

DOI: <https://dx.doi.org/10.18203/2320-1770.ijrcog20210005>

Original Research Article

Impaired circadian rhythm of blood pressure predicting adverse events in preeclampsia

Nitisha Vijayvargia*, Meenakshi Samariya

Department of Obstetrics and Gynecology, JLN Medical College, Ajmer, Rajasthan, India

Received: 14 August 2020

Accepted: 24 December 2020

***Correspondence:**

Dr. Nitisha vijayvargia,

E-mail: nitishavijayvargia4@gmail.com

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ABSTRACT

Background: Physiologically Blood pressure is higher during the day time (between 09 AM to 6 PM) and lower at night (10 pm to 3:00 am). During night both systolic and diastolic blood pressure readings drop by about 10-20%. In preeclampsia, the nocturnal decrease of BP is blunted and there is less variation among BP circadian values. Objective of the study is to know whether ratio of morning and nocturnal mean diastolic blood pressures calculated by timed i.e., 6 hourly blood pressure monitoring could be used to predict the prognosis of preeclampsia as in terms of Maternal and fetal prognosis.

Methods: A prospective study is done using 6 hourly blood pressure measurements of antenatal patients in third trimester admitted for gestational hypertension or preeclampsia and their observation till delivery was done.

Results: It is observed that non dipping and increased nocturnal diastolic blood pressures pattern causing reverse dipping pattern are significantly associated with increased severity of disease (p=000). Both maternal (p=0.04) and fetal adverse event (p=0.004) increased significantly with blunting of decrease in nocturnal blood pressures.

Conclusions: We thus can conclude that blunting/reversal of circadian rhythm of blood pressure indicates progress of disease to its more severe form. It thus could be of great help in deciding for monitoring, timing of antihypertensives and prophylactic medications and deciding for termination of gestation.

Keywords: Nocturnal diastolic blood pressure, Reverse dipping pattern, Non-dipping pattern

INTRODUCTION

Preeclampsia

Preeclampsia is a pregnancy specific hypertensive disorder with multisystem involvement. It is marked by widespread endothelial dysfunction and vasospasm occurring after 20 weeks of gestation and may present 4-6 weeks post-partum. These include deranged hepatic, and renal functions, albuminuria, cerebral symptoms or accompanying IUGR. It normalizes by 12 weeks post-partum.

Some clinical findings increase the morbidity and mortality of preeclampsia when present segregate the

patient in more severe category. Those without any feature of severe form are termed as “preeclampsia without severe features”. Previously labelled as mild preeclampsia. Those with severe features called as “preeclampsia with severe features.”

Severe features of preeclampsia, any one of these:

Blood pressure: systolic blood pressure of 160 mmHg or higher and diastolic bp of 110 mmHg or higher.

Thrombocytopenia: Platelet count less than 100000/microliter.

Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dl or a doubling of serum creatinine in absence of other renal disease.

Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration, severe persistent right upper quadrant or epigastric pain unresponsive to medication.

Pulmonary edema:

Cerebral or visual symptoms: Headache (occipital headache), blurring of vision.¹

Circadian rhythm

Physiologically blood pressure is higher during the day time (between 09AM to 6 PM) and lower at night (10 pm to 3:00 am). During night both systolic and diastolic blood pressure readings drop by about 10-20%.² When compared to normotensive pregnancies, pregnant women with essential hypertension preserve a normal circadian variation of BP but with a greater fall in BP at night.³

In preeclampsia, the nocturnal decrease of BP is blunted and there is less variation among BP circadian values.⁴ Even reversal of circadian pattern of blood pressure has been reported. These changes may also develop 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.²

Later chronobiological studies found concordant results, with a decrease in the oscillatory amplitude of BP (i.e., the extent of oscillatory wave from MESOR) in the two last trimesters of hypertensive and preeclamptic pregnancies.⁵ It was also found that in ambulatory blood pressure measurement, lesser decrease or no decrease in night time diastolic blood pressure was best predictor of adverse events in pregnancies with hypertension.⁶ As expected, reversed BP rhythm is found to be associated with the more severe form of preeclampsia.⁷

These studies are mainly done using ABPM (ambulatory blood pressure monitoring). However there had been issues regarding tolerance of same by patients. Wider application of such methods to determine prognosis also involves economic restraints.

Aims and objectives

Aim and objectives of the study were to know whether ratio of morning and nocturnal mean diastolic blood pressures calculated by timed blood pressure monitoring could be used to predict the course of preeclampsia as in terms of maternal and fetal prognosis.

METHODS

This is a prospective study done at JLN medical college i.e., tertiary level health care center at Ajmer for 4 months from December to march 2020 .6 hourly BP monitoring was done for 3 days or during hospital stay of patient whichever is more for patients admitted with diagnosis of preeclampsia or gestational hypertension antenatally at >28 weeks of gestation and were followed up till they deliver.

The patients of severe pre-eclampsia were given antihypertensives and MgSO₄ prophylaxis and patients of mild preeclampsia were restricted for taking any antihypertensives.

We took ratio of morning mean diastolic pressure (between 6 am to 10 am) and nocturnal mean diastolic pressure (between 10 pm to 3 am) of minimum 3 days of admission (M/N) and correlated the values with maternal and fetal prognosis in the corresponding patient. We applied Pearson's chi-squared tests through IBM® SPSS® statistics 21 software to determine if this ratio i.e., M/N is significantly low in those patients having adverse maternal or fetal events.

Prognosis of the disease is assessed by occurrence of HELLP, eclampsia, end organ dysfunction, uncontrolled hypertension, IUGR, oligohydramnios or doppler abnormalities.

Inclusion criteria

Inclusion criteria included all patients of age 20 to 30 years in third trimester admitted as case of diagnosed gestational hypertension or preeclampsia

Exclusion criteria

Exclusion criteria excluded patients with IUD. Patients with chronic hypertension, diabetes or GDM, heart disease, twin pregnancies, SLE, thyroid disorders were excluded from the study to exclude other cardiovascular comorbidities and indoor patients with admission duration <3 days.

RESULTS

We analyzed 42 patients admitted with following diagnosis

Table 1: Class of patients observed.

Gestational age (weeks)	Mild pre-eclampsia	Severe pre-eclampsia	Gestational hypertension
28 to 34	4	8	0
34.1 to 40	20	0	10

Mean ratio (M/N) (morning diastolic BP/nocturnal diastolic BP)

As found above the ratio of mean morning and nocturnal blood pressure decreases as one observes gestational hypertension, preeclampsia without severe features and preeclampsia with severe features respectively.

To check significance of this ratio M/N we applied chi square test. Calculated test value of chi square was 66.73,

p value was 0.000 (<0.05). We can conclude that there is significant association between M/N ratio and categories of severity. Hence, we conclude that as M/N ratio is

decreasing severity is increasing significantly.

This also shows that non dipping or increased nocturnal diastolic blood pressures causing reverse dipping pattern are associated with increased severity of disease.

Table 2: Mean ratio (M/N) (morning diastolic BP/nocturnal diastolic BP).

Variables	Gestational hypertension (n=10)	Mild preeclampsia (n=24)	Severe preeclampsia (n=8)
Mean morning diastolic BP (M)	93.66	89.66	98.025
Mean nocturnal diastolic BP (N)	79.49	91.99	104.04
Mean ratio (M/N)	1.17	0.97	0.94
Mean ratio of all (M/N)	1.01±0.12		
Chi square test	66.73		
P value	0.000		

Table 3: Mean M/N (morning diastolic BP/nocturnal diastolic BP) ratio and maternal and fetal outcome.

Mean M:N ratio range	Total no. of patients	Fetal complication	Maternal complication	Total cases with complications	No adverse event
0.76 TO 0.88	6	6	4	6	0
0.89 TO 1.01	21	16	10	17	4
1.02 TO 1.14	6	1	NAD	1	5
1.15 to 1.27	9	NAD	NAD	0	9
Chi square test	18.18		8.008	20.244	
P value	0.00403		0.045	0.000151	

Mean M/N ratio and maternal and fetal outcome

As mean ratio of diastolic pressures (M/N) in cases of gestational hypertension and preeclampsia was 1.01±0.12. We analyzed the prognosis by dividing the patients from 2 SD below to 2 SD above the mean value.

The ratio value of <1 indicates the patients with reverse dipper profile. As depicted above as the mean ratio falls the incidence of maternal complications (HELLP, eclampsia, end organ dysfunction, uncontrolled hypertension) increase with maximum being 66.66 % at mean ratio value 0.76 to 0.88 followed by 47.6 % in range of 0.89 to 1.01; and above 1.01 no adverse maternal event was noted.

We applied chi square test over the rate of maternal complications observed. We found that they increase significantly with decrease in the ratio of mean morning to nocturnal diastolic blood pressures with p value 0.04.

We also observed significant (p=0.004) increase in adverse fetal outcomes with decreasing mean ratio as evident by occurring of events as IUGR, oligohydramnios and still birth occurred mostly in subsequent 2 weeks of observations.

9 patients had mean ratio value above 1.15 and were not observed to have any maternal and fetal complications.

These were all diagnosed cases of gestational hypertension.

DISCUSSION

There is about 10 to 20 % fall in BP during night hours as compared with morning BP recordings in those with normal circadian pattern (normotensive pregnancies).²

If we calculate the ratio of morning to nocturnal diastolic pressure (M/N) in normotensives. It's in range of 1.10 to 1.20 corresponding to 10 to 20 percent fall of nocturnal diastolic blood pressure. In our study mean ratio of all 42 patients having gestational hypertension and preeclampsia was 1.01±0.12. Those patients with mean ratio above 1.15 did not have any maternal or fetal complications.

In a study by Nobre et al using ambulatory blood pressure monitoring, on the basis of pressure reduction in night time patients were classed as dipper (>10% decrease), non-dipper (<10% decrease), reverse dipper (increased nocturnal hypertension), and extreme dipper (>20%

decrease) profiles. Evidences suggested that those with non-dipper and reverse dipper profile had higher risk of mortality and of cerebrovascular events.⁷

We had similar results using timed (6 hourly) blood pressure monitoring, those with non-dipper (M/N ratio 1 to 1.09) and reverse dipper profile (M/N ratio <1) had 90 and 60 percent of complications (maternal or fetal) respectively. Those cases with dipper profile (M/N >1.10) were reported to have no maternal or fetal complications.

Similarly, in study by Correia et al using diastolic blood pressure analysis Non dipper profile was associated with worse profile compared to those with dipper profile.⁶

As depicted above as the mean ratio falls the incidence of maternal complications increase with maximum being 66.66% at mean ratio value 0.76 to 0.88.

The complications observed in this range were pulmonary edema (n=1), eclamptic fits (n=2), uncontrolled hypertension (n=1).

Here 3 patients reported to have pulmonary edema or fits belonged to category of preeclampsia without severe features. Thus, in these reverse dipper profiles was the only indicator of severity of disease process.

It is to be noted here that the 2 patients who did not report to have any adverse maternal event belong to category of preeclampsia with severe features. So, they were given magnesium sulfate prophylaxis and antihypertensives as well. This has affected the outcome in this range of patients.

In range of 0.89 to 1.01 we had 47.6 % patients with maternal complications.

Among these 4 patients diagnosed as preeclampsia with severe features and 6 patients diagnosed with preeclampsia without severe features.

Of 6 patients without severe features 1 presented with fits on day third of admission, rest presented with uncontrolled hypertension (n=2), abruption placentae (n=1), partial HELLP syndrome (n=1), and deranged renal function (n=1) within subsequent 2 weeks of observation.

Thus overall, 9 of 14 patients with maternal complications i.e., 64.3 percent could have been better managed with taking care of non-dipper or reverse dipper profile of diastolic BP also. The other 5 patients as already diagnosed as preeclampsia with severe features were given antihypertensives and magnesium sulfate prophylaxis with required monitoring.

Also using timed measurements, there was better compliance and less expenditure required for monitoring then it would be if we used ambulatory BP monitoring.

Moreover, in a study by Ayala et al, based on such chronotherapeutic studies, bedtime rather than morning time ingestion had been shown to reduce BP and seems to considerably improve the prophylactic property of Aspirin Ayala et al. This simple, safe, and cost-effective way to improve the outcome of some high-risk pregnancies should encourage clinicians to prescribe this medication in the evening.⁸

These results could be better remarked by increasing sample size.

The reason for this blunted or reverse circadian rhythm of BP in preeclampsia is unknown.

There is exaggerated sensitivity to vasopressors such as angiotensin II and nor epinephrine in preeclampsia.⁹ The absence of an angiotensin II, adrenaline, or nor adrenaline drop at night in subjects with increased vascular reactivity could contribute to their nocturnal hypertension.¹⁰

Moreover, sometimes these differences remain subtle and within the normally accepted physiological range. Setting of ABP (ambulatory blood pressure) normal values for each trimester and a standardized analysis of BP circadian pattern convenient to clinical use are still required

CONCLUSION

We thus can conclude that blunting/reversal of circadian rhythm of blood pressure indicates progress of disease to its more severe form. 6 hourly monitoring is rather simple and cost effective for patients. There, is increase in maternal complications like, uncontrolled hypertension, eclampsia abruptio placentae with decreasing mean ratio of morning and nocturnal diastolic blood pressures (M/N). There also is an increase in fetal complications like IUGR, oligohydramnios with decreasing mean ratio (M/N).

Monitoring the circadian pattern of blood pressures 6 hourly for patients of preeclampsia thus could be of great help in deciding for monitoring, timing of antihypertensives and prophylactic medications and deciding for termination of gestation.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Vijayvargia N, Samariya M. Impaired circadian rhythm of blood pressure predicting adverse events in preeclampsia. *Int J Reprod Contracept Obstet Gynecol* 2021;10:511-5.