Usefulness of Ambulatory Blood Pressure Monitoring in Pregnant Women With Type 1 Diabetes

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OBJECTIVE — Pregnancy in type 1 diabetes is associated with an increased risk of developing pregnancy-induced hypertension (PIH). Ambulatory blood pressure monitoring (ABPM) has been used to screen for preeclampsia in nondiabetic pregnancy. To date, there are no data regarding ABPM during pregnancy in normotensive type 1 diabetic women. This study sought to establish blood pressure (BP) profiles for pregnant type 1 diabetic women using ABPM and determine whether the BP pattern can define a population at risk for developing PIH.

RESEARCH DESIGN AND METHODS — ABPM was carried out for one 24-h period during each trimester—in the first trimester between weeks 7 and 12, in the second trimester between weeks 20 and 24, and in the third trimester between weeks 30 and 34—in 22 normotensive pregnant type 1 diabetic and 10 pregnant nondiabetic women.

RESULTS — The incidence of PIH was fourfold greater in type 1 diabetic women than in control subjects. Diabetic women showed higher daily diastolic BP in the third trimester compared with nondiabetic pregnant women. Diabetic women who developed PIH in the third trimester showed significantly higher BP profiles throughout gestation than those who remained normotensive. Receiver operator characteristics curves for nighttime systolic BP showed the best predictive capacity for PIH, with a cutoff >105 mmHg (85% sensitivity and 92% specificity).

CONCLUSIONS — Our study confirms the early increase of BP in patients who will develop PIH and suggests that nighttime systolic BP >105 mmHg in the second trimester is a useful predictor of PIH. ABPM may be useful in screening for PIH in pregnant diabetic women.

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Pregnancy-induced hypertension (PIH), including gestational hypertension, preeclampsia, and eclampsia, is one of the problems that may appear during the course of any pregnancy, leading to an increase in both maternal and fetal morbidity and mortality. It has been reported that pregnant patients with type 1 diabetes present a greater risk of developing PIH than that observed in nondiabetic pregnant women (20 vs. 5%) (1–4). This association of diabetes and hypertension makes pregnancy in patients with diabetes a high-risk obstetric situation because of the adverse effects on the maternal and fetal outcomes of pregnancy.

Several studies have attempted to establish an ideal marker for predicting PIH; however, to date, there is still no early, simple, and reliable screening test. The development of instruments capable of monitoring blood pressure (BP) in a noninvasive ambulatory setting over 24 h—ambulatory blood pressure monitoring (ABPM)—has been a great help in detecting changes in BP and compensates for some of the limitations of casual BP measurement. ABPM provides a large number of BP measurements for one subject, improving the precision and the ability to detect a change in BP, and also allows assessment of the circadian rhythm of the BP (5).

ABPM has been used in nondiabetic pregnant women as a predictor of the development of PIH. Thus, some BP changes in the second trimester of gestation have been related to later development of PIH (6–8).

The aims of this study were to establish BP profiles using ABPM in the three trimesters of gestation in patients with type 1 diabetes and to determine whether the BP pattern can define a population at risk for developing later PIH.

RESEARCH DESIGN AND METHODS

Patient selection

Patients with type 1 diabetes, without a history of prepregnant hypertension (BP <140/90 mmHg for systolic/diastolic pressure), normal ABPM recorded in the first trimester of pregnancy (mean 24-h systolic/diastolic BP <130/80 mmHg) (9) and normal renal function (creatinine <106 μmol/l, excretion of urinary albumin <20 mg/day) were included in the study. Normotensive nondiabetic pregnant patients matched for age, number of previous pregnancies, and BMI were studied as the control group. All the patients were included in the study before the 10th week of gestation. They were assessed by both an endocrinologist and obstetrician and were seen every 2 weeks until the 32nd week and then every week until delivery.

Patients were managed with diet and intensified insulin therapy in an optimized glycemic control scheme. They were requested to self-monitor their capillary blood glucose values with reflectance meters seven times a day: before and 1 h after meals and at bedtime. Insulin doses were adjusted throughout pregnancy (three to four doses

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Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; PIH, pregnancy-induced hypertension; ROC, receiver operating characteristics; UAE, urinary albumin excretion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Maternal baseline characteristics in pregnant women with type 1 diabetes and control subjects*

	Type 1 diabetes	Control group
n	22	12
Age (years)	30.0 ± 3.7	31.0 ± 2.2
Primigravidae (%)	58	55
BMI (kg/m^2)	23.7 ± 2.3	23.2 ± 2.2
Age at diagnosis (years)	17.0 ± 9.4	—
Duration of diabetes (years)	13.0 ± 7.7	—
White class (*n*)		
B-C	17	—
D-R	5	—
HbA_{1c} (%)	6.9 ± 0.8	—
Insulin dose (U · kg^{-1} · day^{-1})	0.70 ± 0.18	—

Data are *n*, means ± SD, or %. B-C and D-R represent White's classes of diabetes in pregnant women.

of regular insulin plus NPH insulin at bedtime) in an attempt to maintain fasting glucose values between 70 and 90 mg/dl and postprandial levels <140 mg/dl. Body weight, BP, and qualitative determination of proteins in the urine were recorded. To evaluate metabolic control and confirm the efficacy of insulin treatment, HbA_{1c} was determined when the patient was first seen and then every 4 weeks until birth by high-speed liquid chromatography based on the ion exchange method. Normal HbA_{1c} range is 3.4–5.5% in our laboratory. The interassay variation coefficient was 1.46%. Moreover, 24-h urinary albumin excretion (UAE) was recorded each trimester

ABPM (Spacelabs 90207; Spacelabs, Redmond, WA) was carried for one 24-h period during each trimester; in the first trimester between weeks 7 and 12, in the second trimester between weeks 20 and 24, and in the third trimester between weeks 30 and 34. BP measurements were programmed every 20 min throughout the day. Daytime was defined as from 0900 to 2200 and nighttime from 0000 to 0700. The patients were instructed to keep their arm immobile during BP measurement, and only registers with >85% success were included in the study.

Gestational hypertension was defined as a casual BP >140/90 mmHg on 2 occasions for both the systolic and diastolic pressure detected after the 20th week of gestation. Preeclampsia was defined as gestational hypertension and proteinuria >300 mg/24 h, with or without edema.

This study was approved by the Ethics Committee of the Hospital Clinic and informed consent was given by all the participants.

Statistical analysis

Data are expressed as means ± SD. ABPM values were analyzed with appropriate software (BBP base station software; Spacelabs Medical, version 4.06.01, 1993). An analysis of variance of repeated measurements was carried out to compare the results obtained in the three determinations. Receiver operating characteristics (ROC) curves were generated using true Epistat statistical software. The best threshold value of BP for each measurement in the first and second trimester of gestation was established by ROC curves for the development of PIH. The point closest to the upper left on an ROC curve was considered as the best cutoff point, Sensitivity, specificity, positive and negative predictive values, and relative risk were calculated. The Student's *t* test or χ^2 were used to evaluate the differences between the two groups when appropriate. A *P* value <0.05 was considered significant.

RESULTS — A total of 22 patients with type 1 diabetes and 12 control women were studied. Baseline clinical characteristics of both groups are shown in Table 1.

One woman in the control group was excluded because she developed gestational diabetes in the second trimester of pregnancy. The incidence of PIH was significantly higher in the diabetic group (eight patients [36%], five with gestational hypertension and three with preeclampsia) than in the control group (one woman [8%] with gestational hypertension).

In the diabetic group there were no differences between patients who remained normotensive (non-PIH) and those who developed PIH in relation to age, duration of disease, percent of primigravidity, White class, BMI, HbA_{1c}, and insulin dose.

There were no significant differences in HbA_{1c} throughout the pregnancy between the non-PIH and PIH groups (6.1 ± 0.5 vs. 6.4 ± 0.6; 5.6 ± 0.8 vs. 5.5 ± 0.4; 5.8 ± 0.6 vs. 6.0 ± 0.4 in the first, second, and third trimesters, respectively). In the third

Table 2—*ABPM measurement by trimester in patients who developed PIH and in patients who remained normotensive (non-PIH)*

	First trimester		Second trimester		Third trimester	
	Non-PIH	PIH	Non-PIH	PIH	Non-PIH	PIH
Mean 24-h BP						
Systolic	108.1 ± 5.5	115.5 ± 6.5*	107.9 ± 5.6	118.7 ± 10.0*	113.2 ± 5.0	129.7 ± 4.9*
Diastolic	64.2 ± 4.4	67.1 ± 4.8	63.9 ± 4.1	69.3 ± 4.8*	68.7 ± 4.2	78.4 ± 4.5*
Daytime BP						
Systolic	110.8 ± 5.7	118.1 ± 7.1*	111.1 ± 5.9	121.3 ± 11.4*	116.4 ± 5.6	131.4 ± 5.4*
Diastolic	66.5 ± 4.2	69.2 ± 5.7	66.9 ± 4.1	71.5 ± 5.7*	71.7 ± 4.0	80.1 ± 5.7*
Nighttime BP						
Systolic BP	99.0 ± 7.6	106.2 ± 5.4*	97.4 ± 8.0	109.7 ± 7.0*	104.0 ± 7.3	124.2 ± 8.2*
Diastolic BP	55.7 ± 6.7	59.6 ± 4.4	53.8 ± 6.4	61.7 ± 2.7*	60.0 ± 6.9	72.4 ± 5.0*

Data are means ± SD. *$P < 0.05$, PIH vs. non-PIH.

Table 3—*ABPM measurements in type 1 diabetic women who remained normotensive* (n = *14*) *and control subjects* (n = *10*)

	First trimester		Second trimester		Third trimester	
	Control	Diabetic	Control	Diabetic	Control	Diabetic
Mean 24-h BP						
Systolic	107.1 ± 7.9	108.1 ± 5.5	107.8 ± 6.7	107.9 ± 5.6	112.0 ± 4.2	113.2 ± 5.0
Diastolic	61.2 ± 4.2	64.2 ± 4.4	64.4 ± 2.8	63.9 ± 4.1	65.5 ± 2.4	68.7 ± 4.2
Daytime BP						
Systolic	110.3 ± 8.9	110.8 ± 5.7	112.8 ± 7.9	111.1 ± 5.9	113.8 ± 5.2	116.4 ± 5.6
Diastolic	64.1 ± 5.3	66.5 ± 4.2	65.8 ± 3.5	66.9 ± 4.1	67.1 ± 2.7	71.7 ± 4.0*
Nighttime BP						
Systolic	96.1 ± 6.4	99.0 ± 7.6	99.2 ± 4.0	97.4 ± 8.0	106.1 ± 4.4	104.0 ± 7.3
Diastolic	51.0 ± 2.7	55.7 ± 6.7	53.4 ± 1.6	53.8 ± 6.4	59.6 ± 3.1	60.0 ± 6.9

Data are means ± SD. *$P < 0.05$ vs. control group.

trimester, UAE was higher in patients who developed PIH (4.0 ± 2.1 vs. 3.1 ± 0.7 in the first; 4.5 ± 2.9 vs. 4.9 ± 5.6 in the second; and 4.4 ± 4.2 vs. 127.1 ± 272.5 in the third trimester [$P < 0.01$] in the non-PIH and PIH groups, respectively).

In diabetic patients systolic and diastolic BP significantly increased in the third trimester (110.8 ± 6.8/65.2 ± 4.6 in the first trimester; 111.8 ± 9.0/65.9 ± 5.0 in the second trimester; and 119.6 ± 10.6/71.7 ± 6.2 in the third trimester, $P < 0.001$). From the first trimester patients who developed PIH showed significantly higher BP profiles than the patients who remained normotensive throughout gestation (Table 2). The nighttime fall was maintained in all patients during the first trimester; in the second trimester, two women lost their nocturnal dip and developed PIH in late pregnancy. When ABPM results of nondiabetic normotensive pregnant women and diabetic pregnant women who remained normotensive throughout gestation were compared, the only difference observed was a higher daily diastolic BP in the third trimester in the diabetic group (Table 3). The use of ROC curves showed that the best threshold to predict the development of PIH in patients with type 1 diabetes was nocturnal systolic BP during the second trimester of gestation (weeks 20–24) with a cutoff >105 mmHg (sensitivity of 85%, specificity of 92%, positive predictive value 87, negative predictive value 95, and relative risk 6.1) (Fig. 1 and Table 4).

CONCLUSIONS — In this prospective study of a group of diabetic women who were homogeneous for their BP and kidney function, using an accurate method for BP measurement we found a fourfold greater prevalence of PIH than in control patients, thereby supporting the suggestion that diabetes poses a clear risk for developing PIH. This condition contributes to the increased maternal and fetal morbidity observed in diabetic pregnancy. Early PIH detection and adequate treatment may imply a better obstetric and neonatal outcome in pregnant women.

Studies using ABPM in nondiabetic normotensive pregnant women have shown conflicting results. Some authors have described a trend to a reduction in BP levels during the second trimester suggesting a lowering of the systemic vascular resistance that coincides with increased cardiac output and blood volume (10,11). These BP changes return to the prepregnant levels at the end of gestation (12). However, other investigators have not found a variation in BP in the second trimester of pregnancy in normotensive pregnant women (13,14). In our study systolic and diastolic BP, both in patients with type 1 diabetes and in the control group, showed a significant increase in the third trimester of pregnancy in comparison with BP levels determined in the first trimester. However, we did not observe a reduction in BP in the second trimester of pregnancy in either group.

Table 4—*ROC curves and predictive value of different measurements for later PIH in the first and second trimesters of pregnancy*

ABPM and trimester	Cutoff (mmHg)	Sensitivity	Specificity	PPV	NPV	RR
Mean BP						
First	80	62	56	41	70	1.6
Second	80	50	71	50	71	2.4
Systolic mean 24-h BP						
First	110	87	50	46	77	3
Second	110	58	90	87	69	3.5
Systolic daily BP						
First	110	75	42	42	75	3
2nd	110	50	87	87	50	1.7
Systolic nighttime BP						
First	105	50	78	57	73	1
Second	105	85	92	87	95	6.1
Diastolic mean 24-h BP						
First	65	62	58	41	76	1.6
Second	65	66	92	90	71	1.7
Diastolic daily BP						
First	65	75	35	40	71	3
Second	65	50	75	62	64	1.7
Diastolic nighttime BP						
First	60	37	71	42	66	0.6
Second	60	62	78	62	78	2.9

PPV, positive predictive value; NPV, negative predictive value; RR, relative risk.

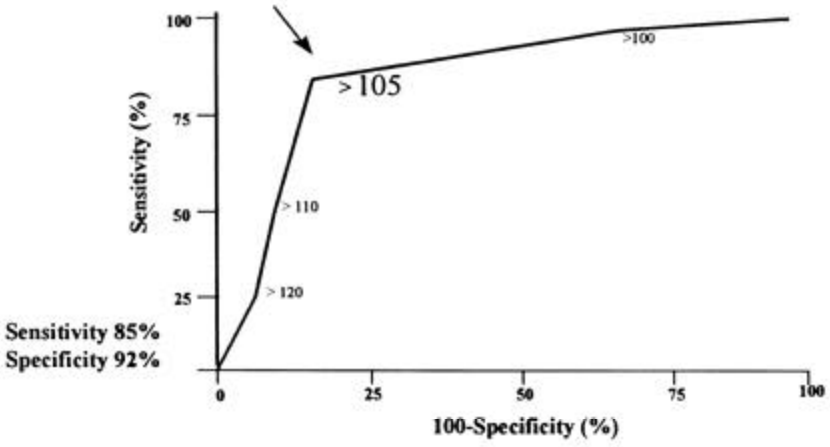

Figure 1—*ROC curve of nighttime systolic BP in the second trimester as a screening test for PIH.*

To date there is no adequate inexpensive and easily performed method to detect patients who will later develop PIH. Some studies in nondiabetic pregnant women have observed a correlation between higher BP levels, measured by ABPM, in the second trimester and the development of later PIH (10,11). Although within the accepted range of normotension, in our study diabetic pregnant women who developed PIH in the third trimester presented higher systolic and diastolic BP levels throughout the first and second trimesters in comparison with patients who did not develop PIH. These results support the fact that PIH is not a clinical event that suddenly appears at the end of gestation and suggest that the physiopathological mechanisms of hypertension are already activated in the first trimester of pregnancy in both nondiabetic and diabetic pregnant women who later develop PIH. Our results agree with those of Napoli et. al. (15) who, in a group of diabetic pregnant women, observed that patients who developed PIH had significantly higher levels of BP from the first trimester.

It is well known that in humans BP has a clear circadian rhythm. It is higher in the midmorning, falls progressively throughout the remainder of the day, and is lowest at midnight. Similar to other authors, on analysis of BP evolution throughout the day we observed higher nocturnal BP levels during the second trimester of pregnancy in patients who developed PIH. This reduction in the physiological circadian variation of BP has been related to an increase in circulating plasma volume or a variation in vascular tone, possibly mediated by internal vasoactive substances or vascular sensitivities (16). In this regard some authors have observed that an inverted circadian rhythm of BP precedes the clinical appearance of preeclampsia by several weeks (11,12). Our data do not support these findings, because, as a group, the circadian rhythm BP was maintained. However, it is interesting to point out that in the previous studies, diabetic women were not included. Therefore, in our experience, nighttime systolic BP measurement allows the possible early identification of a subgroup of diabetic pregnant women who could develop PIH, supporting the idea that ABPM is a useful diagnostic method in pregnancy.

Similar to other investigators (3,4), we did not find that women who developed PIH had poorer metabolic control throughout pregnancy than women who did not develop PIH, thereby confirming that PIH is not related to metabolic control. It is noteworthy that in this study the women had good glycemic control, as shown by the normal mean HbA_{1c}.

ABPM has therefore proved to be useful in pregnant women for the assessment of BP changes and thus could be an effective technique as an early marker for PIH. It is important to point out that according to our results nocturnal systolic BP >105 mmHg in the second trimester of pregnancy is a good predictor for detecting type 1 diabetic patients who will develop PIH. Could the availability of this information contribute to an improved prognosis for these patients through the early application of appropriate therapeutic measures? Further studies will be needed to answer this question.

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