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ORIGINAL ARTICLE

Circadian Pattern of Blood Pressure in Normal Pregnancy and Preeclampsia

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Abstract
Aims & Objective To find out the circadian pattern of blood pressure in normotensive pregnant women and in women with preeclampsia.
Method A cross-sectional prospective observational case control study. Blood pressure was sampled in thirty-five normotensive pregnant women (control) and thirty five preeclamptic women (study group) by using non-invasive automatic ambulatory blood pressure monitoring machine for 72 h.
Results Blood pressure (BP) was not constant over 24 h period and it oscillated from time to time in control group. BP was maximum during early part of afternoon. However, in preeclampsia besides quantitative increase in BP, circadian BP oscillations were less pronounced and in around 50% subjects BP was maximum during evening and night hours.
Conclusion Both systolic and diastolic BP showed definite reproducible circadian pattern in both preeclamptic and normotensive pregnant women. This pattern both quantitatively and qualitatively was different in preeclamptic women. Standardized 24 h BP monitoring allows quantitative and qualitative evaluation of hypertensive status and is important for timing and dosing of antihypertensive medications.

Keywords Circadian pattern · Preclampsia · MESOR · Amplitude · Acrophase

Introduction

There is a spectrum of clinical manifestation of gestational hypertension/preeclampsia but hypertension remains the most reliably accessible sign. Both systolic and diastolic-blood pressure is not constant over 24 h period. It shows characteristic circadian pattern in all individuals, including non-pregnant and pregnant women in response to internal clock and mental and physical activity.

Blood pressure is higher during the day time (between 10 AM to 6 PM) and lower at night. During night both systolic and diastolic blood pressure readings drop by about 10–20%. There is a characteristic dip in blood pressure

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between midnight and 3 AM, followed by slow and steady rise in blood pressure between 3 AM and 6 AM. After arousal there is sudden steep elevation of blood pressure. This rapid increase in blood pressure continues for 4–6 h i.e. between 6 AM to 12 PM. This pattern is found in all individuals including non-pregnant and normotensive pregnant women [1, 7].

However in preeclamptic women the nocturnal blood pressure fall may be diminished or lost. Even reversal of circadian pattern of blood pressure has been reported [2, 3]. These changes develops much before the actual onset of hypertension in preeclampsia. Blood pressure (BP) assessment in pregnant women has relied mostly on a few measurements taken in the physician's office. These casual time-unspecified measurements perform poorly and cannot predict the dangerous life threatening hypertensive episodes and doesn't help in regularization of dose and timing of antihypertensive medication. So conventional method is not sufficient enough and precise for blood pressure monitoring in preeclampsia [4, 6].

We have monitored the circadian pattern of blood pressure in normotensive pregnant women and in preeclamptic women by using non-invasive ambulatory blood pressure monitoring device (ABPM device-TM-2430).

Material & Methods

This study was prospective observational case and control study conducted for 1 year.

Selection of Cases

The subjects were selected from the admitted pregnant women in the Department of Obstetrics & Gynaecology, CSM Medical University, Lucknow.

- Total 70 pregnant women were studied which were divided into two groups.
- Control Group ($n = 35$) comprised of normotensive pregnant women with more than 20 weeks period of gestation without any systemic or metabolic disease.
- Study Group ($n = 35$) were the patients in whom systolic blood pressure was $\geq$140 mm Hg and diastolic blood pressure was $\geq$90 mm Hg at 2 consecutive measurements at 6 h interval, developing after 20 weeks of gestation in previously normotensive women and associated with proteinuria of $\geq$1+dip stick.

The subjects with chronic hypertension, chronic renal disease and endocrinal disease were excluded from the study. All subjects underwent detailed history, examination and routine and special investigations as required.

Method

All subjects underwent conventional baseline blood pressure recording and automatic ambulatory blood pressure recording by ABPM device after informed consent.

Ambulatory blood pressure monitoring is a technique by which multiple indirect blood pressure readings are taken automatically over a period without limitation of daily activities of the person [4].

ABPM device was applied to subjects between 9 a.m. and 4 p.m. for consecutive 72 h. All subjects were suggested to go to bed before 11 P.M. (23:00) as far as possible during the period of observation. Systolic and diastolic BP of each individual was sampled every 30 min during 8 a.m. to 10 p.m. and every hour during 10 p.m. to 8 a.m. During recording all women were living in their usual diurnal waking and nocturnal resting routine and following their normal routine. They were not allowed to take any antihypertensive drugs during the observation period. Those subjects were eliminated who have a night resting span of less than 6 h and more than 12 h.

Statistical Analysis

Data of both systolic and diastolic blood pressure was stored in a software which is inbuilt in the ABPM device. These data were downloaded into a personal computer. These original oscillometric datas from each blood pressure series were first synchronised according to the sleep awake cycle.

Blood pressure data series of each individual was analyzed by the cosinor method to evaluate her circadian rhythm which provided 24 h cosine curve.

This analysis provided estimates of the following parameters of circadian pattern of BP:

1. *Midline Estimating Statistics of Rhythm* (*MESOR*) It is defined as the average value of the rhythmic function fitted to BP data (in mm of Hg).
2. *Amplitude* It is defined as measure of one half of the maximum and minimum extent of rhythmic variation of BP in a best fitted 24-hr cosine curve (in mm of Hg).
3. *Acrophase* It is a measure of timing *i.e.* the lag from a reference time point (in this study local midnight 00:00) of the crest time in the cosine curve of the BP circadian rhythm.
4. *Hyperbaric Index* (*HBI*) It is defined as total area of blood pressure above the threshold of BP over 24 h. It is a measure of total load exerted on arterial wall.
5. *Percentage Time Elevation* (*PTE*) It is defined as percentage of time of 24 h during which BP exceed the upper limit of threshold.

After accumulating the data, of each individual they were subjected to statistical analysis using χ^2 test and Student '*t*' test. Probability of <0.05 was considered statistically significant.

Results

Table 1 shows that demographic characters of both groups were comparable. There was no significant difference in the two groups as regard to age, body mass index, gravidity and gestational age.

Table 2 shows that the mean value of MESOR of both systolic and diastolic blood pressure was significantly much higher in preeclamptic women as compared to normotensive pregnant women.

The amplitude of systolic blood pressure was 10.19 ± 4.06 mm Hg for normotensive pregnant women and 8.40 ± 2.91 mm Hg for pregnant women with preeclampsia. For diastolic blood pressure it was 7.86 ± 2.64 mm Hg for normotensive pregnant women and 6.08 ± 2.14 for pregnant women with preeclampsia. We observed that in our study amplitude was less for both systolic and diastolic BP in preeclamptic group than normotensive pregnant women but it was statistically significant only for diastolic blood pressure (Table 2).

In the present study blunting of circadian pattern (amplitude <7.5 mm Hg) was more common in preeclamptic women compared to normotensive pregnant women. In preeclamptic women blunting of circadian pattern of systolic BP was found in 40% of women and for diastolic BP was found in 65% of womens. However, in control group blunting of circadian pattern was present only in 23% women for systolic BP and 34.3% for diastolic BP (Table 3).

Table 1 Comparison of demographic characters between study and control group women

Demographic characters	Control (*n* = 35)	Study (*n* = 35)	*P*-value
Age	25.81 ± 4.05	26.16 ± 3.6	NS
Body mass index	22.20 ± 1.97	23.70 ± 2.79	
Gravidity			
(a) Primigravia	13	12	NS
(b) Multigravida	22	23	NS
Gestational age			
(a) 22–28 weeks	3	2	NS
(b) >28–34 weeks	17	15	NS
(c) >34–40 weeks	15	18	NS

NS Non significant

Table 2 The comparison of MESOR and amplitude of ciradian pattern of BP between two groups

Variable	Control (*n* = 35)	Study (*n* = 35)	*P*-value
MESOR in mmHg			
(a) SBP	109.05 ± 7.42	137 ± 7.42	<0.001
(b) DBP	66.35 ± 5.99	87.77 ± 8.51	<0.001
Amplitude in mmHg			
(a) SBP	10.19 ± 4.06	8.40 ± 2.91	0.058
(b) DBP	2.64 ± 7.86	6.08 ± 2.14	0.043

SBP systolic blood pressure, *DBP* diastolic blood pressure

Table 3 Comparison of absence of circadian rhythm between control and study group (i.e. blunting of circadian pattern) (amplitude less than 7.5 mm Hg)

S. no.	Blood pressure	Control (*n* = 35)	Study group (*n* = 35)	*P* value
1.	For systolic BP	8 (23%)	14 (40%)	0.122
2.	For diastolic BP	12 (34.3%)	22 (65%)	0.004

Acrophase

Table 4 shows the distribution of subjects according to acrophase and comparison of acrophase between two groups. In most of the normotensive pregnant women and in about half of the preeclamptic women, acrophase of both systolic and diastolic blood pressure was set around 12–17 h. However in rest half of the preeclamptic women and few normotensive women acrophase shifted to evening hours (*P* = 0.006 for SBP, 0.04 for DBP) and night hours (*P* = 0.021 for SBP and 0.006 for DBP).

Hyperbaric Index (HBI) and Percentage Time Elevation (PTE)

The calculation of the hyperbaric index in each single case allowed us to quantify the severity of BP excess over the normal range and to define the time of the day when the elevation took place, whereas the percent time elevation let us quantify the duration of BP excess in the 24-h period.

It was seen that both hyperbaric index and percentage time elevation both are much higher in preeclampsia as compared to normotensive pregnant women both for systolic and diastolic blood pressure (Table 5).

Discussion

Hypertension being the most accessible and very important clinical sign of preeclampsia and it should be very precise.

Table 4 Distribution of subjects according to acrophase

Group	% of Subjects with		
	Acrophase at afternoon 11:52–18:40 h	Evening shift of acrophase 18:41–22:00 h	Night shift of acrophase (Reverse pattern) 22:00–06:00 h
Systolic blood pressure			
Control ($n = 35$)	91.43% ($n = 32$) (Mean—15:05 ± 1:59 h)	5.71% ($n = 2$)	2.86% ($n = 1$)
Study ($n = 35$)	48.58% ($n = 17$) (Mean—14:15 ± 1:16 h)	25.71% ($n = 9$)	25.71% ($n = 9$)
P-value	9.14×10^{-5}	0.006	0.021
Diastolic blood pressure			
Control ($n = 35$)	91.43% ($n = 32$) (Mean—14:24 ± 1.44 h)	5.71% ($n = 2$)	2.86% ($n = 1$)
Case ($n = 35$)	51.42% ($n = 18$) (Mean—13:53 ± 1.52 h)	22.87% ($n = 8$)	25.71% ($n = 9$)
P-value	0.0002	0.04	0.006

Table 5 Distribution of subjects according to HBI and PTE

Variables	Control ($n = 35$)	Study ($n = 35$)	*P*-value
Hyperbaric index			
(a) SBP	16.88 ± 12.19	327.63 ± 125.51	<0.001
(b) DPB	21.8 ± 10.62	341.63 ± 128.93	<0.001
Percentage time elevation			
(a) SBP	10.66 ± 6.62	65.44 ± 21.11	0.001
(b) DBP	14.97 ± 10.82	74.62 ± 20.51	<0.001

SBP systolic blood pressure, *DBP* diastolic blood pressure

Conventional method is not sufficient enough and precise for blood pressure monitoring in preeclampsia. Ambulatory blood pressure monitoring addresses many sources of error associated with the conventional blood pressure monitoring and day-night difference index. This day-night circadian index is very useful for management of preeclampsia and in prediction of dangerous hypertensive episodes.

This study confirms that both systolic and diastolic blood pressure readings fluctuate over 24 h and show a definite reproducible circadian rhythm in the both the normotensive pregnant women and in preeclamptic women. In this study it was also observed that blood pressure not only shows a characteristics circadian rhythm but also oscillates within a short time span.

However, highly statistically significant difference in the circadian pattern of both systolic BP and diastolic BP have been found between two groups.

In preeclampsia MESOR of systolic and diastolic blood pressure were much higher than nomotensive pregnant as expected.

Amplitude (half of maximum and minimum value of rhythmic variation of blood pressure) in a 24-h cosine curve of both systolic and diastolic BP was lower for preeclamptic women in comparison to normotensive pregnant women i.e. less diurnal variation of systolic and diastolic BP in preeclamptic women, as reported in previous studies [5] but this difference was statistically significant only for diastolic BP.

It was also found that blunting of circadian rhythm of systolic and diastolic blood pressure (lesser diurnal variability of blood pressure) is more common in preeclamptic women in comparison to normotensive pregnant women.

In most of the normotensive pregnant women both systolic and diastolic BP were higher in early part of afternoon i.e. acrophase was in early part of afternoon while in preeclamptic group about 50% women showed this pattern and in the rest half of preeclamptic women acrophase of both systolic BP (in 48.58% subjects) and diastolic BP (51.42% subjects) were shifted to evening/night hours. Severity of preeclampsia favoured the evening and night shift of acrophase.

The blunting of nocturnal drop of blood pressure and reverse pattern of circadian rhythm of blood pressure both have important clinical implications if we consider that cardiovascular system not set to sustain an excessive load during night and in clinical practice blood pressure is usually measured at other time of day.

Several possibilities have been proposed to explain the blunting of nocturnal BP fall and reversed circadian BP rhythm in preeclampsia e.g. disturbance in hypothalamic pituitary adrenal periodicity and in sympathetic nervous system or a compensatory mechanism to maintain the organ blood flow during sleep in response to ischemia [5].

Several of the humoral agents controlling circulation and BP, like the renin-angiotensin aldosterone system, free epinephrine and free nonepinephrine show a temporal sequence of circadian rhythmicity in non-pregnant and normotensive pregnant women. While in preeclamptic women circadian rhythmicity of these agents was blunted [8–10].

The hyperbaric index and percentage time elevation were much higher in preeclamptic women in contrast to normotensive pregnant women for both systolic and diastolic BP. The calculation of hyperbaric index in each case allowed us to quantify the severity of blood pressure excess over the threshold value. The hyperbaric index represents a better determinant of blood pressure load than the MESOR. Higher hyperbaric index is associated with increased cardiovascular risk [11].

Conclusion

Both systolic and diastolic BP shows definite reproducible circadian pattern in both preeclamptic and normotensive pregnant women. This pattern both quantitatively and qualitatively was different in preeclamptic women. Blood pressure monitoring by ambulatory method is very precise. Standardized 24 h BP monitoring in pregnant women allows quantitative and qualitative evaluation of hypertensive status and is very important for regularization of timing and dosing of antihypertensive medications.

ABPM may have several roles in the future antenatal management of hypertension including modification of existing classification system, a clinical confirmatory role and a possible predictive role for preeclampsia.

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