

Night/day ratio as predictor of preeclampsia in normoalbuminuric, diabetic women: early signs of blood pressure disorders

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Abstract

Purpose Day/night ratio from diurnal ambulatory blood pressure (AMBP) in pregnant women with type 1 diabetes mellitus (T1DM) and in non-diabetic women was evaluated for its association with preeclampsia, retinopathy, HbA1c, and birth weight.

Methods One hundred and sixty-one women were recruited for AMBP performed with a Spacelab 90207 monitor. The pregnant women were 50 non-diabetic women and 111 T1DM women with normoalbuminuria and no hypertension. ANOVA, regression, and ROC curves analysis were applied.

Results Women with simplex retinopathy had higher night/day ratio and lower birth weight than those without retinopathy. Women who developed preeclampsia had night/day ratio similar to those with simplex retinopathy. In first trimester they had higher blood pressure than those who did not develop preeclampsia.

Conclusions Simplex retinopathy and preeclampsia are associated with a reduced night/day ratio even with normal blood pressure but night/day ratio provides no better prediction of preeclampsia than the absolute values.

Keywords Pregnancy · Diabetes · Night/day ratio · Preeclampsia

Introduction

Diurnal ambulatory blood pressure (AMBP) in pregnancy is used for the purpose to evaluate circadian rhythm to disclose slight increases and alterations of BP, detect hypertension and distinguish it from white coat hypertension. It is suggested that blunting of BP or reversal of night time BP ('non-dipping') may help find those at risk of preeclampsia and gestational hypertension [1]. Several ways of evaluating circadian rhythm exist; however, these include assumptions of how BP behaves due to modeling at evaluation and biological rhythm [2, 3].

In diabetic pregnancy reno-vascular co-morbidity influences the results and is strongly associated with hypertension, preeclampsia, and pregnancy outcome. Studies of prediction of hypertensive disorders in diabetic pregnancy are hampered by a combination of monitor with questionable validation and the mixed setting of low-risk/high risk pregnancies, i.e. parity, pre-pregnancy microalbuminuria [4] and type 2 and gestational diabetes [5]. We, therefore, found interest in evaluating the use of night/day ratio in AMBP in normoalbuminuric women with type 1 diabetes mellitus (T1DM) and a group of non-diabetic, non-preeclamptic women. Thus, the evaluation excluded women micro- and macroalbuminuria and hypertensive disorder and included glycemic regulation in form of HbA1c and pregnancy outcome like birth weight. The aim was to find subtle changes in non-diabetic women during pregnancy and to have a comparison for similar changes in diabetic pregnancy with no co-morbidity (i.e. normoalbuminuria, no retinopathy or preeclampsia). Along the same lines, two

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groups with retinopathy and preeclampsia, respectively, were included to evaluate BP methods ability to predict outcome at an early stage and to see differences and similarities in the diabetic co-morbidity and pregnancy outcome, which may influence the benefit of BP measurements.

Materials and methods

One hundred and sixty-one women were consecutively recruited for AMBP during first trimester. The women were 50 non-diabetic women and 111 T1DM women with normal albuminuria and no hypertension; 51 had simplex retinopathy and 20 of the diabetic women developed preeclampsia of which 13 had retinopathy (Table 1). The study was part of an evaluation of morbidity in diabetic pregnancy with respect to nephropathy and retinopathy approved by the local Ethical Committee (jr.nr.1992/2523, 1998/4147, and 2026-99). It was performed in concordance with the Helsinki II declaration and all women gave their informed consent. We have previously reported on the reproducibility, consistency, precision, and trend over scale of measurement in the diabetic and non-diabetic, pregnant

women and the prognostic value by the absolute levels of BP in diabetic pregnancy [6, 7]. The diabetic women were recruited before pregnancy when possible, while the non-diabetic women were asked at first ultrasound scan during pregnancy and were intended as control group. The diabetic women attended the maternity ward for visits every second week during pregnancy until week 32 and hereafter weekly. A birth weight ratio was computed by dividing the observed birth weight with the expected birth weight for the same gestational age and gender from the background population.

BP was measured using a portable oscillometry monitor (SpaceLab 90207, Redmond, WA, USA), previously validated in normotensive and hypertensive pregnancies [8, 9]. The details on validation of monitors, the clinical setting, and the timing during the day of BP are found on the British Hypertension Society's homepage at www.bhsoc.org.

The equipment was programed for cuff insufflations every 20 min from 06:00 to 23:00 h, and every hour during the night. At inclusion and after demonstration of equipment in the supine position three oscillometric and hereafter three auscultatory BP were measured. The average of these three auscultatory measurements was termed the

Table 1 Clinical data in first trimester

Group	Normal-non-DM	DM –retinopathy	DM +retinopathy	DM +preeclampsia
No.	50	53	38	20
Retinopathy	–	–	+	13+ / 7–
Preeclampsia	–	–	–	+
Age (yrs)	27 ± 3	29 ± 4	28 ± 4	28 ± 3
Onset of diabetes (yrs)	–	22 ± 7	13 ± 6	17 ± 8
HbA1c (%)*	4.8 ± 0.3	6.9 ± 0.9	7.8 ± 1.1	7.3 ± 0.9
Weight*	74 ± 12 a	67 ± 12	67 ± 7	66 ± 14
Height	167	167	167	166
Gestational age (wk)*	40 ± 2 a	36 ± 1	35 ± 2	35 ± 2
Birth weight (g)*	3593 ± 428	4042 ± 618 b	3399 ± 840	3638 ± 660
Birth weight ratio*	1.03 ± 0.1 c	1.40 ± 0.2	1.28 ± 0.3	1.41 ± 0.2
Sysdy* (mmHg)	114 ± 6 d	115 ± 9 e	119 ± 6	123 ± 11
Diady* (mmHg)	66 ± 5 d	70 ± 6	71 ± 5	74 ± 7
Sysni* (mmHg)	103 ± 6 d	104 ± 8 f	109 ± 8	111 ± 10
Diani* (mmHg)	56 ± 5 d	57 ± 6	61 ± 6	62 ± 7
Sysdiu* (mmHg)	114 ± 9 g	113 ± 8	117 ± 6	121 ± 10
Diadiu* (mmHg)	65 ± 5 d	68 ± 6 f	69 ± 5	72 ± 7
MAP* (mmHg)	82.5 ± 5	84.8 ± 7 f	87.2 ± 5	90.2 ± 8
Systolic ND-ratio	0.91 ± 0.04	0.90 ± 0.03	0.92 ± 0.05	0.91 ± 0.05
Diastolic ND-ratio	0.84 ± 0.06 d	0.82 ± 0.05	0.85 ± 0.06	0.83 ± 0.07

DM type 1 diabetes mellitus, MAP mean arterial BP, Sysdy and Diady systolic and diastolic day BP, Sysni and Diani systolic and diastolic night BP, Sysdiu and Diadiu systolic and diastolic diurnal BP

* ANOVA $p < 0.01$, Newman–Keul's post hoc test (all $p < 0.05$): **a** Non-diabetic versus each of all other, **b** Retinopathy versus each of all other, **c** Non-diabetic versus retinopathy and preeclamptic, diabetic women, **d** Non-diabetic versus +retinopathy and preeclampsia, **e** –Retinopathy versus preeclamptic, diabetic women, **f** –Retinopathy vs. + retinopathy and preeclampsia, **g** Non-diabetic women and –retinopathy each versus preeclamptic, diabetic women

clinical BP. All auscultatory measurements were recorded with use of a random zero sphygmomanometer (Hawksley, Lancing, UK). The women followed their normal physical and daily activity throughout pregnancy and the women stated whether the measurement of BP took place on a workday or not. The measurement of BP took place in gestational week 13, 25, and 33 for women with T1DM and week 18 and 33 in normal women. Night/day ratio was calculated as a mean night AMBP/mean day AMBP (ND-ratio). Night time was defined from 11 p.m. until and including 6 a.m. An activity diary accompanied the AMBP and women with night work and inverse sleeping rhythms were excluded.

The women were identified as chronic hypertensive if pregestational or first trimester BP confirmed a blood pressure of at least 140 systolic or 90 mmHg diastolic. Preeclampsia was defined as systolic/diastolic BP of 140/90 mmHg or greater when she was normohypertensive before week 20 and, simultaneously, albuminuria in excess of 300 mg in previously normoalbuminuric women. Pregnancy-induced hypertension was hypertension without signs of preeclampsia. None of the women took antihypertensive drugs during the BP measurement.

Statistics was performed with SPSS version 16.0 for Windows. Difference between two means was tested with Student's *t* test if data followed Gaussian distribution; otherwise Mann–Whitney's test was used. The variable urinary albumin excretion rate (UAE) was normalized by logarithm computing. Comparison of the difference between means was tested with analysis of variance (ANOVA). Linear regression analysis was performed with preeclampsia as dependent variable and each BP variable separately, UAE, HbA1c, and duration of diabetes as independent variables. Receiver-operator-characteristic curves were studied for following variables: BP (means for the systole and diastole: day, night, and diurnal, respectively), UAE, HbA1c, age, parity, and duration of diabetes. The area under the curve (AUC) was calculated using the categorical variable of preeclampsia (1.0) with 95 % confidence interval. A two-sided $p < 0.05$ was the level of significance. Values are given as mean $\pm$ SD, if not otherwise stated.

Results

BP increased throughout the groups with non-diabetic having the lowest BP, followed by the diabetic women without retinopathy and then the women with retinopathy (Table 1). The women, which developed preeclampsia, had night/day ratio similar to those with simplex retinopathy but showing higher first trimester BP than those who did not develop preeclampsia. Women with simplex retinopathy had higher diastolic ND-ratio (Fig. 1) and lower birth weight than

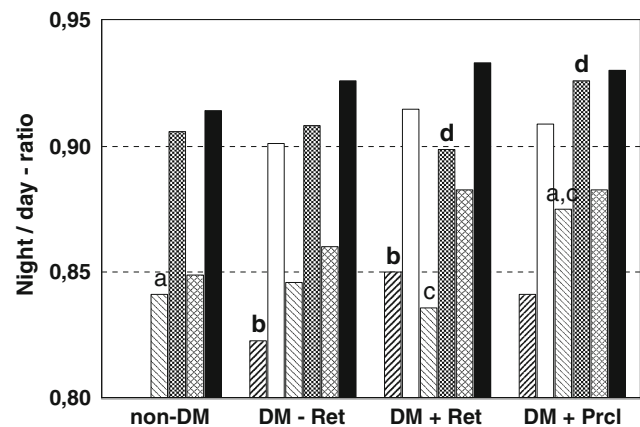


Fig. 1 Night/day ratio in first, second, and third trimester of 111 diabetic and second and third trimester of the 50 non-diabetic women. *Non-DM* Non-diabetic women ($n = 50$), *DM -Ret* Diabetic women without retinopathy ($n = 53$), *DM +Ret* Diabetic women with simplex retinopathy ($n = 38$), *DM +Prcl* Diabetic women with preeclampsia ($n = 20$). a: diastolic ND-ratio; non-DM versus DM +Prcl, $p < 0.04$; b: DM -Ret versus DM +Ret, $p < 0.03$; c: DM +Ret versus DM +Prcl, $p < 0.02$; d: systolic ND-ratio; DM +Ret versus DM +Prcl $p < 0.04$. *Striped left downwards bar*: Diastolic first trimester; *white bar*: Systolic first trimester; *striped right downwards bar*: Diastolic second trimester; *gray bar*: Systolic second trimester; *chequered bar*: Diastolic third trimester; *black bar*: Systolic third trimester

those diabetic women without retinopathy (Table 1). ND-ratio in first trimester was associated with birth weight even after adjusting for gestational age ($r = 0.23$, $p < 0.02$ and $r = 0.21$, $p < 0.03$, diastolic and systolic ND-ratio, respectively, $p < 0.02$). For the diabetic women without retinopathy the systolic as well as the diastolic ND-ratio increased from first to third trimester, whereas in the other groups no significant increase was observed. In predicting preeclampsia the ND-ratio in first trimester performed no better than the absolute values (Table 2). On the contrary, both systolic and diastolic day-BP had larger AUC when analyzing data and performed better in predicting preeclampsia when calculating a ROC curve than night BP and ND-ratios (Fig. 2). Duration of diabetes, parity, age, HbA1c, and UAE were close to the line of chance finding (AUC: area (95% confidence intervals): duration: 0.57 (0.43, 0.71), age 0.47(0.34,0.61), parity: 0.42 (0.28, 0.56), HbA1c first, second and third trimester: 0.53 (0.39, 0.66), 0.55 (0.42, 0.68) and 0.47 (0.36, 0.62), respectively, and UAE first and second trimester: 0.45 (0.30, 0.59) and 0.58 (0.45,0.71), respectively). Only UAE in third trimester was significantly predictive for preeclampsia (AUC: 0.68 (0.54, 0.82)). At regression analysis BP variables showed significant association with glycemic regulation, i.e., HbA1c in all three trimester with a few exceptions (Table 3), also when adjusted for UAE and duration of diabetes. Birth weight ratio in non-diabetic women was found associated with HbA1c in second trimester ($r = 0.33$, $p < 0.02$) and in third trimester ($r = 0.47$, $p < 0.01$).

Table 2 Evaluation of area under curve for BP values in prediction of preeclampsia in 111 normoalbuminuric T1DM pregnancies

Test result variables	Area under the curve	Std. error ^a	Asymptotic <i>p</i> value ^b	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Sysdy1	0.67	0.07	0.015	0.54	0.81
Diady1	0.66	0.07	0.022	0.53	0.80
Sysni1	0.66	0.06	0.026	0.53	0.79
Diani1	0.65	0.07	0.042	0.50	0.79
NDsys1	0.52	0.08	0.77	0.37	0.67
NDdia1	0.55	0.08	0.49	0.39	0.71
Sysclin1	0.58	0.09	0.38	0.40	0.75
Diaclin1	0.63	0.09	0.17	0.44	0.81
Sysdy2	0.71	0.07	0.006	0.57	0.85
Diady2	0.65	0.08	0.05	0.50	0.80
Sysni2	0.78	0.05	0.000	0.68	0.88
Diani2	0.75	0.07	0.001	0.62	0.88
NDsys2	0.65	0.07	0.047	0.52	0.78
NDdia2	0.67	0.07	0.02	0.55	0.80
Sysclin2	0.69	0.09	0.04	0.52	0.86
Diaclin2	0.75	0.08	0.0007	0.58	0.91
Sysdy3	0.81	0.06	0.000	0.69	0.93
Diady3	0.75	0.07	0.002	0.62	0.88
Sysni3	0.77	0.08	0.001	0.62	0.92
Diani3	0.73	0.08	0.006	0.57	0.89
NDsys3	0.50	0.07	0.99	0.36	0.64
NDdia3	0.58	0.08	0.33	0.43	0.74
Sysclin3	0.75	0.08	0.01	0.59	0.92
Diaclin3	0.84	0.07	0.001	0.71	0.97

The test result variable(s): sysdy1, diady1, sysni1, diani1, NDdia1, NDsys1 has at least one tie between the positive actual state group and the negative actual state group

Sys Systolic, dia diastolic, dy day BP, ni night BP, ND night/day ratio, 1 first trimester, 2 second trimester, 3 third trimester

^a Under the nonparametric assumption

^b Null hypothesis: true area = 0.5

Discussion

Our data show that the association of diurnal BP with preeclampsia is not confined to women with reno-vascular morbidity but is also present in pregnant women with normoalbuminuria. Similarly, interactions between BP and glycemia and albumin excretion were found. This study, thus, extends previous finding on associations of BP, glycemia, albumin excretion rate, and autonomic function in normoalbuminuric, non-pregnant diabetic subjects before transition to microalbuminuria [10]. We did not study on the change in albuminuria as pregnancy was considered is a

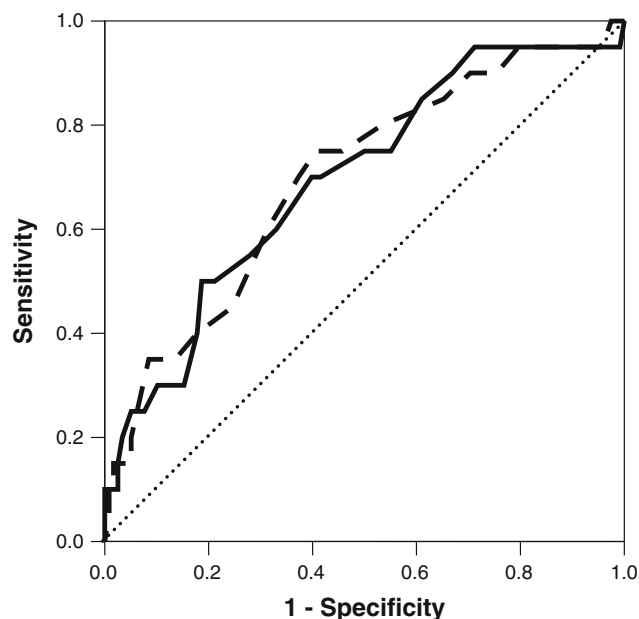


Fig. 2 ROC curve for prediction of preeclampsia in 111 normoalbuminuric T1DM pregnancies *Solid line*: Systolic day BP first trimester; *interrupted line*: Diastolic day BP first trimester; *stipulated line*: Area of 0.5 = chance finding. Diagonal segments in curves are produced by ties

too short time for de novo transitions but it is suggestive for the importance of BP methodology and selection of studied women. In diabetic subjects blunting of the diurnal variation may have counteracted the ‘night dipping’ as previously reported in preeclampsia [1, 2, 10–12]. Thus, diurnal variation of BP does not predict the risk for preeclampsia. This blunting occurs already in the normoalbuminuric range as confirmed in non-pregnant subjects and corroborates the argument of parallel changes in the AER and BP [4, 7, 10, 13]. The reasons for the lack of association with ND-ratio and hypertension in pregnancy are numerous and may be of non-diabetic nature. Abnormal body fluid regulation, water accumulation, postural hypotension, nocturnal polyuria, and hypertension are seen in non-diabetic, non-pregnant subjects with autonomic failure [13]. Nevertheless, these symptoms mimicking autonomic dysfunction are common in pregnancy; in particular in third trimester when nearly 50% of women have at least one of the symptoms. The source of the rhythm remains speculative and the correlation with a definite endogenous rhythm like the circadian melatonin concentration has been suggested [14].

Our measurements during pregnancy show consistent higher levels of BP in diabetic women with respect to those who would later develop preeclampsia suggesting that less sophisticated analysis performs well in predicting risk. Inverse rhythm is rare and low night/day ratio overlaps considerably within the group of pregnant women. The advantage of using the raw data and their averages from the

Table 3 Regression analysis for selected BP variables in 111 diabetic and 50 non-diabetic women

	Significant variable ^a	r	p value	r ^b	p value
Sysdiu1	HbA1c	0.33	0.001	0.35	0.001
Diadiu2	HbA1c	0.32	0.001	0.33	0.001
Sysdiu2	HbA1c	0.21	0.009	0.33	0.042
Diadiu2 ^c	logpro / HbA1c	0.28/0.37	0.005/0.001	0.33 (logpro)	0.014
Sysdiu3 ^c	logpro / HbA1c	0.38/0.31	0.001/0.001	0.43 (logpro)	0.01
Diadiu3	HbA1c	0.46	0.001	0.31	0.036
NDsys1	HbA1c	0.18	0.027	0.22	0.038
NDdia1	HbA1c	0.29	0.002	0.30	0.003
NDsys2 ^d		0.02	0.78	0.08	0.71
NDdia2 ^d		0.1	0.24	0.16	0.16
NDsys3 ^d	HbA1c	0.17	0.046	0.16	0.28
NDdia3	HbA1c	0.26	0.003	0.29	0.022

Sys systolic, Dia diastolic, diu diurnal BP, ND night/day ratio, 1 First trimester, 2 Second trimester, 3 Third trimester, logpro logarithm of urinary albumin excretion rate

^a Significant variables in unadjusted analysis

^b Regression coefficient adjusted for duration of diabetes and urinary albumin excretion

^c Two variables significant in unadjusted analysis, one only (logpro) in adjusted analysis

^d Calculations shown for HbA1c

measurements is that fewer assumptions need to be made of their biological background.

Defining day and night BP by fixed time may have underestimated a reduction of BP by up to 3–10 % if evaluated individually [13, 15]. However, looking at the absolute figures of ND-ratio our average ratio in diabetic women with normoalbuminuria was 0.83, which is comparable with the range of ratios in non-pregnant, diabetic subjects from 0.80 to 0.89 depending on methods of calculation [13, 15]. These methods, however, all confirmed the presence of blunting in normoalbuminuric, non-pregnant, diabetic subjects with different methods of timing; thus, it is doubtful whether potential underestimation in our study adds up to any differences in conclusion.

The hemodynamic changes during non-diabetic, diabetic, and hypertensive pregnancy include early increase of cardiac output, lower BP and lower systemic resistance partly due shunting to the uterus and increase of heart rate. Most of the changes occur within the first 12 weeks of pregnancy. Arterial compliance, systemic vascular resistance, intravascular volume, and degree of tissue edema affect the transmission of pressure measured in a cuff. The diagnosis of preeclampsia itself can be a challenge, the levels arbitrary, and may mimic similar BP achieved by circulatory pathophysiology unrelated to pregnancy. The diagnosed range of hemodynamic states is thus from high-output-low-resistance to low-output-high-resistance states [16]. In concordance, despite consistent findings of higher BP early in pregnancy in women which later develop preeclampsia, the BP is within the normal range and with

progressing gestation, medication, and non-standardized setting of hydration, the value of diurnal BP is arguable [7, 11, 12, 17].

The association of ND-ratio with retinopathy and lower birth weight suggest that vascular regulatory changes are present, which affect several target organs. We corroborate the finding of Napoli et al. that normoalbuminuric T1DM women are still at high risk of preeclampsia [1]. The ROC curve and the increasing AUC later in pregnancy add no strength to the argument because a number of early onset preeclampsia will be missed by later BP measurements.

In conclusion, we find that simplex retinopathy and preeclampsia are associated with a reduced night/day ratio even with normal blood pressure. Night/day rhythm provides no better prediction of preeclampsia than the absolute values.

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Conflict of interest statement None.

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