

Twenty-four-hour blood pressure monitoring in normoalbuminuric normotensive type 1 diabetic women during pregnancy

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Abstract

We monitored blood pressure (BP) for a 24-h period in type 1 diabetic women at each trimester of pregnancy (10–13, 20–22, and 30–33 weeks of gestation) to identify early alterations of BP profile in pregnancies complicated by hypertension. **Patients and methods:** We prospectively studied 71 type 1 diabetic pregnant women and 48 nondiabetic pregnant women (homogeneous by age and pre-pregnancy BMI) consecutively recruited at 10 ± 2 weeks of pregnancy in the space of 2 years (1999–2000). They were all normotensive ($< 130/80$ mm Hg) and normoalbuminuric ($AER < 20 \mu\text{g}/\text{min}$) at entry to the study. **Statistics:** Analysis of variance (ANOVA) and simple regression and χ^2 were applied as appropriate by an Apple software program (Stat View). **Results:** In diabetic women, we recorded higher levels of diastolic BP (even if within a normal range) at each time point; diabetic vs. nondiabetic women: first trim daytime diastolic BP: 71.35 ± 8.75 vs. 67.7 ± 9.7 , $P = .01$; second trim nighttime diastolic BP: 62.15 ± 6.45 vs. 58.05 ± 6.7 , $P = .05$; third trim nighttime diastolic BP: 66.03 ± 8.72 vs. 60.7 ± 6.5 , $P = .01$. Among diabetics, those who later developed pregnancy-induced hypertension (36.6%) showed significantly higher values of BP at the first and third trimester compared to those who remained normotensive. In the two groups, there were no differences in age and pre-pregnancy BMI by contrast of diabetes duration (hypertensive vs. normotensive, 19.18 ± 7.3 vs. 14.35 ± 9.1 years, $P = .03$) and age of diagnosis (hypertensive vs. normotensive, 9.6 ± 5.5 vs. 14.7 ± 8.6 years, $P = .01$). Positive correlation was found between fasting blood glucose and diastolic BP at each trimester of pregnancy.

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Hypertension is among the most common medical complications in pregnancy (5–10% of all pregnancies) (Roberts & Redman, 1993). It is well accepted that pregnancy-induced hypertension is more common in women with preexisting diabetes (Hanson & Persson, 1998; Lapolla et al., 1998; Napoli, Bueti, De Vecchis, & Fallucca, 1990; Napoli et al., 1997). Since blood pressure (BP) is the result of a continuous spectrum of change, which is characterized by a circadian

biorhythm, only one reading, even if carefully and accurately taken, represents a fraction of a 24-h profile. Therefore, it may deviate significantly from the representative level for that patient (Franx, Elfering, Merkus, & Montfrans, 1994; Halligan, O'Brien, O'Malley, Darling, & Walshe, 1991; Öney & Meyer-Sabellek, 1990). Moreover, 24-h ambulatory blood pressure monitoring (ABPM) in pregnancy might disclose slight increases and alterations of 24-h BP profile, which are not visible by conventional BP measurement.

1. Objective

The aim of the present study was to identify which of the following clinical characteristics, modifiable and nonmodi-

Abbreviations: BP, blood pressure; ABPM, 24-h ambulatory blood pressure monitoring; PIH, pregnancy-induced hypertension; EPH, preeclampsia (edema proteinuria hypertension)

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fiable, most influence BP leading to hypertensive disorders of pregnancy in type 1 normoalbuminuric diabetic women. For this purpose, we observed the relationships between 24-h BP at each trimester of pregnancy, age and diabetes duration, BMI, metabolic control, in 71 diabetic out-patients affected by type 1 diabetes, who were normotensive and normoalbuminuric at enrollment. A further objective was to observe if an alteration of 24-h BP profiles were associated with hypertension in late pregnancy.

2. Patients and methods

We prospectively studied 71 diabetic out-patients in pregnancy. All women were normoalbuminuric ($<20 \mu\text{g}/\text{ml}/\text{min}$) and normotensive at the beginning of the study, according to standard measurement (systolic BP ≤ 130 , diastolic BP ≤ 80 upon first visit) (Consensus Report National High Blood Pressure Education Program, 1990). They were recruited consecutively from January 1st, 1998 to December 2000, at the 10 ± 2 weeks of gestation. The diabetic pregnant women were also classified according to White's Classification 18 WC B, 12 WC C, and 41 WC D. All the out-patients were clinically followed longitudinally throughout pregnancy, from the first trimester to delivery.

Forty-eight normotensive nondiabetic pregnant patients (OGTT negative between the 28th and 32nd week of gestation on the basis of the "Carpenter and Coustant" criteria), homogeneous for age, number of previous pregnancies, BMI, without any risk factors of diabetes, were followed longitudinally throughout all pregnancy as control group. All women were caucasian, and their main clinical and metabolic characteristics are reported in Table 1. All subjects with a microalbuminuria, history of hypertension, cardiovascular, or kidney diseases were excluded from the study. Pregnancy dating, based on menstrual history and physical examination, was definitely confirmed by an early ultrasound examination before the 16th week of gestation. All subjects were treated with no other therapy than the one for diabetes or which might influence BP levels at each recording. The diabetic women were visited at regular intervals (1–2 weeks). At each visit, home capillary blood glucose profiles, insulin requirement and adjustments, hypoglycaemic reactions, and body weight were recorded. Glycaemic control was obtained with split-dosage regimens of insulin (regular insulin three to five times daily), using both short- and intermediate-acting insulin along with dietary

prescription. We tried to reach the following glycaemic goals: fasting blood glucose levels $<5 \text{ mmol}/\text{l}$ and 120-min postprandial values $<6.6 \text{ mmol}/\text{l}$ (American Diabetes Association, 2001). Patients were taught to self-monitor their blood glucose levels four to six times a day, by using the same type of glucometer, which was given to the patients by our staff. All data were recorded in a diary kept by the patients at each control visit. Maternal glycohaemoglobin (HbA1c) checking was assayed (HPLC Menarini, Firenze) every 4–6 weeks. At each clinic visit, the number and degree of hypoglycaemic reactions registered during the previous 1 or 2 weeks were recorded. The degree of hypoglycaemic episodes was graded as follows: Grade 1 (mild): slight symptoms spontaneously resolved, Grade 2: symptoms resolved by taking oral carbohydrate, Grade 3 (severe): symptoms resolved by requiring assistance from another person, and Grade 4: like Grade 3 plus admittance to hospital. The study protocol consisted of ambulatory 24-h BP monitoring by an automatic recorder at each trimester of pregnancy. More specifically, BP was recorded between the 12th and 14th week for the first trimester, between the 18th and 22nd week for the second trimester, and between the 30th and 35th week of gestation for the third trimester. Five patients dropped out at the third trimester, because we had to treat their hypertension, which had developed sooner than the time point defined by our protocol for 24-h BP monitoring (32–35 weeks). Finally, in case of hypoglycaemic episodes, 24-h BP monitoring was repeated a few days later, not later than 1 week.

The Diasys integra took auscultatory and oscillometric measurements for the systolic and diastolic BP and peripheral pulse. These measurements were taken on the left arm every 30 min during the day (from 08:00 to 22:00 h) and at night (from 22:00 to 08:00 h) (Franx et al., 1994). A standard arm cuff ($14.5 \times 24\text{-cm}$ bladder) was used if the upper arm circumference was $<32 \text{ cm}$. For larger arms, a cuff with a $16.5 \times 33\text{-cm}$ bladder was used. A recording was considered successful if $>80\%$ readings were valid and the device was tolerated. All women were synchronized to light–dark alternations and a meal schedule. In these subjects, we recorded the mean of 24-h, daytime, nighttime systolic, and diastolic BP levels. We also calculated day/night Δ with the following formula: (the mean of day values – the mean of night values)/daytime values. None of the studied women were affected by autonomic neuropathy. Conventionally, BP measurement was always taken by mercury sphygmomanometer

Table 1
Clinical and metabolic data of controls and diabetic pregnant women (mean \pm S.D., 95% CI)

Subjects	No.	Age (year)	Pre-pregnancy BMI (kg/m^2)	Weight gain (kg)	Diabetes duration (year)	Age of onset (year)	Parity, nulliparous (%)
Controls	48	30.8 \pm 4.5 (29.14–31.47)	22.3 \pm 3.1 (21.14–23.48)	14.2 \pm 1.6 (12.15–16.24)			50% (24/48)
Diabetics	71	29.1 \pm 4.3 (28.03–30.14), ns	22.82 \pm 2.76 (22.18–23.52), ns	12.6 \pm 4.6 (11.38–13.8), ns	16.2 \pm 8.9 (13.9–18.4)	13.2 \pm 8.3 (11.2–15.3)	47% (37/71), ns

Table 2
Diastolic and systolic BP (mm Hg) in diabetic and control pregnancies (mean \pm S.D., 95% CI)

	Day 1st trim	Night 1st trim	24-h 1st trim	Day 2nd trim	Night 2nd trim	24-h 2nd trim	Day 3rd trim	Night 3rd trim	24-h 3rd trim
Diabetic women (71)							(66)		
(1) Diastolic BP	71.3 \pm 8.7 68.4–74.3	60.6 \pm 7.4 57.9–63.2	67.5 \pm 7.6 64.7–70.2	71.6 \pm 7.1 68.8–64.4	62.1 \pm 6.4 59.5–64.7	68.5 \pm 6.6 65.9–71	71.4 \pm 7.8 68.8–74.1	66.03 \pm 8.7 63.1–68.9	69.7 \pm 7.6 66.9–71.8
(2) Systolic BP	117.5 \pm 16.3 112.1–122.9	99.91 \pm 13 95.3–104.5	110.5 \pm 14.5 105.4–115.6	115.7 \pm 8.4 112.4–118.9	102.9 \pm 9 99.3–106.5	112.9 \pm 8.7 109.5–114.3	115 \pm 12.8 110.6–119.3	107.1 \pm 14.7 102.1–112.1	113.2 \pm 12.6 109.1–117.3
Nondiabetic women (48)							(48)		
(3) Diastolic BP	67.7 \pm 9.7 63.1–71.8	56.8 \pm 9.3 52.2–61.4	65.11 \pm 7.2 61.48–68.8	69.1 \pm 12 62.84–75.4	58.05 \pm 6.7 54.6–61.5	66.05 \pm 2.3 61.1–70.9	68.5 \pm 7.9 64.8–72.3	60.7 \pm 6.5 57.8–63.6	67.3 \pm 8.2 63.5–71.2
(4) Systolic BP	113.6 \pm 13 106.4–119.5	98 \pm 12.2 91.7–104.3	109.8 \pm 11.2 104.2–115.4	117 \pm 12 110.4–123.6	103.1 \pm 10.7 97.5–108.5	112.9 \pm 11.4 107.1–118.7	113.9 \pm 9.2 109.6–118.2	99.1 \pm 7 96–102.3	110.1 \pm 8 106.3–113.8
1 vs. 3	.01	ns	ns	ns	.05	ns	ns	.01	ns
2 vs. 4	ns	ns	ns	ns	ns	ns	ns	.02	ns

under standard conditions, during each visit in the late morning (between 10 and 12 a.m.). Korotkoff's fifth tone was considered to determine diastolic BP values. Hypertensive disorders were defined on the basis of resting mercury sphygmomanometry according to the Consensus Report National High Blood Pressure Education Program (1990). Then, eligible women were assigned antihypertensive treatment with α -methyl-dopa and/or calcium channel blockers. Consent: written informed consent was obtained by all the women participating in the study.

2.1. Statistical analysis

All data were presented as mean \pm S.D. and 95% CI. Statistical analysis was performed with the use of an Apple software program (Stat View), analysis of variance (ANOVA), and 95% CI (multifactorial or repeated measures). Simple regression analysis was performed when appropriate χ^2 as nonparametric test, was performed to compare percentages. *P*-values $<$.05 were considered significant.

3. Results

Personal data are reported in Table 1. BP mean levels were found lower in nondiabetic women compared to diabetic women (Table 2). Nighttime BP levels were always significantly lower than daytime BP levels ($P <$.001–.0001) at each time point, both in diabetic and nondiabetic pregnant women (Table 2). In both groups, a slight reduction of day/night Δ was observed at the third trimester, compared to the

first one. Lower levels of day/night Δ systolic BP values were observed in diabetic pregnancies compared to nondiabetic women, in late pregnancy (48 normal pregnancies vs. 66 diabetic pregnancies at the third trimester: systolic 12.9 \pm 6.0 vs. 6.6 \pm 6.7, ANOVA, $P <$.0008).

3.1. Clinical investigation (age, diabetes duration, and BMI)

No correlation was found between the age of the women and BP levels. A negative correlation was already observed between the age of diagnosis and diastolic 24-h BP levels at the first trimester ($r = .42$, slope: -0.384 , $P = .01$), as well as a positive correlation was observed between the diabetes duration and diastolic 24-h BP levels of the first trimester ($r = .44$, slope: $+0.475$, $P = .005$).

Finally, no correlation was found between pre-pregnancy BMI and BP levels.

3.2. BP and metabolic control in pregnancy

In order to investigate the influence of metabolic control on hypertension in type 1 diabetic pregnant women, we found the following significant positive correlation between fasting capillary blood glucose levels and BP: at the first trimester, with 24-h diastolic BP values ($n = 66$, $P = .05$, $r = .3$, $r^2 = .1$, slope = 0.1); at the second trimester with 24-h diastolic BP values ($n = 64$, $P = .02$, $r = .4$, $r^2 = .1$, slope = 0.1); at the third trimester, with nighttime diastolic BP levels ($n = 64$, $P = .05$, $r = .3$, $r^2 = .1$, slope = 0.1). However, during the third trimester when a good metabolic control was obtained, women who also reported more than

Table 3
Hypoglycemic episodes ($>$ 3/week) and BP levels (mm Hg) at the third trimester of diabetic pregnancies (mean \pm S.D.)

Hypoglycemic reactions	No.	24-h diastolic BP	24-h systolic BP	Daytime diastolic BP	Daytime systolic BP	Nighttime diastolic BP	Nighttime systolic BP
Yes	23	71 \pm 2.3	116.3 \pm 4.1	71.1 \pm 2.4	117.9 \pm 4.1	68.6 \pm 2.5	112 \pm 4
No	43	65 \pm 1.3	105.5 \pm 2	66.4 \pm 1.6	108.4 \pm 2.2	60.5 \pm 1.4	97.8 \pm 2.2
<i>P</i>		.025	.05	.05	.025	.0025	.0025

Table 4
BP levels (mm Hg) in normotensive and hypertensive diabetic pregnancies (mean±S.D.)

	Normotensive I trim 45	Hypertensive I trim 26	<i>P</i> <	Normotensive II trim 44	Hypertensive II trim 25	<i>P</i> <	Normotensive III trim 44	Hypertensive III trim 22	<i>P</i> <
24-h diastolic	64.3±5.5	75.2±3.3	.0001	67.4±4.8	71.1±8.2	ns, .16	66.4±4.8	76.2±8	.0001
24-h systolic	108.6±13.3	115.2±13.7	ns	110.8±5.6	117±11.9	ns, .07	108.4±9.7	123.6±13.3	.0004
Day diastolic	67.5±7.1	78.8±3.3	.0001	71.1±5.4	73.2±9	ns, .4	68.1±5.9	78.7±7.2	.001
Day systolic	113±14.1	127±12.5	.01	114.4±6.1	118.1±11.4	ns, .2	110.7±10.5	124.3±13.5	.004
Night diastolic	58.1±5.7	67±6.1	.0009	62±4.3	63.5±9	ns, .5	62.8±5.6	74±9.5	.0001
Night systolic	96.6±10.6	108.4±13.4	.01	101.8±7.5	105.1±11.8	ns, .4	101.6±10.9	119.7±15.4	.0004

three hypoglycaemic reactions a week (mostly of degree 2), showed higher levels of BP (see Table 3). No correlation was ever found between BP levels and the number of hypoglycaemic episodes or HbA1c levels.

3.3. Pregnancy-induced hypertension

According to the definition of hypertension, 26 out of 71 (36.6%) developed hypertension in pregnancy; in particular, 8/71 (11.26%) were complicated by EPH and 18/71 (25.3%) by transient hypertension. The women who remained normotensive were 45/71 (63.4%). The women who later developed hypertension showed significantly higher values of BP at the first and third trimester compared to those who remained normotensive (see Table 4).

Evaluating the BP nocturnal decline by studying BP profiles and day/night BP Δ , we observed an altered profile in pregnancies complicated by hypertension (Fig. 1). Finally, we recorded lower levels of day/night systolic BP Δ (normotensive vs. EPH, 7.83 ± 5.6 vs. 0.5 ± 8.3 , $P = .01$) and day/night diastolic BP Δ (normotensive vs. EPH, 9.66 ± 8.9 vs. 2.97 ± 6.3 , $P = .06$ ns) in women developing EPH.

Moreover, women who developed hypertension (EPH + transient) had a longer diabetes duration than normotensive

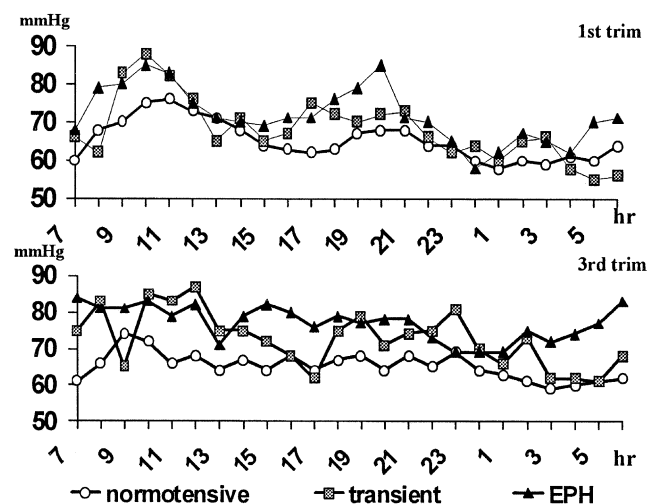


Fig. 1. Twenty-four-hour diastolic BP at the first and third trim of pregnancy in diabetic women who remained normotensive vs. those who developed hypertension.

(19.18 ± 7.3 vs. 14.08 ± 8.9 , ANOVA, $P = .03$) as well as a younger age of diagnosis (9.6 ± 5.5 vs. 14.7 ± 8.6 , ANOVA, $P = .01$) by contrast of age (28.6 ± 4.3 vs. 29.07 ± 4.4 years, ns) and pre-pregnancy BMI (23.13 ± 2.5 vs. 22.6 ± 3 years). Among hypertensive pregnancies (18/26), 68.57% were nulliparous as opposed to (16/45) 35.5% of those who remained normotensive ($\chi^2 = .01$).

In all subjects, the creatinine levels were always normal, slightly higher in those who developed hypertension but never reaching the level of significance (creatinine levels normotensive vs. hypertensive at the first trimester: 71.9 ± 14 vs. 74.16 ± 7.5 $\mu\text{mol/l}$, ns; at the second trimester: 66.1 ± 14 vs. 72.6 ± 9.3 $\mu\text{mol/l}$, ns; at the third trimester: 71.8 ± 12.5 vs. 77.8 ± 15 $\mu\text{mol/l}$, ns).

Hypertension complicated (5/48) 10.4% of our nondiabetic pregnant women.

4. Discussion

BP values were always lower in nondiabetic pregnant women compared to diabetic pregnant women. The differences between the two groups were already visible for diastolic BP values at the first trimester, despite the fact that we only studied normotensive and normoalbuminuric type 1 diabetic pregnant women (Flores et al., 1999). The observation of the 24-h BP profile in diabetic and control groups showed nighttime BP values always lower than daytime BP in both groups. Nevertheless, day/night BP Δ values were lower in diabetic women. The absence of any correlation between the age of the women and BP levels might be explained by the young age of these subjects and by the fact that they were normal or slightly overweight type 1 diabetic women. However, the age of diagnosis and diabetes duration influenced the 24-h BP pattern in early pregnancy. The finding of significantly positive correlation between capillary blood glucose levels and diastolic BP levels made us consider the role of glucose toxicity (Hii-lesmaa, Suhonen, & Teramo, 2000). These and other data led to the hypothesis that circulating blood glucose, independently of insulin and even at “normal levels”, is a physiological determinant of cellular ion homeostasis (Bargallo & Resnick, 1994). However, an increased BP in women, in whom a good metabolic control was invalidated by frequent hypoglycaemic episodes, led us to consider the

role of counterregulatory hormones on cardiovascular responses to spontaneous and induced stimuli. Evidence exists that short-term changes in blood glucose concentrations (hypoglycaemias as well as acute hyperglycaemia) modify the cardiovascular responses to spontaneous and induced stimuli contributing to the hypertensive process (Yeap, Russo, Fraser, Witter, & Horowitz, 1996). In our population, hypertension complicated 36.6% of pregnancies. In pregnancies that later developed hypertension, we already observed higher levels of serum creatinine and albumin excretion rate, although within the normal range ($<20 \mu\text{g}/\text{min}$), at enrollment.

On the other hand, early morphological changes of the placental vascular bed responsible for an increased vascular peripheral resistance are soon visible in pregnancies later complicated by hypertensive disorders (Roberts, Taylor, & Goldfein, 1991). Hence, attention must be paid to slight and steady increases of BP throughout pregnancy (Hermida et al., 2000). Differences both in BP values (even though apparently within “normal range”) and in day and nighttime BP profiles gain a clinical meaning (Benedetto et al., 1998). In particular, a significant decrease of systolic day–night BP Δ was recorded in women developing EPH.

Since we did not compare the conventional method with 24-h BP monitoring, we cannot conclude that the latter is better than the former; however, the finding of an alteration of 24-h BP profiles, particularly during nighttime, supports the fact that 24-h BP monitoring adds information, which is not obtainable differently. Therefore, the 24-h BP monitoring should be implemented in at risk populations such as in diabetic pregnant women, especially in nulliparous (Brown et al., 1997). Finally, our results lead us to believe that both alert pregnancy planning and monitoring, characterized by an optimal and stable metabolic control from preconception until delivery, can improve its management and prognosis, even reducing the risk of hypertension later in pregnancy.

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