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EFFECT OF DIPPING PATTERN OF GESTATIONAL HYPERTENSION ON MATERNAL SYMPTOMS AND PHYSICAL FINDINGS, BIRTH WEIGHT AND PRETERM DELIVERY

Đorđe Ilić[1,2], Aleksandra Ilić[1,3], Snežana Stojšić[3], Anastazija Stojšić-Milosavljević[1,3], Jelena Papović[4], Dragana Grković[3], Olivera Rankov[2], Aleksandra Milovančev[1,3] and Lazar Velicki[1,3]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[2]Department of Obstetrics and Gynecology, Clinical Center of Vojvodina, Novi Sad, Serbia;
[3]Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia;
[4]Institute of Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia

SUMMARY – The study aimed to determine if the non-dipping pattern of blood pressure (BP) influences preterm delivery in gestational hypertension (GH), but also maternal clinical findings and birth weight. Sixty women with GH, i.e. 30 women with a dipping BP profile (control group) and 30 non-dippers (study group), were included in the study. Echocardiography was performed in all subjects, as well as ambulatory blood pressure monitoring (ABPM) during third trimester. ABPM was repeated 6-8 weeks after delivery. Thirteen women with preterm delivery were classified as non-dippers and only four as dippers (p=0.01). The average and peak systolic and diastolic night-time BP had negative linear correlation with birth weight (p<0.0005). Total vascular resistance (p<0.0005) and mass index (p=0.014) were significantly higher as compared with women with term delivery, while ejection fraction (EF) (p=0.007) and circumferential systolic velocity (p=0.042) were significantly reduced in the preterm delivery group. Multivariate binary logistic regression identified the average night-time systolic BP, left ventricular mass index and EF as independent predictors of preterm delivery. Study results suggested a relationship of the non-dipping BP pattern in GH with preterm delivery, birth weight, and maternal clinical findings.

Key words: *Pregnant women; Echocardiography; Hemodynamics; Blood pressure; Prenatal care*

Introduction

Ambulatory blood pressure monitoring (ABPM) ensures the best insight into the blood pressure (BP) pattern, i.e. circadian rhythm[1]. It is recognized as the only reliable method of diagnosis of white coat hypertension[2]. Circadian rhythm is the ratio between average night-time and daytime BP. BP normally decreases during the night, which is defined as a dipping pattern of BP (decline of nocturnal BP is more than 10% of daytime BP). The absence of dipping is known as a non-dipping pattern (decline of nocturnal BP is less than 10% of daytime BP)[1]. Night-time BP is a stronger predictor than daytime BP of clinical cerebrovascular and cardiovascular outcomes, and of deterioration of the left ventricular (LV) geometry in adults[3,4].

It has been shown that ABPM recorded higher values of BP compared to office blood pressure measurement, but also more frequent absence of preserved circadian rhythm of BP in hypertensive pregnancies[5,6]. ABPM in pregnant women showed advantage in the prediction of gestational hypertension (GH), premature childbirth, and low birth weight, compared with the conventional BP measurements[7-14]. One recent

Correspondence to: *Aleksandra Ilić, MD, PhD*, Put doktora Goldmana 4, 21204 Sremska Kamenica, Serbia
E-mail: aleksandra.ilic@mf.uns.ac.rs

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study showed the non-dipping pattern in GH to be associated with deterioration of maternal hemodynamics, but also with intrauterine growth restriction (IUGR)[15]. It is well known that preeclampsia is associated with preterm delivery and lower birth weight[16]. The question arises whether the non-dipping pattern of BP in GH in non-proteinuric women is also associated with a higher risk of premature birth compared to hypertensive pregnant women with a dipping profile. There is not enough relevant data on the influence of non-dipping BP profile on preterm delivery and lower birth weight in GH. Also, there is a lack of data on the association of dipping pattern and maternal clinical findings. Starting from the fact that the non-dipping profile is associated with IUGR and worsening of maternal hemodynamics, we have assumed that there may be a relationship of the absence of the dipping pattern in GH with maternal symptoms and physical findings, premature delivery, and low birth weight of the newborns.

Subjects and Methods

Patient selection

The study was designed and conducted as a prospective case-control study. A total of 60 primigravidae, with singleton first pregnancy, who met the criteria for GH[17] were included. All women were free from comorbidities and proteinuria. They underwent complete echocardiography (ECG) study and ABPM between 32nd and 37th gestational week (GW) and ABPM 6 to 8 weeks after delivery. Study participants were classified into dippers (control group, n=30) and non-dippers (study group, n=30) based on the values of daytime and night-time BP recorded by ABPM and criteria for BP pattern. Therapy with methyldopa was instituted only after ECG and ABPM had been performed. The research was conducted in accordance with the prevailing ethical principles and was approved by the Institutional Review Board.

Clinical follow-up

Clinical investigation was performed during the first encounter with the patient, together with history data (collected either verbally or through a questionnaire) and physical examination. The collected data were entered into the hospital electronic database.

Blood pressure measurements

Blood pressure measurements were performed on the assessment visit and according to the Guidelines on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology and recommendations of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy[17,18]. The higher BP value was taken as valid in the case of a significant (>10 mm Hg) systolic blood pressure (SBP) difference between the arms[17-19].

Pregnant women were told to perform normal activities during the 25-hour BP measurement and recording period. Recording was performed using the Meditech Cardio Tens device. They were also instructed to record information that may have influenced BP. Measurements were recorded and considered technically acceptable if they met the criteria as described in the previous publication[15]. ABPM was performed one hour after ECG, providing an overview of daytime and night-time peak, minimal and average (arithmetic mean of total values) values of SBP and diastolic blood pressure (DBP). Mean arterial pressure (MAP) was obtained using the formula: (SBP + (2x DBP))/3.

Transthoracic echocardiography

All participants underwent ECG examination at rest, in the left lateral position using a GE E9 device with a M5S-D probe, equipped with simultaneous ECG monitoring. Cardiac remodeling, systolic, diastolic and global function of the left ventricle were assessed. Recording of 3 cardiac cycles was done during the end-expiration phase and stored for further evaluation. All data were recorded and analyzed by the same investigator (A.I.), who was blinded to the pregnancy characteristics of the women. Cardiac parameters were indexed for body surface area (BSA).

Remodeling of the left ventricle

Chamber quantification and wall thickness were evaluated according to the recommendations of the American Society of Echocardiography (ASE)[20,21]. The Devereux formula was used to evaluate myocardial mass of the left ventricle (LVMass)[22].

After measurement of the left ventricular end-diastolic dimension (LVEDd) and left ventricular posterior wall thickness at diastole (PWd), relative wall thickness (RWT) was calculated as RWT = 2x PWd / LVEDd.

Systolic and global cardiac function

Estimation of systolic function was performed from the apical 4-chamber (4CH) and 2-chamber (2CH) views, as well as according to the ASE recommendations[21]. Cardiac output (CO) was calculated as the product of stroke volume (SV) and heart rate (HR) derived from ECG monitoring (CO = SV x HR) and then normalized for BSA as CO index.

Volume independent parameter of systolic function, velocity of longitudinal shortening of the LV - s`, was assessed by tissue doppler imaging (TDI) transmitral inflow velocities during systole, at the septal (s`s) and lateral mitral valve annulus (s`l)[23,24].

After measurement of the left ventricular end-diastolic (LVEDd) and end-systolic dimension (LVESd), as well as the ejection time of the left ventricle (ET), velocity of circumferential systolic shortening of myofibrils (Vcf) was calculated as Vcf [circum/s] = (LVEDd-LVESd)/LVEDd x ET x 100.

Finally, global cardiac function was evaluated as Tei index, after assessment of the isovolumetric contractility time (IVCT, time interval between closing of the mitral valve and opening of the aortic valve) and isovolumetric relaxation time (IVRT, time interval between closing of the aortic valve and opening of the mitral valve)[25].

Diastolic function

Diastolic function was evaluated based on the recommendations of the European Association of Echocardiography (EAE) and ASE in the apical 4CH view[26]. To assess left ventricular filling, a pulsed-wave (PW) doppler was performed from apical 4CH at the mitral valve leaflet tips. The sample volume was taken 1 to 3 mm between the mitral leaflets. The index of the LV filling pressure, $E/e`_{av}$, was calculated as the average ratio between the peak velocity of early diastolic filling (E) and early velocities of septal end lateral mitral annulus (e`s and e`l) measured using TDI.

Systolic volume of the left atrium (LAVs) was measured in the apical 4CH view according to the EAE recommendations[27], normalized for BSA as LAVs index.

Hemodynamic parameters

Total vascular resistance (TVR) was estimated in dynes x sec^{-1} x cm^{-5} as: TVR = (MAP /CO) × 80.

Pregnancy outcome

Pregnancy evolution and outcome were evaluated by one investigator (Đ.I.), blinded to the results of maternal cardiac and BP findings, in order to evaluate preterm delivery, birth weight and Apgar score. Preterm delivery was considered if it occurred before 37 GW.

Postpartum control

All participants underwent clinical assessment and ABPM 6 to 8 weeks after delivery. Patients with BP ≥140/90 mm Hg were excluded from the study because they did not meet the criteria for GH[17].

Statistical analysis

Statistical analysis was performed using SPSS 17.0. A p threshold was set at 0.05 with values lower considered statistically significant. The Kolmogorov-Smirnov test was used for determination of quantitative data distribution. Differences in the mean values were tested by the independent samples t-test or Mann-Whitney U test and results were expressed as mean (standard deviation) or median (25^{th} to 75^{th} percentile), accordingly. The associations between categorical variables were tested using the χ^2-test. Results were expressed in the form of frequency distribution or percentages. Correlation between BP and birth weight was assessed with Pearson's correlation coefficient. Univariate and multivariate binary logistic regression was performed to define predictors.

Results

All participants became normotensive within 6 weeks after delivery and all of them were of Caucasian origin. There were no significant differences according to age, height, weight, BMI, and delivery mode between dippers and non-dippers. Birth weight below 5 percentiles was significantly more represented in non-dippers *vs.* dippers (p=0.003). Apgar score, both in the first and fifth minute, was significantly lower in non-dippers (p=0.001). The rate of preterm delivery was more common in women with the non-dipping pattern of BP as compared to dippers (p=0.01) (Table 1).

Table 1. Demographic profile, clinical assessment and pregnancy outcome of women with gestational hypertension (dippers and non-dippers)

Parameter	Dippers (n=30)	Non-dippers (n=30)	p
Age	30.57±5.59	31.17±5.5	ns
GW on assessment	34.01±3.27	33.77±4.01	ns
Height (cm)	16.,9±5.75	167.93±5.87	ns
Weight (kg)	87.9±18.5	86.3±15.2	ns
Body mass index (kg/m^2)	31.82±5.72	30.51±4.5	ns
Birth weight (g)	3017.3±525.4	2612.4±692.3	0.008
Preterm delivery	4 (13.3%)	13 (43.3%)	0.010
Apgar score 1st min	8.73±1.08	7.37±1.77	0.001
Apgar score 5th min	9.67±0.55	8.90±1.06	0.001
Birth weight <5 percentile	5 (16.7%)	17 (56.7%)	0.003
Cesarean delivery	17 (56.7%)	20 (66.7%)	0.595

GW = gestational week; ns = nonsignificant

Symptoms and physical findings of hypertensive pregnant women according to dipping pattern are presented in Table 2. Insomnia, pain in the upper abdomen, and presence of edema were more often present in non-dippers as compared to dippers.

There was a negative linear correlation between the level of average and maximum night-time BP, both systolic and diastolic, with birth weight (Fig. 1).

In order to relate studied parameters in GH with preterm delivery, the relationship of all parameters with preterm delivery was analyzed. All variables with a statistically significant difference according to delivery date are shown in Table 3. Participants with preterm delivery had higher BP values, with stronger difference in the values of night-time BP.

The parameters of diastolic function (E, e`s, e`l, E/e`$_{av}$, IVRT, LAVs) did not differ significantly according to delivery date. There was no significant difference in other studied parameters (s`, IVCT, Tei index) between preterm and term delivery either.

Binary logistic regression results are shown in Table 4. Multiple regression analysis revealed a significant independent relationship between the average nocturnal SBP, LV mass index, and EF with preterm delivery.

Table 2. Symptoms and physical findings in dippers and non-dippers

Parameter	Dippers (n=30)	Non-dippers (n=30)	p
Chest pain	1 (3.3%)	0 (0%)	ns
Dyspnea	9 (30%)	8 (26.7%)	ns
Upper abdominal pain	1 (3.3%)	7 (23.3%)	0.023
Insomnia	0 (0%)	19 (63.3%)	<0.0005
Palpitations	15 (50%)	9 (30%)	ns
Headache	10 (3.3%)	10 (33.3%)	ns
Muscle cramps	3 (10%)	3 (10%)	ns
Fatigue	11 (36.7%)	11 (36.7%)	ns
Vision disturbances	1 (3.3%)	4 (13.3%)	ns
Face edema	4 (13.3%)	16 (53.3%)	0.001
Hand edema	15 (50%)	28 (93.3%)	<0.0005
Leg edema	26 (86.7%)	27 (90%)	ns

ns = nonsignificant

Discussion

Previous reports suggest that symptoms such as upper abdominal pain, visual disturbance, presence of edema (especially face and hands), as well as preterm delivery, low birth weight and IUGR are often present in preeclampsia[16,28]. There is a lack of data on the relationship of the non-dipping pattern in GH with maternal symptoms and physical findings, preterm delivery, and birth weight. Our study showed that all mentioned parameters were present at an increased frequency in the non-dipping group in GH, except for one symptom, i.e. interference with vision, which was also more frequently present in non-dippers, but without statistically significant difference. Thus, we can assume that the pathophysiological changes and consequences in pregnant women with GH and non-dipping pattern are more similar to those in preeclampsia than in uncomplicated GH.

All participants that gave birth to premature babies had higher values of BP, but statistical significance was more obvious when comparing the values of

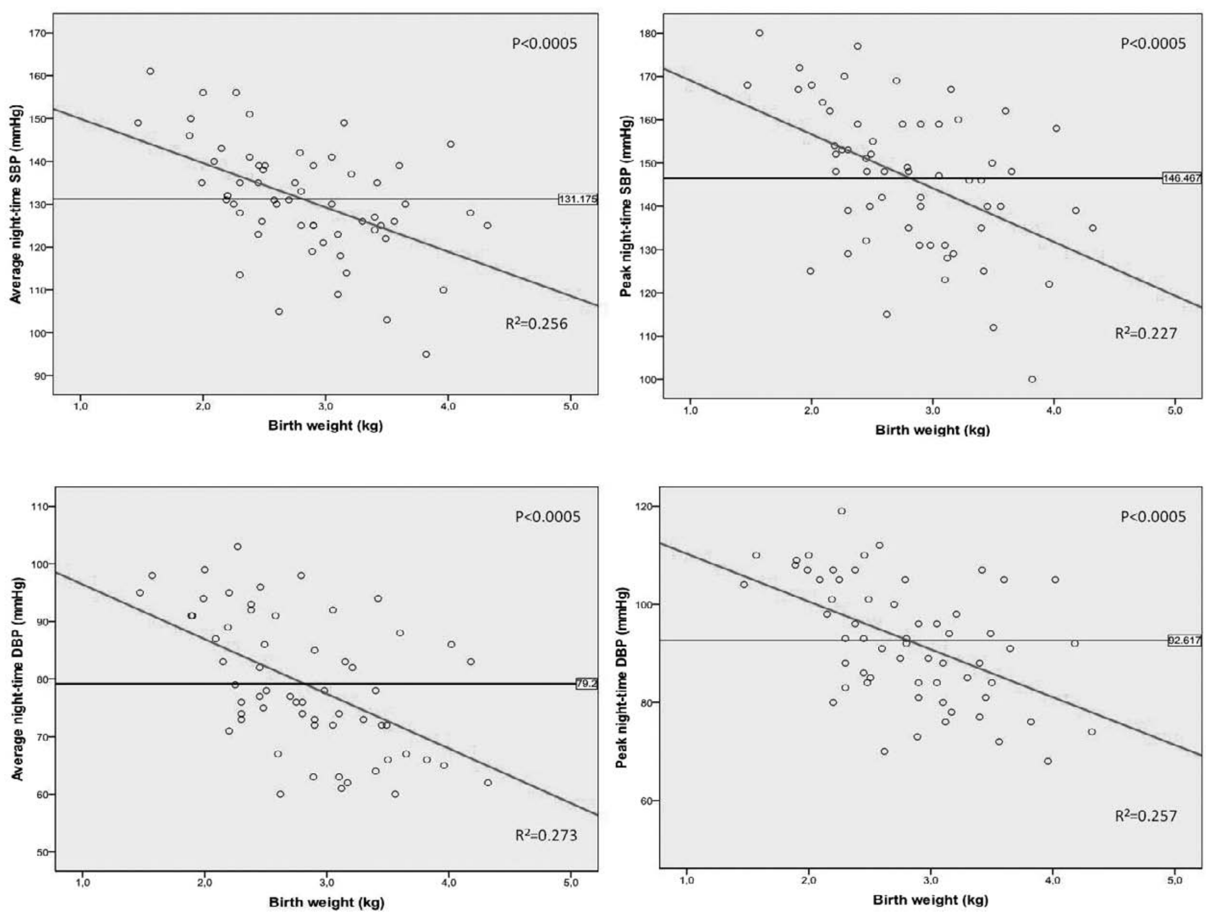

Fig. 1. Linear correlation between: birth weight and average night-time systolic blood pressure (upper left panel); birth weight and peak night-time systolic blood pressure (upper right panel); birth weight and average night-time diastolic blood pressure (lower left panel); birth weight and peak night-time diastolic blood pressure (lower right panel).

night-time BP. The value of average nocturnal systolic BP showed highest influence on preterm delivery. With BP increase of 1 mm Hg, the risk of premature birth increased by 11%, indicating a significant role of non-dipping pattern in GH in preterm delivery.

Peek *et al.* showed that the height of diastolic BP measured by ABPM had a statistically significant effect on premature birth[29], while Samadi *et al*. demonstrated two times more preterm termination of pregnancy in pregnant women with GH than in the normotensive group[30]. Although they did not analyze the dipping profile of BP, the influence of elevated BP on preterm delivery was also shown by other authors[8,10,13,31].

Our research revealed that, besides the effect of non-dipping pattern on preterm labor, it also had an influence on lower birth weight. Thus, there was a moderate negative linear correlation of average and peak values of night systolic and diastolic BP with birth weight.

Besides, significantly lower values of Apgar scores in non-dippers suggested that babies of the non-dippers experienced intrauterine suffering.

The influence of BP and disturbed circadian rhythm on low birth weight was shown by most authors[8,14,29,31,32], whereas others demonstrated that BP values did not affect the weight of newborns significantly[11,33]. It is worth mentioning that in most of these researches, the authors analyzed normotensive pregnant women.

Except for the influence of the non-dipping pattern of BP in GH, we highlighted the impact of some ECG parameters of maternal cardiac function and geometry on preterm delivery. The circumferential systolic velocity of the left ventricle was statistically sig-

Table 3. Parameters with statistically significant relationship with preterm delivery in pregnancies with gestational hypertension

Parameter	Preterm delivery (n=17) Mean ± SD	Term delivery (n=43) Mean ± SD	p
Average daily SBP (mm Hg)	146.82±7.76	141.26±9.18	0.031
Average nocturnal SBP (mm Hg)	140.71±11.77	127.41±11.74	<0.0005
Average DBP (mm Hg)	94.06±6.73	89.4±6.59	0.017
Average nocturnal DBP (mm Hg)	87±9.77	76.12±10.98	0.001
Peak nocturnal SBP (mm Hg)	157.18±16.05	142.23±15.24	0.001
Peak daily DBP (mm Hg)	108.47±8.50	101.67±8.47	0.007
Peak nocturnal DBP (mm Hg)	100.94±10.91	89.33±11.41	0.001
MAP (mm Hg)	111.65±6.2	106.68±6.17	0.007
LV mass index (g/m^2)	95.15±11.65	87.08±10.87	0.014
LVEDV (mL)	90.82±17.63	103.91±22.9	0.039
EF (%)	61.29±2.62	63.4±2.66	0.007
SV index (mL/m^2)	28.61±5.82	32.64±7.36	0.048
CO (L/min)	5.55±1.04	6.36±0.96	0.006
Vcf (circum/s)	1.32±0.23	1.44±0.19	0.042
TVR (dyne*s^{-1}*cm^{-5})	1588.6±313.72	1311.79±235.68	<0.0005

SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean blood pressure; EF = ejection fraction of left ventricle; LVEDV = left ventricle end-diastolic volume; SV index = stroke volume normalized for body surface area; CO = cardiac output; Vcf = circumferential systolic velocity; TVR = total vascular resistance; LV mass index = left ventricle mass normalized for body surface area

Table 4. Binary logistic regression

	Univariate binary logistic regression		Multivariate binary logistic regression	
	p	OR (95% CI)	p	OR (95% CI)
Average nocturnal SBP (mm Hg)	0.002	1.115 (1.043-1.193)	0.006	1.109 (1.031-1.194)
EF	0.012	0.740 (0.585-0.937)	0.052	0.75 (0.561-1.002)
LVEDV	0.042	0.969 (0.939-0.999)	ns	
SV index	0.55	0.913 (0.832-1.002)	ns	
RWT	0.6	1.435 (0-2.94)	ns	
LV mass index	0.021	1.072 (1.011-1.137)	0.051	1.068 (1-1.141)

OR = odds ratio; 95% CI = 95% confidence interval; SBP = systolic blood pressure; EF = ejection fraction of left ventricle; LVEDV = left ventricle end-diastolic volume; SV index = stroke volume normalized for body surface area; RWT = relative wall thickness; LV mass index = left ventricle mass normalized for body surface area; ns = nonsignificant

nificantly lower in women whose pregnancy terminated before the 37th week of gestation. Also, the statistically significant influence on preterm termination of pregnancy had lower values of other parameters of systolic function such as EF, LVEDV, stroke volume of the left ventricle, SV index, and cardiac output. An increase of EF by 1% reduced the risk of preterm delivery by 26% (OR 0.740; 95% CI 0.585-0.937), while an increase in SV by 1 mL reduced that risk by 5% (OR 0.946; 95% CI 0.903-0.992). This could be explained by the fact that there is a lack of intravascular volume in women with the non-dipping pattern that influenced deterioration of maternal systolic function and, on the other hand, worse pregnancy outcome[15].

Vasapollo *et al.* also demonstrated that lower levels of CO, EF, LVEDV and SV were related to IUGR in pregnant women who had higher levels of BP, but within the reference values, compared with controls[7,10].

The more frequent presence of insomnia in pregnant women with the non-dipping pattern of BP could be explained by elevated BP during the night, which leads to waking and the inability to sleep again. Also, endothelial dysfunction that caused the lack of intravascular volume in non-dippers with gestational hypertension[15], is probably responsible for face and hand edema in these women, but also for visual disturbance and pain in the upper abdomen (also caused by edema of these organs). All of that may suggest a similar pathophysiological mechanism of the non-dipping pattern of BP in GH, and of preeclampsia. On the other hand, children born from pregnancies complicated by preeclampsia had increased blood pressure and body mass index later in life[34].

Interestingly, there was no significant difference in diastolic function in preterm delivery compared to delivery at term. This could be explained by the fact that diastolic function is not so affected by the lack of intravascular volume as the systolic function.

A recent study showed that personal and family history of vascular disease was recognized as a significant risk factor for the occurrence of preeclampsia[35]. On the other hand, hypertensive disorder in pregnancy, especially preeclampsia, is independently related with an increased 10-year risk of cardiovascular disease (CVD)[36], and women with preterm delivery are at an increased risk of future CVD events[37].

Our study revealed that preterm delivery was strongly associated with the non-dipping BP pattern, impaired maternal systolic function, and changes in LV geometry. Independent predictors of preterm delivery were average night-time systolic BP, myocardial mass index, and EF of the left ventricle.

Conclusion

The non-dipping pattern of blood pressure in GH is a prognostic factor for worse pregnancy outcome in terms of preterm delivery and lower birth weight. It is also associated with worse clinical findings of non-dipper women, which implies the presence of edema, upper abdominal pain, visual disturbance, and insomnia. Also, an increase in myocardial mass, and on the other hand, reduction of the left ventricular systolic function are related to preterm delivery.

All the above points highlight the need for more frequent monitoring of daytime and night-time BP, indicating that it is necessary to perform ECG examination in women during pregnancy. It may be possible, in this way, by timely administration of antihypertensive therapy, to postpone termination of pregnancy.

Conclusions for practice

If we start from the fact that the previously mentioned maternal symptoms and physical findings, preterm delivery, lower birth weight, and IUGR are often present in preeclampsia, but also in the non-dipping pattern of BP in GH, we cannot ignore the role of ABPM during pregnancy. Definition of the day-night BP profile is of great importance to determine pregnancies with GH who are at a higher risk of, on the one hand, deteriorating of cardiac function and heart remodeling and, on the other hand, of worse pregnancy outcome. Our results also suggest that the non-dipping pattern of BP in GH may be an important parameter for early identification of women at an increased risk of CVD later in life, and may be useful for CVD prevention.

Future research is needed to determine whether the pathophysiological mechanisms in pregnant women with a non-dipping pattern of BP in GH in the absence of proteinuria are more similar to preeclampsia compared to GH with a dipping BP pattern.

Study limitations

We acknowledge several study limitations. Despite the representative number of patients included in this study, results are based on a single center experience with all inherited constraints. Sampling bias consequential to the voluntary nature of participation in the survey could have potentially influenced the results and this was something we could not avoid. Also, various socio-economic features were not included in the analyses, although it would be extremely interesting to evaluate their impact. Lastly, even though we controlled for many potential confounders, there is a fair chance that some factors remained unobserved, for example, aspects of maternal IQ or personality, which could have affected the results.

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Sažetak

UČINAK *DIPPING* PROFILA GESTACIJSKE HIPERTENZIJE NA MAJČINE SIMPTOME I FIZIKALNE NALAZE, POROĐAJNU TEŽINU I PRIJEVREMENI POROĐAJ

Đ. Ilić, A. Ilić, S. Stojšić, A. Stojšić-Milosavljević, J. Papović, D. Grković, O. Rankov, A. Milovančev i *L. Velicki*

Cilj ovoga istraživanja bio je utvrditi povezanost *non-dipping* profila krvnog tlaka (KT) s prijevremenim porođajem, porođajnom težinom novorođenčeta te kliničkim i ehokardiografskim parametrima kod žena s gestacijskom hipertenzijom (GH). Istraživanje je obuhvatilo 60 žena s GH, 30 s *dipping* profilom KT (kontrolna skupina) i 30 *non-dippera* (ispitna skupina). Sve žene podvrgnute su kompletnoj ehokardiografiji i 24-satnom ambulantnom praćenju krvnog tlaka (*ambulatory blood pressure monitoring*, ABPM) tijekom trećeg trimestra, a ABPM je ponovljen 6-8 tjedana nakon porođaja. Ukupno 17 žena imalo je prijevremeni porođaj. Trinaest žena s prijevremenim porođajem imalo je *non-dipping* profil KT, dok su samo četiri žene imale *dipping* profil KT (0,01). Prosječni i maksimalni sistolički i dijastolički noćni KT imali su negativnu linearnu korelaciju s porođajnom težinom (p<0,0005). Ukupna vaskularna rezistencija (p<0,0005) i indeks mase miokarda lijeve klijetke (p=0,014) bili su znatno viši u skupini žena s prijevremenim porođajem, dok su parametri sistoličke funkcije, tj. ejekcijska frakcija (EF) (p=0,007) i brzina cirkumferentnog skraćenja miokarda lijevog ventrikla (p=0,042) bili statistički značajno sniženi u skupini žena s prijevremenim porođajem. Multivarijatna regresijska analiza pokazala je da su prosječni noćni sistolički KT, indeks mase lijevog ventrikla i EF identificirani kao nezavisni prediktori prijevremenog porođaja. Rezultati istraživanja pokazali su da postoji povezanost između *non-dipping* profila KT s prijevremenim porođajem, porođajnom težinom novorođenčeta i poremećajem hemodinamskog statusa majke u GH.

Ključne riječi: *Trudnice; Ehokardiografija; Hemodinamika; Krvni tlak; Prenatalna skrb*