Original Article
The diagnostic and predictive values of N-terminal pro-B-type natriuretic peptides in pregnancy complications and neonatal outcomes

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Abstract: Objective: To investigate the plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels relative to pregnancy complications and clarify the role of NT-proBNP in predicting pregnancy outcomes. Methods: A retrospective cohort study was conducted on 208 singleton pregnant women from August 2015 to October 2018. They were categorized into the early-onset PE (n=52), late-onset PE (n=32), GH (n=21), GDM (n=49), and healthy control (n=54) groups. The NT-proBNP concentrations were measured for all groups, and the correlation between the NT-proBNP levels and the pregnancy complications was analyzed. Results: The NT-proBNP levels were significantly higher in the early-onset and late-onset PE groups than in the other groups (P<0.05). The receiver operating characteristic curve showed that the plasma NT-proBNP levels had excellent diagnostic performance for early-onset and late-onset PE. The areas under the curve (AUCs) were 0.864 and 0.825 at the cut-off values of 142.3 pg/mL and 183.5 pg/mL for these two groups, respectively. The plasma NT-proBNP concentrations were positively correlated with the neonatal outcomes. The AUC was 0.788 when the cut-off value was 257.5 pg/mL. The high NT-proBNP level was associated with a low Apgar score and low birth weight. Conclusion: NT-proBNP is an effective indicator for assisting in the diagnosis of pregnancy complications and predicting newborn outcomes. NT-proBNP can be used to monitor early-onset and late-onset PE.

Keywords: NT-proBNP, preeclampsia, gestational hypertension, gestational diabetes mellitus, neonatal outcomes

Introduction

Preeclampsia (PE), gestational hypertension (GH), and gestational diabetes mellitus (GDM) are major pregnancy complications that can damage organs in pregnant women and are risk factors for neonatal death [1]. Recent surveys have shown that PE incidence is near 3.0%, and most patients have late-onset PE. The maternal mortality rate from PE is 4.2 per 100,000 women [2]. Morbidity from GH ranges from 5%-10%, accounting for 12% of all maternal deaths, and the GDM incidence is approximately 2%-5% among pregnant women [3]. B-type natriuretic peptide (BNP) is a vasoactive peptide that was first isolated and purified from porcine brain tissues by Sudoh in 1988 [4]. Ventricular load and/or wall tension are the main factors that stimulate cardiomyocytes to secrete BNP. NT-proBNP is a deactivated BNP formed by the cleavage of proBNP amino acids. NT-proBNP is regarded as a biomarker for cardiac failure and plays an important role in heart disease diagnosis and prognosis [5]. Pregnant women often have increased blood viscosity and altered vascular function, which further aggravates the heart load, causing cardiac dysfunction. At present, few studies have evaluated the role of NT-proBNP in diagnosing pregnancy complications, and the relationship between NT-proBNP and pregnancy outcomes from pregnancy complications has rarely been reported. This study investigated the plasma NT-proBNP levels in patients with PE, GH and GDM to provide a basis for the clinical and differential diagnoses of pregnancy complications and to provide reference indexes for predicting pregnancy outcomes.

Materials and methods

Study population

We conducted a retrospective cohort study on the pregnant women who underwent routine prenatal examinations at the Department of Gynecology and Obstetrics, West China Second University Hospital, between August 2015 to October 2018. A total of 190 patients with clinically diagnosed GDM, GH, and PE were selected. Multiple pregnancies (n=4), pre-pregnancy diabetes (n=3), chronic hypertension or heart disease (n=7), severe liver or renal dysfunction (n=3), chronic hypertension and heart problems (n=10) and women who presented with concomitant GH and GDM (n=9) were excluded from this analysis. The remaining 154 subjects were divided into four groups: early-onset PE (n=52), late-onset PE (n=32), GH (n=21), and GDM (n=49). 54 singleton pregnant women with normal blood pressure and blood glucose levels were randomly selected as healthy controls. The patients' ages, weights, heights, gestational ages, parity and neonatal outcomes were recorded. The study was approved by the Clinical Research Ethics Committee of West China Second University Hospital (No. 2015-025), and written informed consent was obtained from each participant.

Diagnostic criteria

The diagnostic criteria for PE were a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg in previously normotensive women, with two or more measurement intervals at least 6 hours apart, and urine protein (+) or ≥300 mg/24 h without a concomitant urinary tract infection. PE occurring before 34 gestational weeks was defined as early-onset PE; PE occurring at or after 34 gestational weeks was defined as late-onset PE [6]. GH was defined as a systolic pressure >140 mmHg or a diastolic pressure >90 mmHg from two or more measurement intervals of at least 6 hours apart, occurring after 20 weeks of pregnancy, without accompanying proteinuria [7]. GDM was determined via 75 g glucose tolerance testing after fasting overnight at 24-28 gestational weeks. GDM was diagnosed if one of the plasma glucose values met or exceeded 92 mg/dL at 0 h, 180 mg/dL at 1 h, or 153 mg/dL at 2 h after a 75 g glucose load [8]. Chronic hypertension was defined as having been diagnosed with hypertension before pregnancy or at less than 20 weeks' gestation [6]. Chronic kidney disease was defined as abnormalities of the kidney structure or function according to the 2012 KDIGO guidelines [9]. Midwives or pediatricians provided the one-minute Apgar scores according to standardized procedures [10]. Preterm delivery was defined as delivery before completing 37 gestational weeks [11]. Stillbirth was defined as fetal death after 28 gestational weeks [12].

Plasma NT-proBNP analysis

The plasma samples were collected immediately after determining the relevant diagnosis. Intravenous blood (3 mL) was collected from all the patients and placed into heparin lithium anticoagulant vacuum tubes. The plasma was isolated via centrifuge (3000 r/min for 10 minutes) and stored at -80°C for subsequent determination. A Vitros 5600 automatic biochemical immunoanalyzer (*Ortho* Clinical Diagnostics, New Brunswick, NJ, USA) was used to test for NT-proBNP via enhanced immunochemical luminescence. All the testing procedures were performed in accordance with each instrument's instructions.

Statistical analysis

All the data were analyzed using SPSS 21.0 (IBM, Armonk, NY, USA). The study participants' basic data are presented as the mean ± standard deviation (x±s). T-tests were performed for the between-group comparisons, one-way analyses of variance were used to compare multiple groups, and chi-square tests were used to analyze the countable data. The NT-proBNP values are expressed as medians and ranges, and the plasma NT-proBNP levels were compared using Mann-Whitney U tests. Spearman's correlation coefficient was used to evaluate the correlations. Receiver operating characteristic (ROC) curves were used to evaluate the use of NT-proBNP to diagnose GH, GDM, and PE. Alpha was set at 0.05, and *P*<0.05 was considered statistically significant.

Results

The study participants' basic data

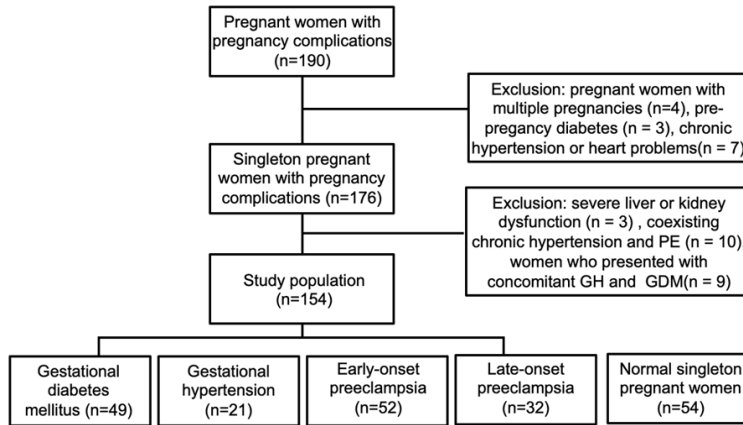The women were divided into the early-onset PE (n=52), late-onset PE (n=32), GH (n=21),

Figure 1. Flow chart showing the population distribution of women with pregnancy complications.

GDM (n=49), and healthy control groups (n=54) (**Figure 1**). Age, systolic blood pressure, diastolic blood pressure, and gestational weeks differed significantly among the groups (*P*<0.05), but the body mass index (BMI) and the fasting blood glucose levels did not (**Table 1**).

Analysis of the NT-proBNP concentrations

The plasma NT-proBNP concentrations were significantly higher in the early-onset PE and late-onset PE groups than they were in the control, GH, and GDM groups. However, the plasma NT-proBNP levels did not significantly differ between the early-onset PE and late-onset PE groups (*P*>0.05) or among the GH, GDM, and control groups (*P*>0.05; **Table 2**).

Correlation analysis of the NT-proBNP and basic pregnancy complication indicators

The plasma NT-proBNP levels were negatively correlated with gestational age and positively correlated with systolic and diastolic blood pressure (**Table 3**). The age, BMI index, fasting blood glucose, and plasma NT-proBNP concentrations were not correlated.

Pregnancy outcome analysis

The pregnancy outcomes differed significantly among the groups (*P*<0.05). The incidence of stillbirth was significantly higher in the early-onset PE group than in the other groups, and the neonatal outcomes were significantly worse in both the early-onset PE and late-onset PE groups than in the other groups (**Table 4**). The

Apgar scores and birth weights were significantly lower in the early-onset PE group than in the other groups (*P*<0.001). The birth weights were significantly lower in the late-onset PE group than in the GH and GDM groups (*P*<0.001) (**Table 5**). The NT-proBNP levels were negatively associated with the Apgar scores and birth weights (**Table 6**).

Analysis of the NT-proBNP diagnostic accuracy

In this study, NT-proBNP showed a good diagnostic efficacy for PE but a weak diagnostic efficacy for GH and GDM. In the early-onset PE group, the area under the curve (AUC) was 0.864 (**Figure 2A**), and the Youden index was 0.531 when the cut-off value was 142.3 pg/mL. In the late-onset PE group, the AUC was 0.825 (**Figure 2B**), and the Youden index was 0.534 when the cut-off value was 183.5 pg/mL. We combined the stillbirth group with the premature group to form an adverse neonatal outcome group considering the small number of cases. Plasma NT-proBNP played a diagnostic role in newborn outcomes; the AUC was 0.788, and the Youden index was 0.436 when the cut-off value was 257.5 pg/mL (**Figure 2C**; **Table 7**).

Discussion

Several factors can affect NT-proBNP secretions during pregnancy. For example, as BMI increases, the plasma NT-proBNP concentrations decrease [13]. Pregnant women with BMIs ≥30 have lower plasma NT-proBNP concentrations than do those with BMIs <30 [14]. In our study, the plasma NT-proBNP concentrations were less affected by BMI in pregnant women, possibly owing to the limited BMI range. As pregnant women age, the risk of hypertension during pregnancy increases [15], which may affect NT-proBNP secretions from the heart. However, in our study, age and plasma NT-proBNP were not significantly correlated, possibly owing to the more concentrated age range of our subjects.

Table 1. Analysis of the participants' basic data

	control group (n=54)	early-onset PE (n=52)	late-onset PE (n=32)	GH (n=21)	GDM (n=49)	P
Age, years	30.7±3.7	31.4±6.1	33.3±5.9	31.1±4.3	33.5±6.0	0.043
Systolic blood pressure, mmHg	112.2±10.3	160.6±18.3	152.3±11.0	145.2±5.6	114.2±9.5	<0.001
Diastolic blood pressure, mmHg	71.6±8.2	104.3±14.3	94.8±7.8	94.4±5.1	71.4±7.6	<0.001
Gestational week, weeks	38.8±0.9	30.2±2.6	36.7±2.1	38.4±0.8	38.0±2.3	<0.001
Fasting blood glucose, mmol/L	4.7±0.6	4.8±0.8	4.6±0.9	4.5±1.0	5.1±1.0	0.345
BMI, Kg/m^2	26.3±2.6	27.7±3.9	28.1±4.1	28.4±3.9	27.5±5.7	0.220

Table 2. Comparison of the plasma NT-proBNP concentrations among the groups

	control group	early-onset PE	late-onset PE	GH	GDM
NT-proBNP, pg/ml	75.3 (42.0-160)	332 (155.5-788.5)[a,b,c]	263 (143-743.8)[a,b,c]	65.8 (35.5-178)	59 (37.4-142)

Note: [a]compared with the normal group, $P<0.05$; [b]compared with the GH group, $P<0.05$; [c]ompared with the GDM group, $P<0.05$.

Table 3. Correlation analysis between the NT-proBNP and basic indicators

	NT-proBNP	
	Spearman correlation	P
Age	-0.055	0.434
Gestational weeks	-0.492	<0.001
BMI index	0.045	0.523
Systolic blood pressure	0.434	<0.001
Diastolic blood pressure	0.383	<0.001
Fasting blood glucose	-0.057	0.414

One previous study showed that NT-proBNP is closely associated with pregnancy complications [16]. In the GH pathogenesis, increased blood pressure in pregnant women is associated with an increased cardiac burden, excessive ventricular volume and pressure overload, and increased wall tension or stretch stimulation of ventricular myocytes, leading to increased NT-proBNP secretions. Although we found that the systolic and diastolic blood pressures were correlated with the plasma NT-proBNP levels, these levels did not significantly differ between the patients with GH and the normal controls (P=0.706). NT-proBNP also lacked power for diagnosing GH, possibly because NT-proBNP originates from the heart as well as the placenta [17]. PE affected the heart and more strongly affected the placenta than did GH. In addition, the effect of GH on the heart can often be adjusted by reducing the traction on the heart, indicating that placental factors more prominently impact the plasma NT-proBNP. We will enroll more GH patients in future studies to

analyze the relationships between these factors.

GDM is a clinically common disease manifested as increased peripheral blood glucose due to abnormal glucose tolerance during pregnancy. Poor blood glucose control can aggravate the abnormal glucose metabolism, thus thickening the small blood vessels and capillary walls, causing lumen narrowing and arterial spasms, and eventually leading to increased blood pressure and heart failure [18]. A study confirmed that poor glycemic control during pregnancy promotes the risk of high blood pressure [19]. However, the plasma NT-proBNP concentrations did not significantly differ between the GDM patients and the normal controls in our study, which is consistent with the results published [14]. We also found that the blood glucose levels and the NT-proBNP concentrations were weakly correlated.

PE is a serious complication during pregnancy. It varies considerably in maternal symptoms and fetal outcomes and is characterized by occult onset and multiple organ dysfunction. Low-dose aspirin and low-dose calcium have been proved to be effective in the prevention of early-onset preeclampsia among high-risk patients. However, there is a certain gap in clinical promotion [7]. Therefore, early diagnosis and treatment for PE is very important for improving pregnancy outcomes. At present, the PE pathogenesis remains unclear. A study compared the plasma NT-proBNP levels in PE patients and healthy pregnant women and demonstrated that elevated NT-proBNP levels

Table 4. Neonatal outcome analysis among the groups

	control group	early-onset PE	late-onset PE	GH	GDM
Full-term and mature	54 (100%)	0	15 (46.9%)	21 (100%)	41 (83.7%)
Premature babies	0	33 (63.5%)	17 (53.1%)	0	8 (16.3%)
Stillbirth	0	19 (26.5%)	0	0	0

Table 5. Apgar score and birth weight analysis among the groups

	control group	early-onset PE	late-onset PE	GH	GDM
Apgar score	9.96±0.19	7.4±3.0[a,b,c,d]	9.38±1.77	10±0	9.81±0.78
Birth weight (g)	3356.6±381.2	1329.9±508.0[a,b,c,d]	2526.8±774.8[a,b,c]	3333.3±346.2	3179.5±722.6

Note: [a]compared with the normal group, $P<0.05$; [b]compared with the GH group, $P<0.05$; [c]compared with the GDM group, $P<0.05$; [d]compared with the late-onset PE group, $P<0.05$.

Table 6. Correlation analysis between NT-proBNP and Apgar score and birth weight

	NT-proBNP	
	Spearman correlation	P
Apgar score	-0.338	<0.001
Birth weight (g)	-0.428	<0.001

are associated with increased left ventricular mass, left ventricular end-systolic and end-diastolic volumes, and significantly reduced left ventricular ejection fractions [20]. The pathophysiological processes of PE includes renin-angiotensin system disorder and blood volume retention caused by peripheral vasoconstriction. These pathological alterations lead to increased ventricular NT-proBNP secretions [21]. A hypertensive status in PE patients causes significantly increased NT-proBNP concentrations [22]. The serum NT-proBNP levels are associated with PE severity during pregnancy [23]. Our results were consistent with those of previous studies. The plasma NT-proBNP levels were significantly higher in the PE patients than in the normal control group, and NT-proBNP had a good diagnostic efficacy in both the early-onset and late-onset PE groups, indicating that the plasma NT-proBNP levels can be used as important indices for clinically diagnosing PE. We also found that diastolic/systolic blood pressure is correlated with plasma NT-proBNP during pregnancy. Blood pressure changes in patients with PE are related to the maternal insufficiency of placental blood perfusion [24]. Insufficient placental blood perfusion induces the release of relevant placental factors into the blood, promotes systemic inflammatory responses and the activation of

vascular endothelial dysfunction, regulates blood pressure, and further affects NT-proBNP synthesis and secretions [14, 25]. Maternal insufficiency of blood perfusion is more significant in early-onset PE than in late-onset PE because early-onset PE is more severely affected by placental factors, and late-onset PE is mainly related to fetal metabolism and maternal load [26]. In our study, NT-proBNP did not significantly differ between early-onset and late-onset PE, possibly because of their different etiologies. Although the influence of placental factors on the maternal body was weakened in late-onset PE, the fetal metabolism led to high maternal loads, and NT-proBNP was constantly released into the blood. Thus, the NT-proBNP levels did not significantly differ between early-onset and late-onset PE. In addition, the sample size was small; therefore, drawing firm conclusions from these results was difficult.

We studied neonatal outcomes in women with gestational complications and found that neonatal outcomes were significantly affected in early-onset and late-onset PE groups, and the incidences of adverse outcomes, such as preterm births and stillbirths, were higher in these two groups. Although the blood NT-proBNP levels did not significantly differ, the adverse outcomes in the late-onset PE group were better than those in the early-onset PE group owing to the different pathogenic bases of the two groups. Early-onset PE affected placental blood perfusion, but late-onset PE led to a longer gestational period, and the children were less influenced [2]. Therefore, early-onset PE more severely impacts neonatal outcomes. The neonatal outcomes were consistent with the Apgar
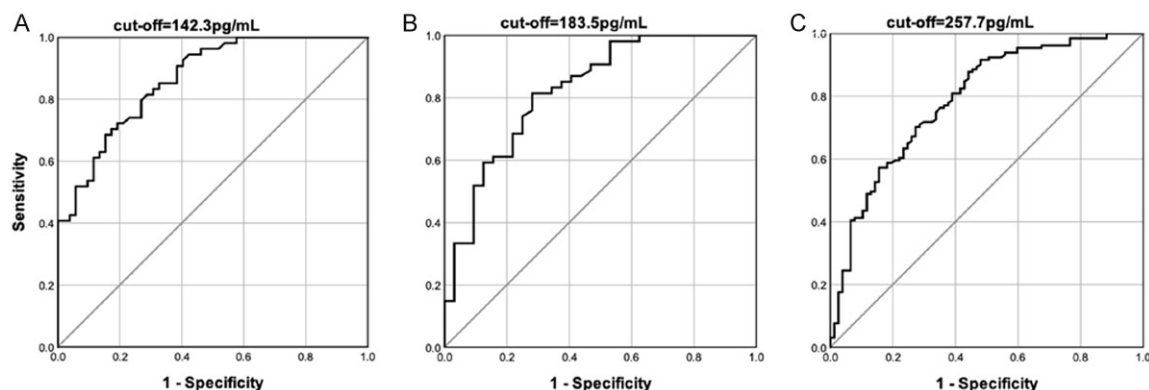
Figure 2. An accuracy analysis of NT-proBNP in early-onset PE, late-onset PE, and newborn outcomes. ROC curve-relationship between NT-proBNP levels (pg/ml) and occurrence of early-onset PE (A), late-onset PE (B) and newborn outcomes (C).

Table 7. Diagnostic efficacy of NT-proBNP for pregnancy complications and neonatal outcomes

	AUC	-95% CI	+95% CI	sensitivity	specificity	Youden index	P
Early-onset PE	0.864	0.799	0.930	0.827	0.704	0.531	<0.001
Late-onset PE	0.825	0.733	0.917	0.719	0.815	0.534	<0.001
Neonatal outcome	0.788	0.724	0.853	0.558	0.878	0.436	<0.001

Note: The AUC of the GH and GDM groups was <0.5 (not shown).

scores and birth weight. The Apgar scores and birth weights were significantly lower in the early-onset PE group than in the late-onset PE group.

This study had some limitations. First, we only researched the value of NT-proBNP in diagnosing pregnancy complications. We will include more cases in the later stages and prospectively measure the NT-proBNP levels serially to provide a valuable reference for predicting pregnancy complications. Secondly, the relationship between the prognoses in PE and NT-proBNP is not clear at present. In our subsequent research, we shall pay more attention to the concentrations of NT-proBNP as they correlate with the therapeutic effects in PE patients.

In conclusion, NT-proBNP concentrations have a good diagnostic value for early-onset and late-onset PE. NT-proBNP can be used to clinically diagnose PE and has a good application value for auxiliary and differentially diagnosing clinical complications during pregnancy. NT-proBNP is correlated with pregnancy outcomes and can be used to predict pregnancy outcomes.

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Disclosure of conflict of interest

None.

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References

[1] Arnaout R, Nah G, Marcus G, Tseng Z, Foster E, Harris IS, Divanji P, Klein L, Gonzalez J and Parikh N. Pregnancy complications and prema-

ture cardiovascular events among 1.6 million California pregnancies. Open Heart 2019; 6: e000927.

[2] Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A and Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstet Gynecol 2014; 124: 771-781.

[3] Toljic M, Egic A, Munjas J, Karadzov Orlic N, Milovanovic Z, Radenkovic A, Vuceljic J and Joksic I. Increased oxidative stress and cytokinesis-block micronucleus cytome assay parameters in pregnant women with gestational diabetes mellitus and gestational arterial hypertension. Reprod Toxicol 2017; 71: 55-62.

[4] Sudoh T, Kangawa K, Minamino N and Matsuo H. A new natriuretic peptide in porcine brain. Nature 1988; 332: 78-81.

[5] Jhund PS, Anand IS, Komajda M, Claggett BL, Mckelvie RS, Zile MR, Carson PE and Mcmurray JJ. Changes in N-terminal pro-B-type natriuretic peptide levels and outcomes in heart failure with preserved ejection fraction: an analysis of the I-preserve study. Eur J of Heart Fail 2015; 17: 809-817.

[6] Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G and Ishaku S; International Society for the Study of Hypertension in Pregnancy (ISSHP). The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens 2018; 13: 291-310.

[7] Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, McAuliffe F, da Silva Costa F, von Dadelszen P, McIntyre HD, Kihara AB, Di Renzo GC, Romero R, D'Alton M, Berghella V, Nicolaides KH and Hod M. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet 2019; 145 Suppl 1: 1-33.

[8] Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, Roura LC, McIntyre HD, Morris JL and Divakar H. The international federation of gynecology and obstetrics (FIGO) initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. Int J Gynecol Obstet 2015; 131 Suppl 3: S173-S211.

[9] Andrassy KM. Comments on 'KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease'. Kidney Int 2013; 84: 622-623.

[10] Mario R, Wauer RR, Katerina S and Helmut K. The Apgar score. Pediatrics 2006; 118: 1315-1316.

[11] Lawn JE, Gravett MG, Nunes TM, Rubens CE and Stanton C; GAPPS Review Group. Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data. BMC Pregnancy Childbirth 2010; 10 Suppl 1: S1.

[12] Swaminathan A, Fell DB, Regan A, Walker M and Corsi DJ. Association between interpregnancy interval and subsequent stillbirth in 58 low-income and middle-income countries: a retrospective analysis using demographic and health surveys. Lancet Glob Health 2020; 8: e113-e122.

[13] Balaceanu A. B-type natriuretic peptides in pregnant women with normal heart or cardiac disorders. Med Hypotheses 2018; 121: 149-151.

[14] Sadlecki P, Grabiec M and Walentowicz-Sadlecka M. Prenatal clinical assessment of NT-proBNP as a diagnostic tool for preeclampsia, gestational hypertension and gestational diabetes mellitus. PLoS One 2016; 11: e0162957.

[15] Luke B and Brown MB. Elevated risks of pregnancy complications and adverse outcomes with increasing maternal age. Hum Reprod 2007; 22: 1264.

[16] Franz MB, Franz MB, Andreas M, Schiessl B, Zeisler H, Neubauer A, Kastl SP, Hess G, Rhomberg F, Zdunek D, Maurer G, Schlembach D, Heinze G, Szekeres T and Gottsauner-Wolf M. NT-proBNP is increased in healthy pregnancies compared to non-pregnant controls. Acta Obstet Gynecol Scand 2011; 88: 234-237.

[17] Junus K, Wikström AK, Larsson A and Olovsson M. Placental expression of proBNP/NT-proBNP and plasma levels of NT-proBNP in early- and late-onset preeclampsia. Am J Hypertens 2014; 27: 1225-1230.

[18] Hong LF, Li XL, Luo SH, Guo YL, Zhu CG, Qing P, Wu NQ and Li JJ. Association of fibrinogen with severity of stable coronary artery disease in patients with type 2 diabetic mellitus. Dis Markers 2014; 2014: 485687.

[19] Ferdinand KC, White WB, Calhoun DA, Lonn EM, Sager PT, Brunelle R, Jiang HH, Threlkeld RJ, Robertson KE and Geiger MJ. Effects of the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide on ambulatory blood pressure and heart rate in patients with type 2 diabetes mellitus. Hypertension 2014; 64: 731.

[20] Borghi C, Esposti DD, Immordino V, Cassani A, Boschi S, Bovicelli L and Ambrosioni E. Relationship of systemic hemodynamics, left ventricular structure and function, and plasma natriuretic peptide concentrations during pregnancy complicated by preeclampsia. Am J Obstet Gynecol 2000; 183: 140-147.

[21] Benedetto C, Zonca M, Marozio L, Dolci C, Carandente F and Massobrio M. Blood pressure patterns in normal pregnancy and in preg-

nancy-induced hypertension preeclampsia, and chronic hypertension. Obstet Gynecol 1996; 88: 503-510.

[22] Mcdonald SD, Lutsiv O, Dzaja N and Duley L. A systematic review of maternal and infant outcomes following magnesium sulfate for pre-eclampsia/eclampsia in real-world use. Int J Gynecol Obstet 2012; 118: 90-96.

[23] Bakacak M, Serin S, Ercan O, Kostü B, Bakacak Z and Kiran H. Association of serum N-terminal pro-brain natriuretic peptide levels with the severity of preeclampsia. J Matern-Fetal Neo M 2015; 29: 2802-2806.

[24] Valensise H, Vasapollo B, Gagliardi G and Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension 2008; 52: 873-80.

[25] Kale A, Kale E, Yalinkaya A, Akdeniz N and Canoruç N. The comparison of amino-terminal probrain natriuretic peptide levels in pre-eclampsia and normotensive pregnancy. J Perinat Med 2005; 33: 121-4.

[26] Crispi F, Domínguez C, Llurba E, Martín-Gallán P, Cabero L and Gratacós E. Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction. Am J Obstet Gynecol 2006; 195: 201-207.