes average hours of nighttime sleep across the sample. Nonsinusoidal-shaped curves correspond to best-fitted waveform models derived by population multiple-component analysis. MESOR (midline estimating statistic of rhythm) is the 24-h average value of the rhythmic function fitted to the data. Amplitude is one-half the difference between maximum and minimum values of the best-fitted curve. Updated from Hermida et al. (2003c).

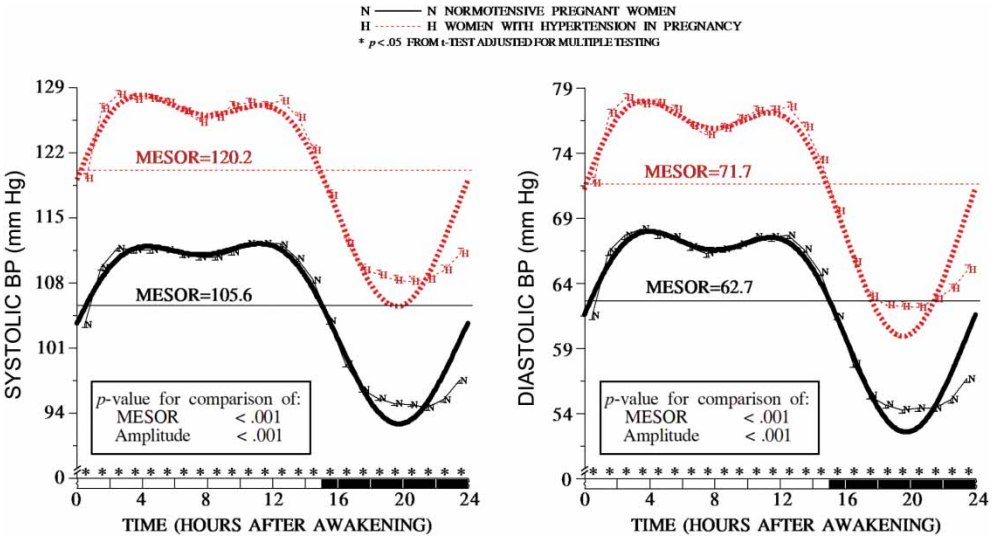

FIGURE 6. Circadian pattern of SBP (left) and DBP (right) in mm Hg of normotensive pregnancies (continuous line) and women who developed gestational hypertension or preeclampsia (dashed line) sampled by 48-h ABPM in the third trimester of pregnancy (≥27 wks of gestation). Each graph shows hourly means and standard errors of data for each group of women. Dark shading along lower horizontal axis of graphs denotes average hours of nighttime sleep across the sample. Nonsinusoidal-shaped curves correspond to best-fitted waveform models derived by population multiple-component analysis. MESOR (midline estimating statistic of rhythm) is the 24-h average value of the rhythmic function fitted to the data. Amplitude is one-half the difference between maximum and minimum values of the best-fitted curve. Updated from Hermida et al. (2003c).

et al., 1998), usually 130/80 mm Hg for the 24-h SBP/DBP means (Chobanian et al., 2003; Mancia et al., 2007; O'Brien et al., 2003). These limits have several shortcomings for use in pregnancy, as documented in the following section.

24-h BP PATTERNS IN MEN, NONPREGNANT WOMEN, AND PREGNANT WOMEN

Apart from the predictable BP changes with gestational age shown in Figures 2 and 3, epidemiologic studies have reported significant sex differences in BP and heart rate (Ben-Dov et al., 2008; Burt et al., 1995; Hermida, 1999; Hermida et al., 2000b, 2002a, 2002d, 2004d, 2012f; Kagan et al., 2007; Pimenta, 2012; Roger et al., 2011; Vriz et al., 1997). Typically, men exhibit lower heart rate and higher BP than women, the differences being larger for SBP than DBP (Hermida et al., 2002a). These differences become apparent during adolescence and remain significant until 55–60 yrs of age (Meininger et al., 2004; Palatini et al., 2001; Pimenta, 2012; Wang et al., 2006). The prevalence and severity of hypertension increase markedly with advancing age in women, such that a higher percentage of women than men have high BP after 65 yrs of age (Ong et al., 2008; Roger et al., 2011). Furthermore, BP control is more difficult to achieve in older women (Lloyd-Jones et al., 2005). Differences in BP regulation may play a role in the documented male-female differences in the pathophysiology of hypertension, treatment responses to medication, organ damage, and cardiovascular risk (Burt et al., 1995; Hermida et al., 2012f; Manfredini et al., 2011; Ong et al., 2008; Pimenta, 2012; Roger et al., 2011; Vriz et al., 1997). Results from a recent prospective study on cardiovascular and cerebrovascular morbidity and mortality of subjects evaluated by periodic, at least annually, 48-h ABPM documented outcome-based reference thresholds for the diagnosis of hypertension to be 10/5 mm Hg lower for ambulatory SBP/DBP in women than men (Hermida et al., 2012f).

The sex differences in BP regulation are illustrated in Figure 7, which represents, first, the circadian pattern of SBP (left) and DBP (right) of 643 clinically healthy young adult men and 504 nonpregnant normotensive women, 18–40 yrs of age (Hermida et el., 2002a). Data on these 1143 normotensive subjects, matched by age, ethnicity, and, to the extent possible, body weight and height to the population of pregnant women described above (Table 1), were obtained using the same sampling scheme, i.e., ABPM performed every 20 min from 07:00 to 23:00 h and every 30 min during the night for 48 consecutive hours with a validated SpaceLabs 90207 device (SpaceLabs). Figure 7 also provides comparison between the circadian BP pattern of normotensive men and women and that of normotensive and hypertensive pregnant women evaluated by 48-h ABPM during their second trimester of gestation as an illustrative example. This figure documents the following: (i) SBP and DBP are significantly elevated in young-adult normotensive men as compared with women ($p < .001$); (ii) as previously documented (Hermida et al., 2003c), SBP and DBP are significantly diminished in normotensive pregnant women as compared with women who developed gestational hypertension or preeclampsia sampled in the second trimester of gestation ($p < .001$), although these differences between healthy and complicated

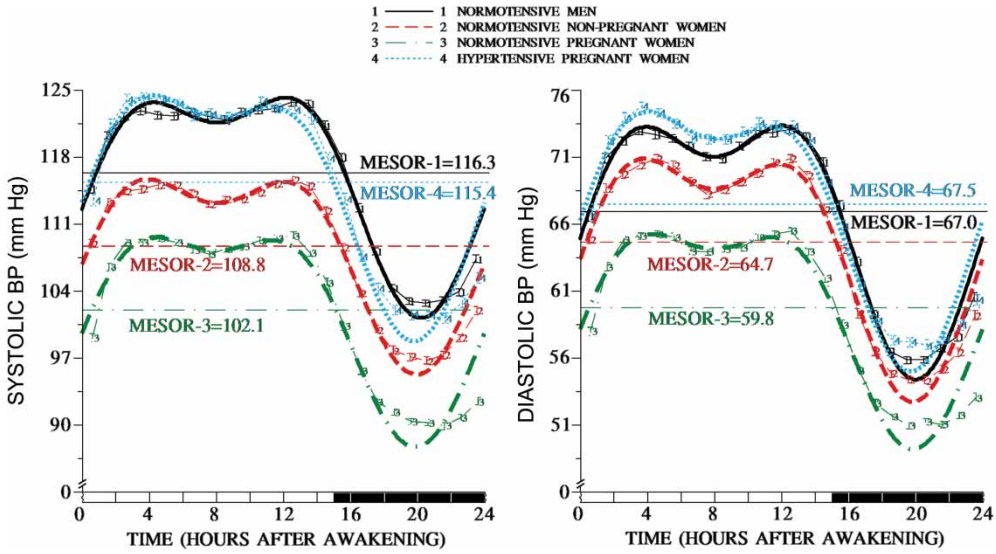

FIGURE 7. Circadian pattern of SBP (left) and DBP (right) in mm Hg of clinically healthy normotensive men (643 individuals), normotensive women (504 individuals), as well as normotensive pregnant women and women who developed gestational hypertension or preeclampsia sampled by 48-h ABPM in the second trimester of pregnancy (14 to 27 wks of gestation). Each graph shows hourly means and standard errors of data for each group of subjects. Dark shading along lower horizontal axis of graphs denotes average hours of nighttime sleep across the subject sample. Nonsinusoidal-shaped curves correspond to best-fitted waveform models derived by population multiple-component analysis. MESOR (midline estimating statistic of rhythm) is the 24-h average value of the rhythmic function fitted to the data. Amplitude is one-half the difference between maximum and minimum values of the best-fitted curve. Updated from Hermida and Ayala (2004).

pregnancies can already be observed during the first trimester of pregnancy (Figure 4); (iii) SBP and DBP are significantly lower in normotensive pregnant women as compared with normotensive nonpregnant women ($p < .001$), as a consequence of the diminished BP during the second trimester of gestation in healthy pregnancies previously documented (Figures 2 and 3); (iv) SBP and DBP are significantly higher in women who developed gestational hypertension or preeclampsia than in normotensive women, either pregnant or nonpregnant ($p < .001$); and (v) SBP and DBP are fully equivalent in women who developed gestational hypertension or preeclampsia when sampled during the second trimester of pregnancy and in clinically healthy normotensive men ($p > .187$ for SBP and DBP).

Although Figure 7, as an example, represents data from pregnant women sampled during their second trimester of gestation, similar conclusions can been obtained from the same women sampled by 48-h ABPM before 14 wks of gestation, i.e., during the first trimester (Ayala et al., 1997a; Hermida et al., 2000a, 2003c). These significant differences in ambulatory BP are found several months before the diagnosis of gestational hypertension can be established when relying on clinic BP measurements, usually within the third trimester of pregnancy. Moreover, the differences of about 12/7 mm Hg in the 48-h mean of SBP/DBP between healthy and complicated pregnancies are found when both SBP and DBP for women with a later diagnosis of gestational hypertension or preeclampsia are below the threshold limits currently accepted for the diagnosis of hypertension in pregnancy (Brown et al., 2001c; Davey & MacGillivray, 1988; Lindheimer et al., 2008). The diminished BP in nongravid women as compared with men and the added decrease in BP during the second half of gestation in normotensive pregnant women have not been taken into consideration when establishing reference thresholds for BP for the diagnosis of hypertension in pregnancy, whether based on unreliable clinic BP measurements (Brown et al., 2001c; Davey & MacGillivray, 1988; Lindheimer et al., 2008) or on the more reproducible ABPM (Chobanian et al., 2003; Mancia et al., 2007; O'Brien et al., 2003).

24-h BP MEAN FOR DIAGNOSIS OF GESTATIONAL HYPERTENSION

In chronic essential hypertension, the correlation between BP level and target organ damage, cardiovascular disease risk, and long-term prognosis is greater for ambulatory BP monitoring (ABPM) than clinic BP measurement (Ayala et al., 2012a; Clement et al., 2003; Eguchi et al., 2008; Hermida et al., 2010, 2011a, 2011b, 2011c, 2012a, 2012c, 2012d; Perloff et al., 1983; Salles et al., 2008; Verdecchia et al., 1994). Accordingly, several investigators have attempted to extrapolate these advantages of ABPM to the diagnosis of hypertension in pregnancy and the prediction of pregnancy outcome. As in essential hypertension, the most common approach for making the diagnosis has been to rely on the ABPM-derived 24-h BP mean. Previous studies that have evaluated the 24-h BP mean for diagnosis of hypertension in pregnancy have found different threshold reference values that only occasionally have been tested prospectively (Bellomo et al., 1999; Hermida & Ayala, 2005a). Moreover, there is considerable controversy regarding the comparative prognostic

value of the awake and asleep BP means for the prediction of complications in pregnancy (Brown et al., 2001a, 2001b; Halligan et al., 1993; Kyle et al., 1993).

Among several other authors, Kyle et al. (1993) investigated the effectiveness of the second-trimester 24-h BP mean as a screening test for hypertension in pregnancy. They reported that the awake SBP mean was elevated at 18 and 28 wks of gestation in women who subsequently developed "preeclampsia," a term applied in their paper to what actually could not even be considered gestational hypertension according to current definitions (Brown et al., 2001c; Davey & MacGillivray, 1988; Lindheimer et al., 2008); "preeclampsia" was defined as women with an increase in clinic DBP ≥25 mm Hg during gestation or clinic DBP ≥90 mm Hg, independent of SBP or proteinuria. Whereas the first criterion— ≥ 30/15 mm Hg increase in clinic SBP/DBP throughout gestation—has been eliminated from the current definition of gestational hypertension (Lindheimer et al., 2008), the second criterion, totally disregarding SBP plus the required proteinuria for the proper definition of preeclampsia, provides a diagnosis based on clinic DBP readings that has very low prognostic value (Hermida & Ayala, 2002; Hermida et al., 1998, 2003a; Penny et al., 1998; Shennan & Halligan, 1998). Despite the significant difference in BP between the compared groups, the best predictive BP parameter was mean arterial BP ≥85 mm Hg at 28 wks of gestation, providing sensitivity of 65%, specificity of 81%, and positive predictive value of 31% for the prediction of this so-called "preeclampsia." Daytime and nighttime BP means were of comparable predictive value.

Penny et al. (1998) used a threshold value of 135/85 mm Hg for the 24-h SBP/DBP means to assess the ability of ABPM to predict development of severe hypertension (clinic SBP/DBP measurements ≥160/110 mm Hg), proteinuria, birth weight <3rd percentile for gestational age, preterm delivery, and admission of the newborn to the neonatal intensive care unit. The authors justified this decision on their claim that the 135/85 mm Hg thresholds for the 24-h SBP/DBP means were comparable to clinic readings of 140/90 mm Hg in nonpregnant populations. However, a revision of the published literature on the average difference between clinic and ambulatory BP values, as measure of the so-called white-coat effect, indicates that the differences between clinic and awake SBP means are commonly within the range of 13–20 mm Hg (Pickering et al., 2002). An added criticism to the approach of Penny et al. (1998) is the use of ABPM thresholds for the diagnosis of hypertension even above those currently recommended for nonpregnant women (Chobanian et al., 2003; Mancia et al., 2007; Pickering et al., 2005). Moreover, as described above, such threshold values established independent of gestational age do not take into account the predictable changes in BP throughout pregnancy, as illustrated in Figures 2 and 3. Despite all these major limitations, the authors concluded that a 24-h BP mean >135/85 mm Hg in the second half of pregnancy was a significantly better predictor than conventional BP values ≥140/90 mm Hg for the development of cuff-measurement-assessed severe hypertension.

Bellomo et al. (1999) also evaluated the prognostic value of ABPM in pregnancy using reference thresholds of 125/74 mm Hg for the 24-h SBP/DBP means, 128/78 mm Hg for awake SBP/DBP means, and 121/70 mm Hg for asleep SBP/DBP means in women sampled on just one occasion during their third trimester of pregnancy. These investigators indicated that the 24-h BP mean is superior to clinic BP measurements for prediction of pregnancy outcome.

Brown et al. (2001a) reported 70% sensitivity when a cutoff value of 62 mm Hg for the asleep DBP mean was used for predicting women who later developed either gestational hypertension or preeclampsia. They also suggested that threshold values of 115 mm Hg for the 24-h SBP mean and 106 mm Hg for the asleep SBP mean were predictive of later gestational hypertension or preeclampsia, but again with relatively low sensitivities, 77% and 54%, respectively. This work actually described the potential ability of the highly reproducible ABPM to predict the poorly reproducible clinic BP ≥140/90 mm Hg later in pregnancy. Higgins et al. (1997) used the same questionable approach of investigating ABPM as a potential predictor of future clinic BP measurements in pregnancy. They studied 1048 women evaluated by 24-h ABPM at 18 to 24 wks of gestation. The best overall predictor for preeclampsia was the 24-h DBP mean, which when using a cutoff threshold value of 71 mm Hg provided a test with sensitivity of only 22% and positive predicted value of 15%. Despite the unquestionably high prognostic value of ABPM as compared with conventional clinic BP measurements, due to poor results from the diagnostic test based on 24-h BP mean, namely the identification by ABPM of women who might or not show elevated clinic BP later in pregnancy, the most extended conclusion in the obstetric field so far is that ABPM does not provide a proper approach for the early identification of gestational hypertension or preeclampsia, and therefore should not be used in pregnancy (Higgins et al., 1997).

Apart from the methodological issues associated with such a sweeping conclusion, i.e., mistakenly considering clinic BP ≥140/90 mm Hg as the "gold standard" to predict complications in pregnancy, authors disregarding the potential benefits of ABPM for predicting hypertensive complications in pregnancy (Brown et al., 2001a; Higgins et al., 1997) have systematically assumed that "ABPM" and "24-h BP mean" are equivalent concepts, as if the 24-h BP mean would be the only prognostic parameter that one could calculate from the data obtained by ABPM. However, during the past two decades, many different features of the ABPM-determined 24-h BP pattern have been assessed as mediators of injury to target tissues, and triggers of and risk factors for cardiovascular events, such as angina pectoris, myocardial

infarction, cardiac arrest, sudden cardiac death, plus ischemic and hemorrhagic stroke. For instance, numerous studies have consistently shown an association between blunted sleep-time relative BP decline (so-called non-dipper BP pattern) and increased incidence of fatal and nonfatal cardiovascular events (Astrup et al., 2007; Boggia et al., 2007; Brotman et al., 2008; Dolan et al., 2005; Hermida et al., 2011a, 2012a, 2012e; Ingelsson et al., 2006; Kario et al., 2001; Nakano et al., 1998; Ohkubo et al., 2002; Sturrock et al., 2000; Verdecchia et al., 1994). Furthermore, several independent prospective studies have also reported that the asleep BP mean is a better predictor of cardiovascular events than the awake or 24-h BP means (Ben-Dov et al., 2007; Boggia et al., 2007; Bouhanick et al., 2008; Dolan et al., 2005; Fagard et al., 2008; Fan et al., 2010; Hermida et al., 2011a, 2012a, 2012d; Kikuya et al., 2005; Minutolo et al., 2011). Moreover, the extent of BP surge upon awakening has been associated with increased cardiovascular morbidity and mortality in some, but not all, studies (Gosse et al., 2004; Israel et al., 2011; Kario et al., 2003; Metoki et al., 2006). So far, the potential prognostic value of different ABPM-derived parameters beyond the 24-h BP mean has been only occasionally evaluated in pregnancy (Hermida & Ayala, 1997, 2001, 2005a).

In a study on 113 pregnant women who provided 759 profiles of ABPM sampled for 48-h every 4 wks from the first obstetric examination until delivery, we investigated the sensitivity and specificity of the 48-h BP mean at each trimester of pregnancy by comparing distributions of values obtained for healthy and complicated pregnancies, without assuming an a priori threshold for diagnosing gestational hypertension based on mean BP (Hermida & Ayala, 1997). Sensitivity ranged from 32% for DBP in the second trimester to 84% for SBP in the third trimester. Specificity, however, was as low as 7% for DBP in the first trimester. Results from this study indicated that the threshold values that would eventually provide the highest combined sensitivity and specificity in the diagnosis of hypertension in pregnancy are 111/66 mm Hg for the 48-h SBP/DBP means in the first trimester of pregnancy, 110/65 mm Hg in the second trimester, and 114/69 mm Hg in the third trimester. The corresponding threshold values for each of the three trimesters of pregnancy were 115/70, 115/69, and 118/72 mm Hg for the awake SBP/DBP means; and 99/58, 98/56, and 104/60 mm Hg for the asleep SBP/DBP means (Hermida & Ayala, 1997). These apparently low values reflect the predictable changes in BP during gestation in normotensive pregnant women and the expected diminished BP in pregnant as compared with nonpregnant women.

In the attempt to validate prospectively these results, we calculated the sensitivity and specificity of the 48-h, awake, and asleep BP means for the early identification of hypertension in pregnancy using the reference threshold values provided above when analyzing data provided by the pregnant women described in Table 1 (Hermida & Ayala, 2005a). As an illustrative example, Figure 8 represents the frequency histograms with the distributions of the 48-h (left), awake (center), and asleep (right) SBP means calculated from the 958 ABPM profiles of 48-h duration obtained in the second trimester of pregnancy. Comparison of histograms of normotensive (top) and hypertensive (bottom) pregnancies did not show clear separation between the two populations for any of the three mean values here investigated. However, the use of previously established thresholds

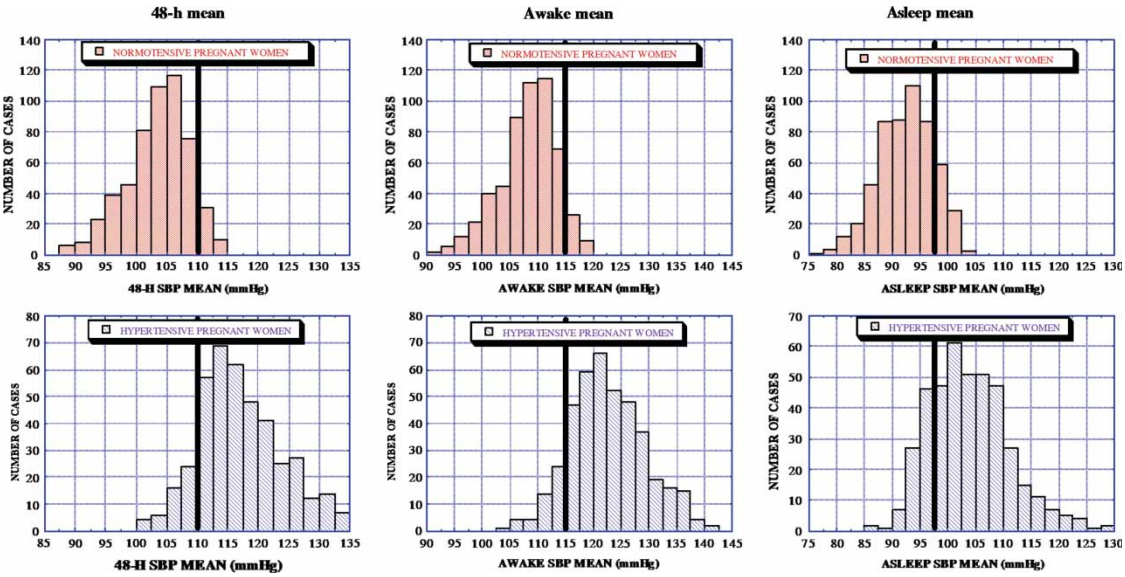

FIGURE 8. Frequency distribution of 48-h (left), awake (center), and asleep (right) SBP means from normotensive (top) and hypertensive (bottom) pregnant women sampled by 48-h ABPM in the second trimester of pregnancy (14 to 27 wks of gestation). The tested reference thresholds of 110, 115, and 98 mm Hg for the 48-h, awake, and asleep SBP means, respectively, are represented as thick vertical lines in each graph. Updated from Hermida and Ayala (2005a).

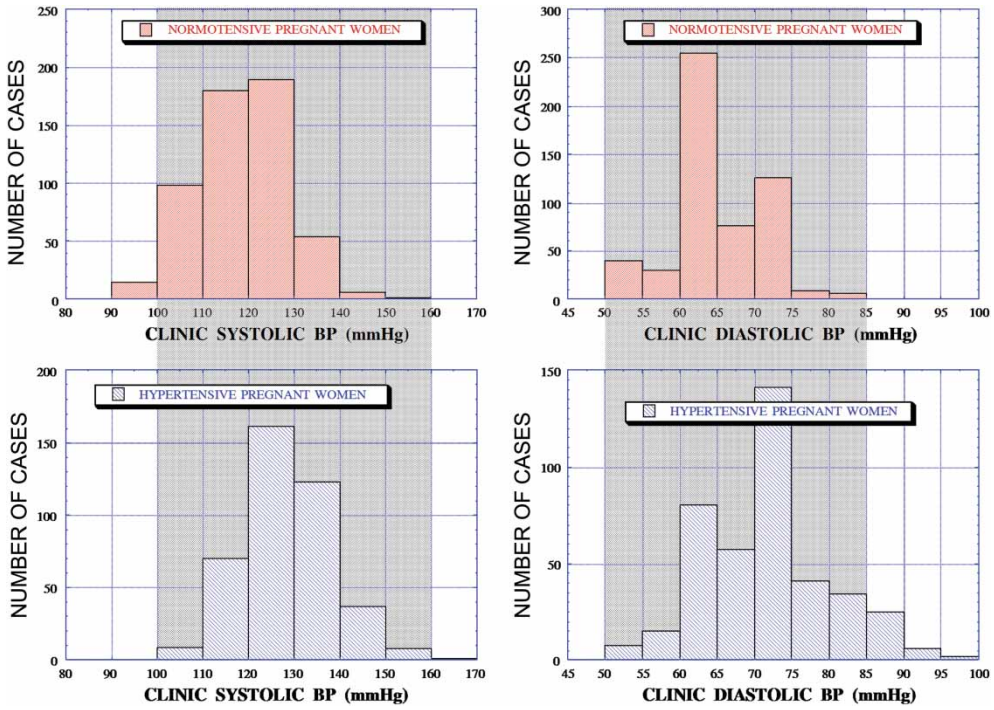

FIGURE 9. Frequency distribution of clinic SBP (left) and DBP (right) from normotensive (top) and hypertensive (bottom) pregnant women evaluated in the second trimester of pregnancy (14 to 27 wks of gestation).

tested prospectively (110, 115, and 98 mm Hg for the 48-h, awake, and asleep SBP means in the second trimester of pregnancy, respectively; Hermida & Ayala, 1997) revealed relatively small overlap between healthy and complicated pregnant women. Only 40 out of the 546 (7.3%) BP profiles representative of normotensive pregnant women in the second trimester of gestation had a 48-h SBP mean >110 mm Hg, whereas 362 out of the 412 (87.9%) series representative of hypertensive women had a 48-h SBP mean above this threshold. Results were similar for the awake SBP mean (Figure 8, center). However, the overlap between the values of normotensive and hypertensive women was slightly higher for the asleep SBP mean; 14.1% of the asleep SBP mean values obtained from normotensive women were above the threshold for diagnosis here tested (98 mm Hg), and 22.6% of the profiles from hypertensive pregnant women were below this threshold (Figure 8, right). Results further indicated a slightly larger overlap on BP mean values between normotensive and hypertensive women in the first trimester, and a slightly smaller overlap for data sampled in the third trimester. Thus, sensitivity and specificity in the diagnosis of hypertension in pregnancy based on mean SBP values increased with gestational age. For the threshold values provided above, sensitivity and specificity of the 48-h DBP mean were consistently lower than they were for the 48-h SBP mean at all stages of pregnancy (Hermida & Ayala, 2005a).

These findings on the prospective evaluation of the prognostic value in pregnancy of mean BP values derived from ABPM were compared with those obtained from clinic BP measurements on the same women (Figure 9). For data obtained during the second trimester, total overlap was 97.7% and 98.2% for clinic SBP and DBP, respectively, between normotensive and hypertensive pregnancies. Women who later developed gestational hypertension or preeclampsia had during the second trimester of pregnancy clinic SBP values as low as 100 mm Hg, with only 33 out of a total of 412 SBP values (8%) actually ≥140 mm Hg. Results thus indicated very poor sensitivity at all stages of gestation, mainly for clinic DBP. Specificity, on the contrary, was very high, as just a very small proportion of women in this study, including those with proteinuric preeclampsia, showed conventional clinic BP values ≥140/90 mm Hg, even during most of their third trimester of pregnancy.

Results from this prospective trial (Hermida & Ayala, 2005a) corroborate, first, the advantages of ABPM over clinic BP values for the early identification of hypertension in pregnancy. Relative to the 130/80 mm Hg reference thresholds for 24-h SBP/DBP means proposed for the general population (Chobanian et al., 2003; Mancia et al., 2007; Pickering et al., 2005), the thresholds provided above as a function of gestational age reflect the expected lower BP in women as compared with men previously documented (Hermida et al., 2002a), the expected further decrease in BP in the gravid as compared with nongravid women (Ayala et al., 1997a; Hermida et al., 1997c, 2000a, 2003c), and the predictable changes in BP as a function of gestational age (Ayala et al., 1997b; Hermida et al., 1997b, 2001a). Results presented in Figure 8 corroborate prospectively the use of those threshold values for mean BP derived from ABPM

for the diagnosis of hypertension in pregnancy. These thresholds, however, have been developed from data obtained exclusively from Spanish pregnant women living in a specific geographic location (northwest Spain). Possible generalization to other ethnic groups or women of different geographic locations should be properly investigated.

Considering the prognostic value of the 24-h, awake, and asleep BP means, it is relevant to mention that women here classified as hypertensive following the criteria described above were characterized by highly significant differences in gestational age at delivery, average newborn weight, as well as incidence of delivery by cesarean section, intrauterine growth retardation, and preterm delivery as compared with women classified as normotensive (Table 1). In summary, this prospective study on women systematically studied by 48-h ABPM throughout gestation indicates that the diagnosis of hypertension in pregnancy based on mean BP values derived from ABPM should be established from thresholds much lower than those currently used in clinical practice. Although sensitivity and specificity in the diagnosis of hypertension can still be somehow improved by the use of other indexes derived from ABPM (Hermida & Ayala, 2002; Hermida et al., 1997e, 1998, 2003a, 2004a), the results indicate that the 48-h, awake, and asleep BP means (Figure 8) provide a diagnostic test markedly superior to clinic BP measurements (Figure 9), rendering ABPM a useful technique for the clinical evaluation and early identification of complications in pregnancy.

TIME-SPECIFIED REFERENCE VALUES FOR AMBULATORY BP IN PREGNANCY

Static threshold values for conventional clinic BP measurements currently used for the diagnosis of hypertension in pregnancy (Brown et al., 2001c; Davey & MacGillivray, 1988; Lindheimer et al., 2008) do not take into account the circadian BP pattern documented in pregnant women at all gestational ages (Ayala et al., 1997a; Benedetto et al., 1996; Hermida et al., 1997c, 2000a, 2003c). Accordingly, it has been suggested that these static diagnostic limits should be replaced by a time-qualified reference limit reflecting the mostly predictable BP variability during the 24 h (Hermida et al., 2001b). Time-specified reference limits can be constructed in different ways; they can be model dependent (Fernández & Hermida, 2000) or model independent (Hermida, 1999; Hermida & Fernández, 1996), and they can be computed as prediction (Hermida et al., 1993; Nelson et al., 1983) or tolerance intervals (Hermida & Fernández, 1996; Hermida et al., 1997d, 1997f). When samples from a reference group of subjects are available, one may construct a prediction interval expected to include any single future observation from the reference population with a specified confidence (Hermida et al., 1993; Nelson et al., 1983). 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 (Hermida & Fernández, 1996; Hermida et al., 1997d, 1997f, 2001b, 2004d). The latter kind of reference interval is commonly used in industry and has been recommended for clinical measurements (Hermida, 1999; Hermida & Fernández, 1996).

Figure 10 shows the tolerance intervals for SBP (top) and DBP (bottom) derived to include 90% of the reference population of normotensive individuals with 90% confidence. Tolerance intervals for SBP and DBP were calculated using the mathematical nonparametric method described in detail elsewhere (Hermida & Fernández, 1996). The tolerance intervals were obtained, first, from data sampled by 48-h ABPM during the second trimester of pregnancy in the reference group of 235 normotensive pregnant women with clinical and demographic characteristics described in Table 1 and, second, from the reference population of 504 nonpregnant normotensive women who provided the information represented in Figure 7. For both groups of pregnant and nonpregnant normotensive women, the graphs in Figure 10 represent the upper and lower limits of the tolerance interval with reference to time

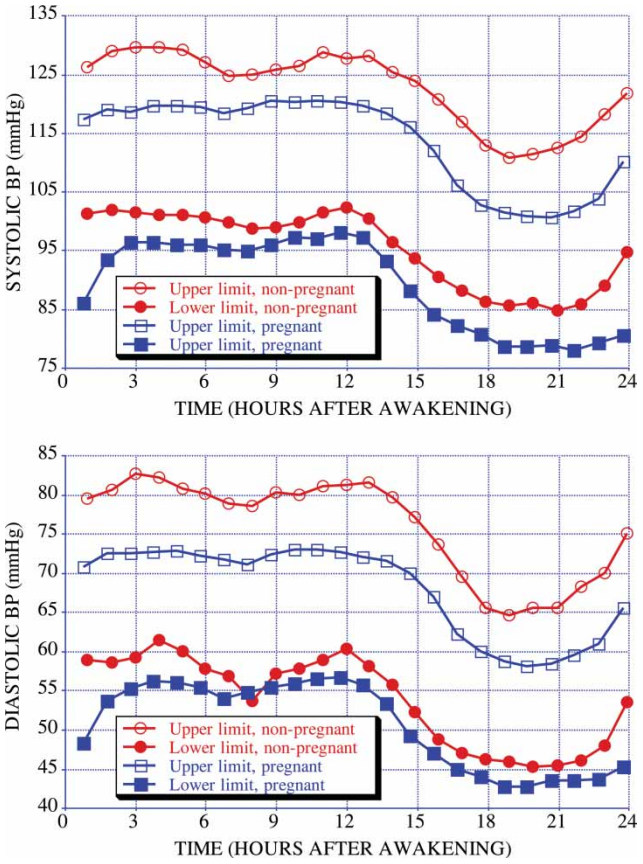

FIGURE 10. Circadian 90% tolerance intervals for SBP (top) and DBP (bottom) obtained from a reference population of 504 normotensive nonpregnant women and from 235 normotensive pregnant women who were assessed by 48-h ABPM in their second trimester of pregnancy (14 to 27 wks of gestation).

during the 24 h defined in terms of hours after awakening from nighttime sleep. The upper limit of the tolerance interval for both groups of women is not only markedly <140/90 mm Hg, but also below the thresholds of 135/85 mm Hg currently recommended for the diagnosis of essential hypertension in both women and men based on awake SBP/DBP means (Chobanian et al., 2003; Mancia et al., 2007; Pickering et al., 2005). Moreover, the values for the upper and lower limits of the tolerance intervals represented in Figure 10 for pregnant women sampled in their second trimester of gestation are markedly lower than those obtained for clinically healthy normotensive nonpregnant women also studied by 48-h ABPM. This finding reflects the expected lower SBP and DBP in normotensive pregnant women compared with nonpregnant women, as documented in Figure 7. The tolerance limits also reflect the circadian pattern of BP variability previously demonstrated in normotensive pregnant women during each trimester of gestation (Ayala et al., 1997a; Hermida et al., 1997c, 2000a, 2003c).

The tolerance limits represented in Figure 10 can be compared with reference thresholds for ABPM in pregnancy previously proposed by different investigators (Brown et al., 1998; Churchill et al., 1997; Ferguson et al., 1994; Halligan et al., 1993; Margulies et al., 1987). Ferguson et al. (1994) found BP to be lower in women sampled by ABPM during three different stages of gestation than in nonpregnant women; their proposed BP reference limits were higher at the end of pregnancy as compared with those obtained for the early stages of gestation in the same women. Brown et al. (1998) found increasing reference standards with gestational age from data sampled on women studied during one or more of four 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. Reference thresholds from all these studies were presented as confidence limits instead of prediction or tolerance intervals and, accordingly, have very restricted diagnostic value (Hermida, 1999; Hermida & Fernández, 1996; Hermida et al., 1997d, 1997g). Although prediction or tolerance intervals will define limits calculated 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 as compared with tolerance or even prediction intervals in clinical applications are important and have been extensively documented before (Fernández & Hermida, 2000; Hermida & Fernández, 1996; Hermida et al., 1997d, 1997g, 2002d).

EARLY IDENTIFICATION OF HYPERTENSION IN PREGNANCY WITH THE TOLERANCE-HYPERBARIC TEST

The circadian pattern that characterizes BP in healthy pregnancies at all gestational ages, as shown in Figures 4 to 6 (Ayala et al., 1997a; Benedetto et al., 1996; Hermida et al., 1997c, 2000a, 2003c), suggests, first, that the diagnosis of hypertension in pregnancy might be improved without reliance only on 24-h BP mean values that disregard information on circadian BP variability (Hermida & Ayala, 1997). This circadian variation also suggests the use for diagnosis of a time-specified reference limit reflecting that mostly predictable BP variability (Figure 10). Once the time-varying threshold, given, for instance, by the upper limit of a tolerance interval (Hermida et al., 2001b), is available, the HBI, as a determinant of BP excess (Halberg et al., 1984; Hermida & Ayala, 2002; Hermida et al., 1996, 1997e, 1998, 2000b, 2002d, 2003a, 2004a), can be calculated as the total area of any given subject's BP above the threshold during the entire 24-h period (Figure 11). The HBI as well as the duration of BP excess (percentage time of excess, defined as the percentage time of the 24 h with BP from the test subject exceeding the upper limit of the tolerance interval) could then be used as nonparametric endpoints for assessing hypertension in pregnancy. This so-called tolerance-hyperbaric test, where diagnosis of hypertension is based on the HBI calculated with reference to a time-specified tolerance limit, has been shown to provide high sensitivity and specificity for the early identification of subsequent hypertension in pregnancy (Hermida et al., 1997e, 1998) and to be a valuable approach for the prediction of pregnancy outcome (Hermida & Ayala, 2002; Hermida et al., 2003a). Because the conventional assessment of gestational hypertension relies on office values ≥140/90 mm

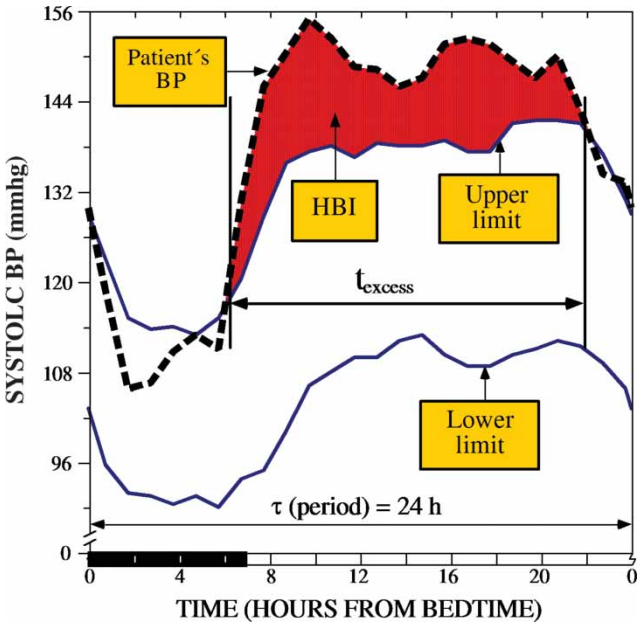

FIGURE 11. The concept of hyperbaric index (HBI), defined as total area of any given subject's BP (dashed line) above a time-varying threshold defined by a tolerance interval (with upper and lower limits shown as continuous lines) during the entire 24-h period. The percentage time of excess (t_{excess}) is defined as the percentage time of the 24 h with BP from the test subject exceeding the upper limit of the tolerance interval.

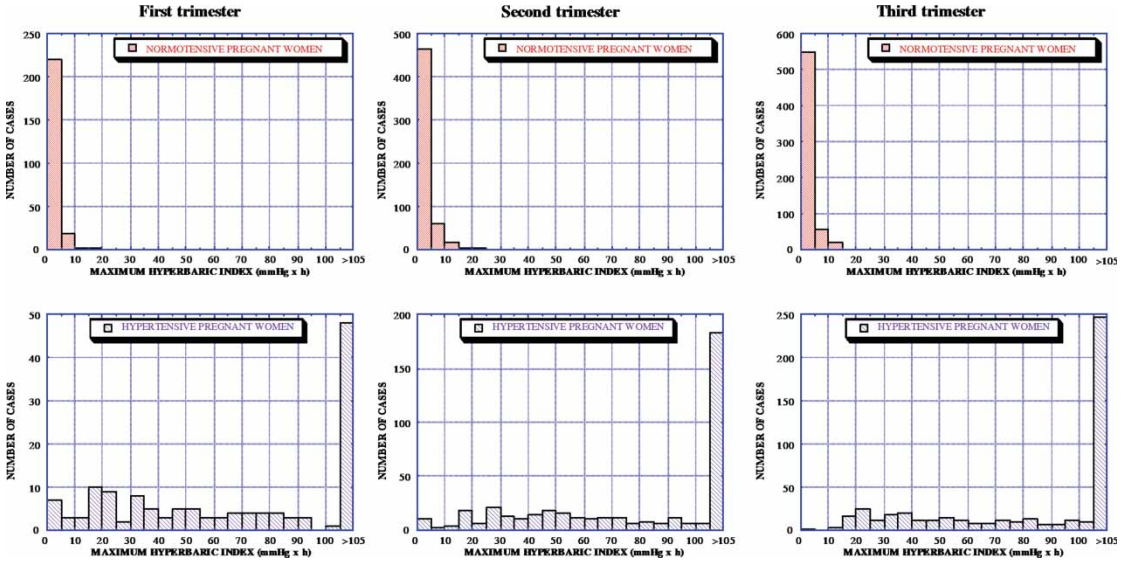

FIGURE 12. Frequency distribution of maximum HBI (maximum of the three values of HBI calculated for SBP, mean arterial BP, and DBP, respectively, using as reference threshold 90% circadian tolerance limits obtained from a reference population of normotensive pregnant women) from normotensive (top) and hypertensive (bottom) pregnant women evaluated by 48-h ABPM in different trimesters of pregnancy. Updated from Hermida et al. (2004a).

Hg for SBP/DBP (Brown et al., 2001c; Davey & MacGillivray, 1988; Lindheimer et al., 2008), results based on the determination of BP excess have been usually expressed as a function of the maximum HBI, defined as the maximum of the three values of HBI determined for SBP, mean arterial BP, and DBP, respectively, for any given individual (Hermida et al., 1996, 1997e, 1998, 2000b, 2002d, 2003a, 2004a).

For women with the clinical characteristics described in Table 1, Figure 12 shows the distributions of the maximum HBI calculated for the BP series sampled by ABPM at each trimester of pregnancy in normotensive (top) and hypertensive (bottom) pregnant women. Results indicate that the maximum HBI of normotensive women exceeded the threshold diagnostic value (15 mm Hg × h) in 1 out of 241 ABPM profiles sampled in the first trimester (<14 wks of gestation) and in 4 out of 546 such profiles sampled in the second trimester of pregnancy (14 to 27 wks of gestation). The graphs at the bottom of Figure 12 indicate that, for hypertensive pregnant women, most ABPM profiles were characterized by a maximum HBI not just exceeding the reference threshold value provided above, but >105 mm Hg × h, a value chosen here only to keep the length of the horizontal axis of the histograms to a reasonable size. Only 34 out of the total number of 1022 ABPM profiles obtained from hypertensive pregnant women in this prospective study showed a maximum HBI below the previously defined threshold for diagnosis at any stage of gestation (Hermida et al., 2004a).

When the diagnosis of hypertension was based on this so-called tolerance-hyperbaric test, results indicated sensitivity of 93% for early identification of hypertension in pregnancy for women evaluated by ABPM during their first trimester of gestation. Sensitivity increased with gestational age, as BP also increased steadily during the second half of gestation in those women who developed hypertension in pregnancy (Figures 2 and 3). The positive and negative predictive values of the test based on the maximum HBI were ≥96% in all trimesters of pregnancy (Hermida et al., 2004a). The characteristics of the diagnostic test as a function of trimester of gestation are described in Figure 13 (top). These graphs represent sensitivity and specificity determined as a function of different threshold values for the maximum HBI. Figure 13 (top) indicates that as one increases the threshold value for diagnosis, specificity increases very rapidly. Sensitivity, on the contrary, smoothly decreases for higher values of HBI. The slopes for increasing specificity and decreasing sensitivity are markedly different. Moreover, Figure 13 also indicates that the range for a threshold value of maximum HBI providing both sensitivity and specificity ≥90% is very high. These results characterize a highly stable diagnostic test (Hermida et al., 1997e, 1998, 2000b, 2002d, 2004a). The bottom graphs of Figure 13 provide similar information for the maximum percentage time of BP excess, which provides a test with slightly lower sensitivity and specificity for all trimesters of pregnancy, as previously documented (Hermida et al., 2004a).

In order to evaluate how early in pregnancy the tolerance-hyperbaric test might be carried out with high sensitivity, we compared the actual date of the diagnosis of gestational hypertension or preeclampsia obtained from conventional clinical reports with the date of diagnosis based on a maximum HBI exceeding the critical threshold of 15 mm Hg × h. Figure 14 (top) indicates that all women who subsequently developed gestational hypertension or preeclampsia were positively identified by the tolerance-hyperbaric test based on 48-h ABPM

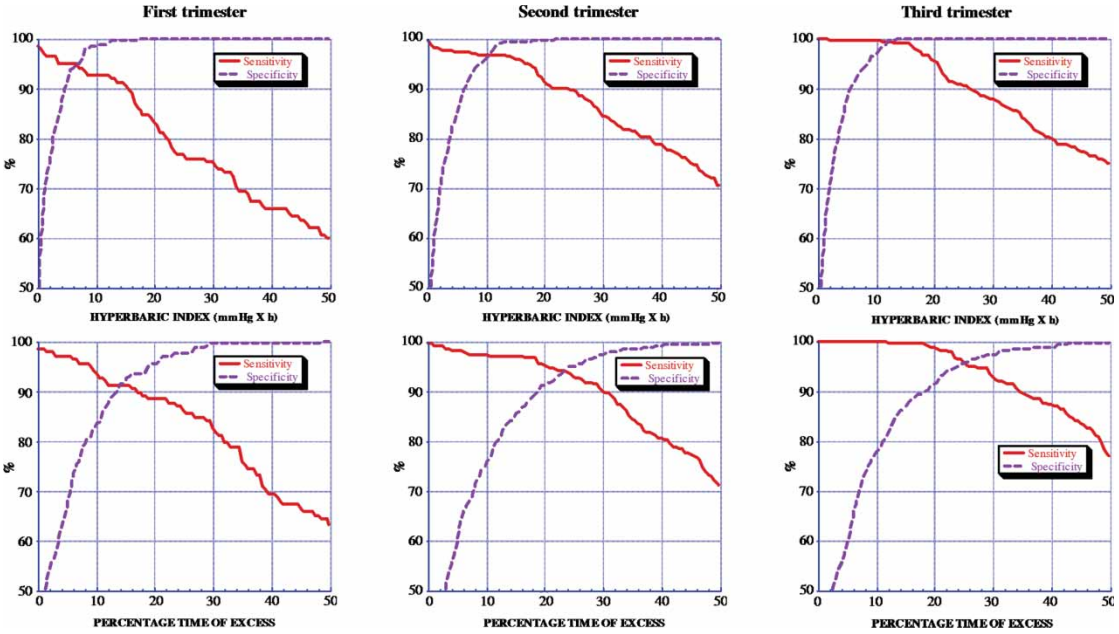

FIGURE 13. Diagnosis of hypertension in pregnancy based on the maximum HBI (maximum of the three values of HBI calculated for SBP, mean arterial BP, and DBP, respectively, using as reference threshold 90% circadian tolerance limits obtained from a reference population of normotensive pregnant women; top) and the maximum percentage time of BP excess (bottom) in women sampled at different trimesters of pregnancy. Updated from Hermida et al. (2004a).

performed before the beginning of the third trimester of pregnancy, although evidence of the condition was not clinically obtained until much later in pregnancy or even at delivery (when a prelabor test of urine confirmed proteinuria). For further comparison, the bottom graph of Figure 14 represents the time delay (in weeks) between the date of the diagnosis based on the maximum HBI and the date of confirmed diagnosis from conventional clinical practice; the average time of early identification of hypertension in pregnancy was 23 wks, more than half the total expected duration of gestation. The tolerance-hyperbaric test thus provides a high sensitivity tool for the very early identification of those pregnant women who, in the absence of any other clinical evidence, will subsequently develop gestational hypertension or preeclampsia. Results shown in Figure 12 further indicate that the identification of hypertension in pregnancy can be obtained in most women by 48-h ABPM performed in the first trimester of pregnancy (<14 wks of gestation), thus providing valuable time for preventive intervention and possible correction of the pathophysiologic changes that characterize preeclampsia (Askie et al., 2007; Hermida et al., 1997a, 1999, 2003b).

Several other authors have shown consistent positive results when testing the ability of the HBI derived from ABPM to predict the outcome of pregnancy (Benedetto et al., 1998; Blanco-García et al., 2007; Carandente et al., 1990; Cornélissen et al., 1989; Shaginian, 2006). Benedetto et al. (1998) performed 24-h ABPM at 8–16 and 20–25 gestational wks in 104 women at risk of gestational hypertension or preeclampsia. Best sensitivity and specificity were obtained between 20 and 25 wks of gestation with the circadian MESOR and the HBI of SBP using as cutoff values 103 mm Hg (sensitivity: 88%; specificity: 75%) and 10 mm Hg × h (sensitivity: 70%; specificity: 92%), respectively. The authors concluded that chronobiological analysis of 24-h ABPM in pregnancy allows definition of objective cutoff values that can be particularly useful in routine clinical practice when the risk of developing gestational hypertension or preeclampsia must be calculated in the individual woman. Shaginian (2006) evaluated 34 apparently healthy pregnant women by 72-h ABPM. He found elevated HBI for SBP in the first trimester of pregnancy for the 17 women who developed gestation hypertension or preeclampsia during the second half of gestation compared with the 17 women who remained normotensive until delivery. Previous results have also indicated the ability of the HBI, but not the clinic BP or 24-h BP mean, to differentiate, as early as at 20 wks of gestation, women who will develop preeclampsia from those who will just develop gestational hypertension (Hermida & Ayala, 2002; Hermida et al., 2003a). Although gestational hypertension on the basis of the maximum HBI may be defined as a value exceeding a relatively low threshold value (15 mm Hg × h), the results indicate that preeclampsia might be predicted by the use of a higher threshold, ~65 mm Hg × h (Hermida & Ayala, 2002).

CLINIC VERSUS AMBULATORY BP FOR DIAGNOSIS OF COMPLICATIONS IN PREGNANCY

A recent prospective study (Hermida & Ayala, 2002; Hermida et al., 2003a) compared the ABPM profiles and pregnancy outcome between three groups of pregnant women: (i) "detected" gestational hypertension,

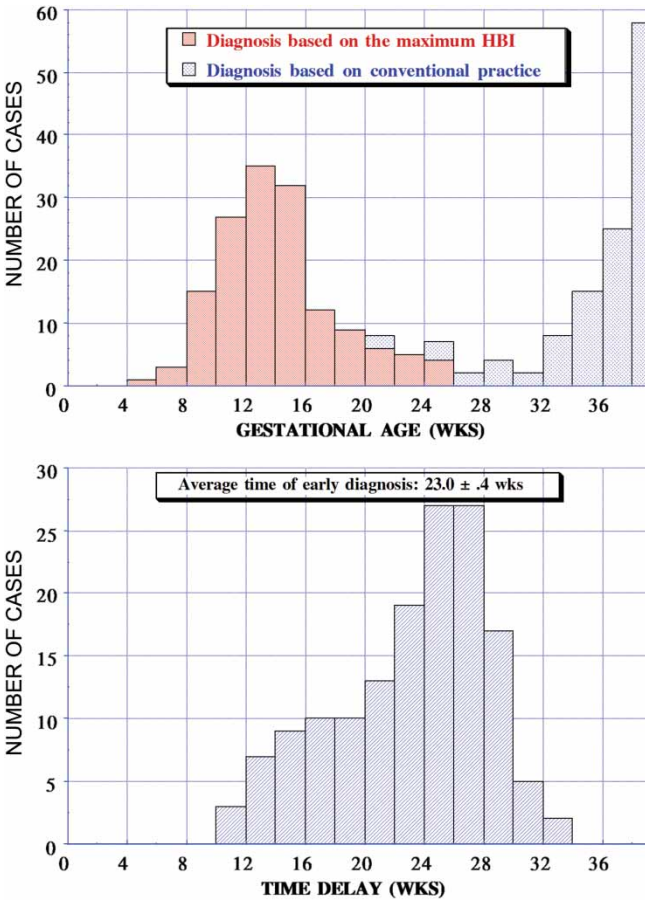

FIGURE 14. Date of diagnosis of gestational hypertension or preeclampsia based on conventional clinical practice or the maximum HBI in women evaluated by 48-h ABPM every 4 wks starting before 16 wks of gestation (top). The time delay between the diagnosis based on the maximum HBI and the clinical confirmation of the condition is shown in the bottom graph. Maximum HBI: maximum of the three values of HBI calculated for SBP, mean arterial BP, and DBP, respectively, using as reference threshold 90% circadian tolerance limits obtained from a reference population of normotensive pregnant women.

defined as clinic BP ≥140/90 mm Hg after 20 wks of gestation and maximum HBI consistently above the threshold for diagnosing hypertension in pregnancy provided above (therefore classified as hypertensive by both independent criteria); (ii) "undetected" gestational hypertension (or masked gestational hypertension), defined as clinic BP <140/90 mm Hg but HBI above the threshold for diagnosis in each and everyone of the monthly profiles of ABPM obtained after 20 wks of gestation (therefore considered "normotensive" according to current obstetric guidelines; Brown et al., 2001c; Davey & MacGillivray, 1988; Lindheimer et al., 2008); and (iii) normotension, defined as clinic BP and maximum HBI both consistently below their respective diagnostic thresholds at all evaluations after 20 wks of gestation. The demographic and perinatal characteristics of the investigated women are summarized in Table 2.

Comparison of the 24-h BP characteristics for "detected" and "undetected" gestational hypertension for women sampled in the first trimester of pregnancy revealed only a small and nonsignificant ($p = .056$) greater 24-h SBP mean by 2.6 mm Hg in "detected" than "undetected" gestational hypertension (Figure 15, left panel). Differences between groups in the 24-h DBP mean (not shown) amounted only .2 mm Hg ($p = .682$). Hourly means of SBP and DBP did not differ significantly between "detected" and "undetected" gestational hypertension at any circadian time, as corroborated by t tests adjusted for multiple testing. In the second trimester of pregnancy, normotensive women were characterized by statistically significant lower 24-h SBP and DBP ($p < .001$). Comparisons between "detected" and "undetected" gestational hypertension (Figure 15, central panel) revealed no significant between-group differences in 24-h SBP and DBP means ($p > .386$). Differences in the 24-h SBP and DBP means between "detected" and "undetected" gestational hypertension were even smaller in the third trimester of pregnancy (Figure 15, right panel). As in the earlier stages of pregnancy, ambulatory BP was highly significantly lower during the third trimester in normotensive pregnant women than in women with either "detected" or "undetected" gestational hypertension ($p < .001$).

Average newborn weight, gestational age at delivery, plus incidence of preterm delivery, intrauterine growth retardation, and delivery by cesarean section were similar between the two groups of women with "detected" and "undetected" gestational hypertension (Table 2). There were statistically significant differences in all those perinatal outcome variables between these two groups and normotensive pregnant women (Table 2).

Results from this prospective study do not support office BP values as a proper "gold standard" for the diagnosis of hypertension in pregnancy (Hermida & Ayala, 2002; Hermida et al., 2003a).

In a recent paper, Vollebregt et al. (2010) evaluated 101 women by 48-h ABPM only once in the first trimester of pregnancy and reported limited accuracy of the HBI in predicting hypertension in pregnancy. Their approach was to use a (highly reproducible; Hermida et al., 2000b, 2004a) ABPM profile in the first trimester of gestation as predictor of elevated (highly variable and poorly reproducible) clinic BP later in pregnancy. This approach, far from novel, has been used in the past by many other obstetricians, as extensively reviewed above (Brown et al., 2001a; Higgins et al., 1997). As one could expect, these reports showed that ABPM was only of limited utility in predicting clinic SBP/DBP ≥140/90 mm Hg later in pregnancy, leading to the questionable conclusion that ABPM should not be used in pregnancy (Higgins et al., 1997). Thus, it is not surprising that current obstetric guidelines, including that of the International Society for the Study of Hypertension in Pregnancy (ISSHP), rely only on clinic BP ≥140/90 mm Hg after 20 wks of gestation to establish the diagnosis of gestational hypertension (Brown et al., 2001c; Davey &

TABLE 2. Demographic and perinatal characteristics of women investigated

Variable	NT	DGH	UGH	*p* value for comparison of: 3 groups	DGH vs UGH
Women, n	234	62	59		
ABPM profiles, n	1404	401	370		
Age, yrs	30.4 ± 5.5	30.0 ± 4.6	30.8 ± 5.1	.385	.726
Weight, kg	63.1 ± 9.7	78.6 ± 17.4	69.6 ± 16.5	<.001	.002
Height, cm	161.8 ± 5.5	163.7 ± 7.0	162.3 ± 7.1	.124	.194
SBP at first visit, mm Hg*	119 ± 10	127 ± 10	122 ± 9	<.001	.012
DBP at first visit, mm Hg*	65 ± 7	71 ± 8	68 ± 8	<.001	.181
SBP at last visit, mm Hg*	118 ± 9	142 ± 11	133 ± 7	<.001	<.001
DBP at last visit, mm Hg*	66 ± 7	84 ± 7	79 ± 6	<.001	<.001
Gestational age at delivery, wks	39.4 ± 1.1	38.7 ± 3.4	38.8 ± 3.5	.044	.814
Newborn weight, g	3334 ± 447	3088 ± 634	3062 ± 653	<.001	.918
Delivery by cesarean section, %	18.4	35.5	40.7	<.001	.715
Intrauterine growth retardation, %	5.1	16.1	17.0	<.001	.791
Preterm delivery (<37 wks), %	3.6	9.7	10.2	.037	.935
Newborn Apgar score† at:					
1 min	8.8 ± 1.0	8.8 ± .9	8.7 ± 1.0	.894	.682
5 min	9.9 ± .4	9.9 ± .4	9.8 ± .7	.297	.334
10 min	10 ± .2	10 ± .1	9.9 ± .2	.492	.312

Values are shown as mean ± SD. NT = normotension; DGH = "detected" gestational hypertension; UGH = "undetected" gestational hypertension.
*Values correspond to the average of 3 to 6 clinic BP measurements obtained by a midwife nurse for each women at the time of their first and last (before delivery) visits to the hospital.
†The Apgar score is determined by evaluating the newborn with five criteria on a scale from 1 to 2, i.e., appearance, pulse, grimace, activity, and respiration.

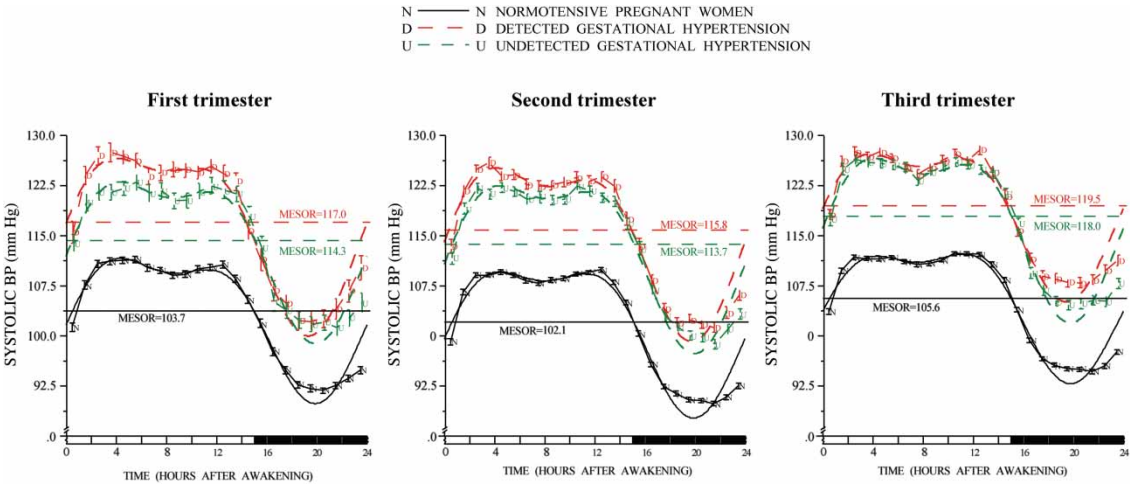

FIGURE 15. Circadian SBP pattern of pregnant women sampled by 48-h ABPM at different stages of pregnancy. Women were divided for comparative purposes into three groups according to the values of clinic BP and maximum HBI at all evaluations after 20 wks of gestation: (i) normotension, both clinic BP and maximum HBI below diagnostic thresholds at all evaluations after 20 wks of gestation; (ii) "detected" gestational hypertension, clinic BP ≥140/90 mm Hg and elevated HBI; and (iii) "undetected" gestational hypertension, clinic BP <140/90 mm Hg but elevated HBI. Each graph shows hourly means and standard errors of data for each group of women. Dark shading along lower horizontal axis of graphs denotes average hours of nighttime sleep across the sample. Nonsinusoidal-shaped curves correspond to best-fitted waveform models derived by population multiple-component analysis. MESOR (midline estimating statistic of rhythm) is the 24-h average value of the rhythmic function fitted to the data. Amplitude is one-half the difference between maximum and minimum values of the best-fitted curve. Updated from Hermida et al. (2003a).

MacGillivray, 1988; Lindheimer et al., 2008). These obsolete guidelines do not even make mention of ABPM, in spite of consensus recommendations of the European Societies of Hypertension and Cardiology, which have stated "24h BP has been shown to be superior to conventional measurements in predicting proteinuria, risk of preterm delivery, infant weight at birth, and, in general, outcome of pregnancy" (Mancia et al., 2007), a statement that either the ISSHP is unaware of or does not value.

We feel the approach used by Vollebregt et al. (2010), i.e., conducting a single ABPM early in pregnancy to predict, later in pregnancy, hypertension that is defined

on the unique basis of clinic BP, is invalid for many reasons (Hermida & Ayala, 2010). When both clinic and ambulatory BP are available, ABPM, and not clinic BP, prevails for diagnosis. This is so because, by comparing clinic and ambulatory BP, one is able to distinguish groups of subjects with normotension, sustained hypertension, isolated clinic (white-coat) hypertension, and masked hypertension (Hermida et al., 2012c; Mancia et al., 2007). As summarized above, we previously demonstrated a comparable prevalence in high-risk pregnancies of 15.2% for masked gestational hypertension (elevated ABPM with "normal" clinic BP) and of 16.1% for sustained gestational hypertension (elevated clinic and ambulatory BP, without proteinuria) (Hermida & Ayala, 2002; Hermida et al., 2003a). Most important, those two groups were fully comparable with respect to perinatal outcome, the issue that really matters in pregnancy, but both groups were characterized by markedly greater incidence of preterm delivery, intrauterine growth retardation, and delivery by cesarean section compared with women with true gestational normotension and also white-coat gestational hypertension (Table 2; Hermida & Ayala, 2002; Hermida et al., 2003a).

By using their inappropriate approach, Vollebregt et al. (2010) undoubtedly included women with masked hypertension in the reference population as well as in the group they called "normotensive individuals," making invalid all conclusions drawn from their study. Moreover, Vollebregt et al. reported a mean and SD of the HBI for their reference population of 4 ± 17 mm Hg × h. This large dispersion indicates that women with HBI above the study's diagnostic threshold (18 mm Hg × h) were included in the reference group. This is one of the major differences between our (Hermida et al., 2001b) and their reported investigation, as our reference thresholds were derived from women who *never* showed an elevated HBI in the ABPM evaluations that commenced early in pregnancy and continued thereafter at monthly intervals until delivery. On the other hand, the inclusion of masked hypertension within the reference population as done by Vollebregt et al. significantly elevated the thresholds derived from ABPM that they used to calculate the HBI. In fact, the thresholds provided by Vollebregt et al. are about 10 mm Hg higher than those found by us, also for Caucasian pregnant women, for the first trimester of pregnancy (Hermida et al., 2001b). Moreover, the average ambulatory BP they reported was 111/65 mm Hg for the reference/normotensive groups, 114/69 mm Hg for gestational hypertension, and 119/72 mm Hg for preeclampsia. For the women we evaluated at <12 wks of gestation, the reported values were 103/61, 114/67, 117/69, and 119/69 mm Hg for normotension, masked hypertension, sustained hypertension, and preeclampsia, respectively (Hermida & Ayala, 2002; Hermida et al., 2003a). Thus, the discrepancies in mean BP between their and our study are evident *only* for the normotensive group, as the former study, but not ours, clearly included masked hypertension within normotension, whereas we properly included masked hypertension as gestational hypertension. Finally, and most important in terms of clinical relevance, the Vollebregt et al. study found perinatal outcome to be more favorable for women with gestational hypertension than for the ones with normotension. This is just the opposite of what the literature in the field leads us to expect. Based on the results of the Vollebregt study, one could question why it would be necessary to worry about gestational hypertension at all. Furthermore, if gestational hypertension, as the data of the Vollebregt et al. study suggest, might increase birth weight, increase dipping, and reduce by one-half the incidence of preterm delivery, maybe women (sarcastically speaking) should consider as a favorable goal to be hypertensive during their pregnancies.

Our studies have consistently found that ABPM in pregnancy is a reproducible approach that allows *early identification*, with high sensitivity and specificity, of women who will show not only consistently elevated ambulatory BP in the second half of gestation, but also an associated poor perinatal outcome (Hermida & Ayala, 2002; Hermida et al., 1997e, 1998, 2003a, 2004a). Vollebregt et al. have not been able to contradict these clinically important findings. They have shown, relying on an investigational approach and methods anchored in the past century, only that ABPM is unable to reliably predict a diagnosis based on clinic BP. Unfortunately, Vollebregt et al. failed to show that ABPM, in fact, is able to predict poor perinatal outcome, as demonstrated by us (Hermida & Ayala, 2002; Hermida et al., 1997e, 1998, 2003a, 2004a) among many others (Benedetto et al., 1998; Blanco-García et al., 2007; Cornélissen et al., 1989; Shaginian, 2006), and as already recognized by international (nonobstetric) guidelines (Mancia et al., 2007).

Finally, it is also pertinent to note that epidemiologic reports from the general obstetric population have established an estimated ~2% prevalence of preeclampsia and 6–8% prevalence of hypertension in pregnancy (Duley, 2009; Roberts et al., 2011; Steegers et al., 2010). Thus, gestational hypertension is estimated to be about 3-fold more prevalent than preeclampsia and to be a condition with markedly worst perinatal outcome than normotension (Duley, 2009; Hermida & Ayala, 2004; Mancia et al., 2007). Surprisingly, in the Vollebregt et al. study the reported incidence of preeclampsia was even higher than that of gestational hypertension and with perinatal outcome of this later group being the best of all the other pregnancy categories. These results not only dispute the credibility of Vollebregt et al.'s methods and report, but they also provide further evidence that the diagnosis of gestational hypertension should not rely on clinic BP, especially when ABPM is available.

DISCUSSION

Although preeclampsia has generally received more attention than just hypertension in the absence of any

other symptom or complication in pregnancy, the long-term follow-up of women with complicated pregnancies has indicated that gestational hypertension is associated with highest incidence of subsequent chronic hypertension (Marín et al., 2000). Thus, although preeclampsia is a more severe obstetric complication, gestational hypertension may have more important long-term implications. Accordingly, following the common standard on most of the cited references in this review, we focused on the identification of BP elevation in pregnancy, whether or not it could be accompanied later by proteinuria. As indicated above, previous results have already shown the ability of the HBI to differentiate to some extent, at the end of the first half of pregnancy, women who will develop preeclampsia from those who will develop gestational hypertension (Hermida & Ayala, 2002).

Common to the current definition of all hypertensive complications in pregnancy, independent of how preeclampsia might be defined, is the use of the constant reference threshold of 140/90 mm Hg for conventional clinic SBP/DBP values obtained at the physician's office (Brown et al., 2001c; Davey & MacGillivray, 1988; Lindheimer et al., 2008; Mancia et al., 2007). Previous results have consistently indicated poor prognostic value of clinic BP determination for the identification of hypertension in pregnancy and prediction of the outcome of pregnancy (Hermida & Ayala, 2002, 2004; Hermida et al., 2003a), as also corroborated by the findings described in Figure 9.

The ideal predictive or diagnostic test should be simple and easy to perform, reproducible and noninvasive, and with high sensitivity and positive predictive value. The tolerance-hyperbaric test is noninvasive since it relies on ABPM. Results summarized in this review are based on ABPM obtained for 48 consecutive hours as opposed to the most common 24-h monitoring (Bellomo et al., 1995, 1999; Brown et al., 2011a; Churchill et al., 1997; Cugini et al., 1992; Halligan et al., 1993; Higgins et al., 1997; Kyle et al., 1993; Margulies et al., 1987; Penny et al., 1998; Shennan & Halligan, 1998; Tranquilli et al., 2004; Waugh et al., 2000). As a compromise with practicability, monitoring over at least 48 h has been shown to present advantages in the analysis of BP variability, diagnosis of hypertension, and evaluation of patient response to treatment (Hermida et al., 1997e, 1998, 2000b). Moreover, accuracy in the derivation of ABPM characteristics (including mean BP values and HBI) depends markedly on the duration of ABPM (Hermida & Ayala, 2003; Hermida et al., 2002b, 2007a, 2012b). Indeed, sampling requirements for the tolerance-hyperbaric test are not very demanding. Although results summarized in the figures of this review were obtained with BP series sampled at 20- or 30-min intervals, the HBI can be well estimated from data sampled at just 2-h intervals with just marginal loss in sensitivity or specificity (Hermida & Ayala, 2003). Although 15-min sampling for ABPM evaluation in pregnancy has been unjustifiably advocated before (Shennan & Halligan, 1998), a larger sampling interval increases compliance and patient acceptability (Taylor et al., 2001). Additionally, the number of reference subjects needed for estimating stable tolerance intervals is also quite small, as previously documented (Hermida & Fernández, 1996; Hermida et al., 1997d, 1997f, 2001b, 2004d). Finally, the tolerance-hyperbaric test provides both high sensitivity and positive predictive value as early as in the first trimester of pregnancy (Hermida & Ayala, 2002; Hermida et al., 1997e, 1998, 2003a, 2004a).

Limitations of ABPM stem from the fact that most ambulatory devices, although advanced, are still expensive and have not been properly validated for their use in pregnancy. Cost, however, should always be evaluated in relation to potential benefit. Results from the prospective evaluation of the tolerance-hyperbaric test indicate that in pregnancy the cost-benefit relationship for ABPM is more favorable compared with clinic BP measurements, simply because ABPM allows proper identification of women at high risk of complications during their pregnancy, whereas clinic BP does not (Hermida & Ayala, 2002; Hermida et al., 2003a, 2004a). Tolerability of ABPM has also been discussed as a possible limitation of the technique in pregnancy. Although compliance is usually very high (Hermida et al., 1998, 2003a, 2004a), reported patient acceptability tends to be lower (Taylor et al., 2001). Patient acceptability, a potential limitation also discussed when criticizing the use of ABPM in general practice (Mancia et al., 2007), is in part related to the ability of the physician to provide useful and convincing information to the patient on the potential advantages of ABPM. Unfortunately, despite the high prognostic value of ABPM as compared with clinic BP values, the most extended conclusion so far is that, due to poor results from the diagnostic test when based on 24-h SBP/DBP means ≥130/80 mm Hg, ABPM does not provide a proper approach for the early identification of gestational hypertension or preeclampsia, and it should not be used in pregnancy (Higgins et al., 1997). The lower BP in nongravid women as compared with men, the added decrease in BP during the second half of gestation in normotensive but not in hypertensive pregnant women, and the circadian pattern with large amplitude that characterizes BP of healthy pregnant women at all gestational ages (Figure 7) were not taken into account in studies providing negative results on the use of ABPM in pregnancy. The establishment of proper reference thresholds for the 24-h BP mean derived by taking all those considerations into account has been shown prospectively to markedly increase the sensitivity and specificity of ABPM for the early identification of complications in pregnancy (Figure 8; Hermida & Ayala, 2005a).

As shown in Figure 12, sensitivity and specificity in the early identification of hypertension in pregnancy based on mean BP values can be improved by the use of other indexes also derived from ABPM (Hermida & Ayala, 2002; Hermida et al., 1997e, 1998, 2003a, 2004a).

In particular, the tolerance-hyperbaric test represents a reproducible, noninvasive, and highly sensitive test for the early identification of subsequent hypertension in pregnancy, including preeclampsia. ABPM during gestation, starting preferably at the time of the first obstetric check-up following positive confirmation of pregnancy, thus provides sensitive endpoints for use in early risk assessment and as a guide for establishing prophylactic or therapeutic intervention (Ayala et al., 2012b; Hermida et al., 1997a, 1999, 2003b). Accordingly, we recommend ABPM as substitute for the unreliable clinic BP measurements as the "gold standard" for the diagnosis of hypertension in pregnancy and the screening of women at high risk for additional complications, including fetal growth retardation and preterm delivery.

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