CEOG Clinical and Experimental Obstetrics & Gynecology

Original Research

High mean blood pressure during the first trimester is predictive of future preeclampsia development in healthy pregnant women: a cohort study in Korea

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Summary

The objective of this study was to determine the association between blood pressure (BP) in early pregnancy and the development of preeclampsia. Among 3,364 pregnant women who began perinatal care in their first trimester and were followed up until delivery, 3,003 healthy pregnant women were included after excluding 354 with comorbidities during pregnancy and seven with missing BP and proteinuria data at follow-up. The mean values of systolic and diastolic BP measurements during the first trimester were retrieved from electronic medical records. Mean BP (MBP) was calculated and plotted using the penalized smoothing spline method to analyze its association with the development of preeclampsia. In the univariate analysis, increased MBP, twin pregnancy, and high body weight were associated with increased odds for the development of preeclampsia; however, only increased MBP and twin pregnancy maintained statistical significance in multivariate analysis. A MBP ≥ 91 mmHg was associated with the development of preeclampsia [adjusted odds ratio (OR) 2.60, 95% confidence interval (CI), 1.42-4.77, $p = 0.002$]. Increased BP during the first trimester in previously healthy pregnant women was associated with the subsequent development of preeclampsia. This is the first study on the association between BP in the early pregnancy period and the development of preeclampsia in healthy Korean pregnant women.

Key words: Non-linear association; Blood pressure; Preeclampsia.

Introduction

Hypertensive disorders occur in approximately 10% of all pregnancies [1]. Approximately half (5-6%) of these disorders can be classified as preeclampsia, either alone or superimposed on chronic hypertension [1, 2]. Preeclampsia is the most critical complication causing maternal mortality and morbidity during pregnancy. In the United States, about 12% of maternal deaths between 1998 and 2005 were attributable to preeclampsia or eclampsia [3].

Since preeclampsia is a progressive disorder, premature delivery is mandatory in many cases. This preeclampsia-related prematurity of newborns is known to result in poor neonatal outcomes [4]. Therefore, the identification of risk factors for the development of preeclampsia is essential to reduce adverse pregnancy outcomes. Nulliparity, multifetal gestation, maternal age, and obesity are well-known variables associated with the development of preeclampsia [5].

Several biomarkers related to preeclampsia have also been identified, such as soluble fms-like tyrosine kinase 1, [6-8] ADAM12 [9], and pregnancy-associated plasma protein-A [10]. However, the predictive value of clinical data and biomarkers is not sufficient to predict preeclampsia [11] and screening beyond obtaining a previous medical history is not recommended according to the current guidelines set forth by the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy (2013) [12]. Although the etiology of preeclampsia is still unclear, so-called defective placentation and subsequent vasoconstriction are accepted as key pathophysiological mechanisms for the development of preeclampsia [1, 13-15]. Hence, elevation of blood pressure (BP) caused by vasoconstriction may occur even earlier than preeclampsia is clinically diagnosed and thus may be an important surrogate marker for subsequent preeclampsia. Therefore, the present authors performed the current study to determine whether mean BP (MBP) during the first trimester is associated with preeclampsia development in healthy Korean pregnant women.

Materials and Methods

Between 2003 and 2015, 3,364 pregnant women began perinatal care in the first trimester and gave birth at Seoul National University Bundang Hospital. The authors excluded 129 patients with chronic hypertension, defined as systolic BP above 140 mm Hg or diastolic BP above 90 mm Hg. They further excluded 225 women with one or more comorbidities defined by the criteria in Table 1 [16-18]. An additional seven women were excluded from

Revised manuscript accepted for publication July 17, 2018

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVI, n. 5, 2019
doi: 10.12891/ceog4792.2019

7847050 Canada Inc.
www.irog.net

Published: 10 October 2019

Table 1. — *Definitions of comorbidities.*

Comorbidity	Definitions
Chronic hypertension	(1) ICD-10 codes I129, I10, I15, and H3502 before index pregnancy or (2) Use of anti-hypertensive drugs before index pregnancy or (3) SBP ≥140 mm Hg two or more times or DBP ≥ 90 mm Hg two or more times before 20 weeks of gestation
Possible	(1) Single record of SBP ≥ 140 mm Hg chronic hypertension or DBP ≥9mm Hg before 20 weeks of gestation or (2) Mean SBP before 20 weeks of gestation ≥ 140 mm Hg or mean DBP before 20 weeks of gestation ≥ 90 mmHg, but not fulfilling criteria of chronic hypertension
Preexisting diabetes	(1) ICD-10 codes E10–E14 before index pregnancy or (2) Use of insulin or oral glucose-lowering drugs before index pregnancy
Chronic kidney disease	(1) ICD-10 code N18 before index pregnancy (2) Dipstick urine protein test results ≥ 1+ two or more times before 20 weeks of gestation (3) Biopsy-proven glomerulonephritis before index pregnancy
Congestive heart failure	ICD-10 codes I11, I13, and I50
Peripheral vascular disease	ICD-10 codes I71–74, and I77
Cerebrovascular disease	ICD-10 codes I60 – 69, G45 – 46, and G81 – G83
Chronic pulmonary disease	ICD-10 codes J40–47, and J60–J66
Connective tissue disorder	ICD-10 codes M05 – M08, and M30 –M36
Peptic ulcer disease	ICD-10 codes K25 – K28
Liver disease	ICD-10 codes B18, I85, K70–76
Malignancy	ICD-10 codes C00 – C96

ICD-10: International Classification of Diseases, 10th revision; SBP: systolic blood pressure; DBP: diastolic blood pressure.

the study due to missing BP and proteinuria data at follow-up, inhibiting a determination of the development of preeclampsia. Finally, the authors included 3,003 healthy pregnancy women in the analysis (Figure 1). The study protocol complied with the Declaration of Helsinki and received full approval from the Seoul National University Bundang Hospital Institutional Review Board (B-1508/310-105). The need for informed consent was waived due to the retrospective nature of the study.

Demographic, physiologic, and laboratory data during the perinatal period were gathered from the hospital's electronic medical records database. Manual data verification was performed after patient datasets were merged. In the prenatal care center, trained nurses measured each patient's BP and weight at every visit and performed dipstick protein tests during visits after 20 weeks of gestation. The earliest recorded weight during the first trimester was used to calculate body mass index (weight [kg] per square of height [m^2]). BP was measured using an automated BP monitor after at least five minutes of rest. If the measured BP was ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic, the authors remeasured and recorded the lower value as the clinical BP. The mean values of the systolic and diastolic BP measurements during the first trimester were retrieved, and the MBP, the main factor of interest in this study, was calculated as follows: mean BP = diastolic BP + (systolic BP-diastolic BP)/3. MBP was then divided into quartiles for analysis: 1Q = < 77 mm Hg, 2Q=77-82 mm Hg, 3Q=82-87 mm Hg, and 4Q ≥ 87 mm Hg. Hypertension was defined as two or more instances of systolic BP ≥ 140 mm Hg or two or more instances of diastolic BP ≥ 90 mm Hg. Gestational hypertension was defined as the development of hypertension after 20 weeks of gestation. New-onset proteinuria was defined by two or more instances of dipstick urine protein test results ≥ 1+ after 20 weeks of gestation. Preeclampsia was defined as gestational hypertension with new-onset proteinuria. Data were expressed as mean ± standard deviation for continuous variables and as percentages for categorical variables.

P-trend was analyzed by a linear-term of one-way analysis of variance (ANOVA) for continuous variables and by a linear-by-linear association for categorical variables. Differences were analyzed by Bonferroni post-hoc analysis of one-way ANOVA for continuous variables and chi-squared tests for categorical variables. Odds ratio (OR) and its 95% CI were calculated by logistic regression analysis. A p value of < 0.05 was considered statistically significant. In multivariate analysis, covariates were chosen based on clinical relevance [5, 19].

The relationship between MBP during the first trimester and preeclampsia development was plotted with the penalized smoothing spline method using the 'pspline' package in the R statistics software (version 3.03). All other analyses were performed using SPSS Statistics software.

Results

The mean age of the study population was 32.5 years, and 66.4% of women were nulliparous and 8.7% had a twin pregnancy. The mean values of systolic and diastolic BP during the first trimester were 114.7 mm Hg and 65.1 mm Hg, respectively. Consequently, the mean MBP was 81.6 mm Hg. A total of 479 (16.0%) women experienced gestational hypertension during their pregnancy, of whom 64 (2.1%) were finally diagnosed with preeclampsia.

The authors analyzed the clinical characteristics of the study population by MBP quartile (Table 2). As MBP increased, the proportions of nulliparous and twin pregnancies increased. The mean MBP values per quartile were as follows: 73 mm Hg in 1Q, 79.6 mm Hg in 2Q, 84.4 mm Hg, and 91.4 mm Hg in 4Q. Patient weight was positively associated with MBP quartile, unlike patient height, which was not associated with MBP. Additionally, the authors performed a logistic regression analysis to identify risk factors for developing preeclampsia (Table 3). In the univariate analysis, increased MBP, twin pregnancy, and increased weight were associated with increased odds of preeclampsia development; however, only increased MBP and twin pregnancy maintained statistical significance in the multivariate analysis.

The authors further explored the relationship between MBP quartile and preeclampsia development (Figure 2).

In the analysis, the odds of developing preeclampsia were

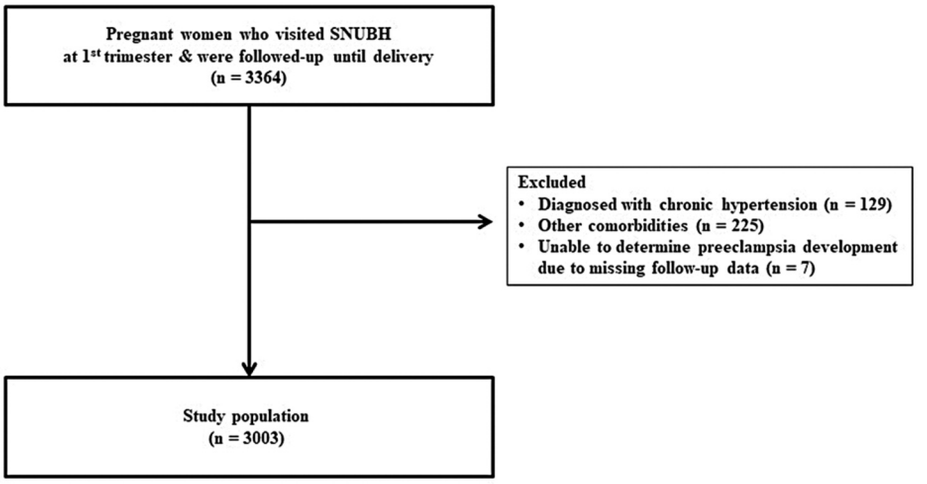

Figure 1. — Flowchart of the study population.

Table 2. — *Clinical characteristics of the study population according to quartile of mean blood pressure during the first trimester.*

	Quartile of MBP				
	1Q (n = 823)	2Q (n = 771)	3Q (n = 719)	4Q (n = 690)	*p*-trend
Age (years)	32.4 ± 3.7	32.3 ± 3.5	32.4 ± 3.6	32.8 ± 4.0	0.017
Nulliparity	63.2	65.9	69.0*	68.1*	0.018
Twin pregnancy	7.4	7.1	7.6	13.0*	<0.001
SBP (mm Hg)	104.1 ± 6.0	112.1 ± 5.4*	118.2 ± 5.2*	126.5 ± 6.7*	<0.001
DBP (mm Hg)	57.4 ± 3.8	63.3 ± 3.0*	67.5 ± 2.7*	73.9 ± 4.6*	<0.001
MBP (mm Hg)	73.0 ± 3.2	79.6 ± 1.4*	84.4 ± 1.4*	91.4 ± 3.9*	<0.001
Height (cm)	160.5 ± 4.9	161.0 ± 5.1	160.8 ± 5.1	161.1 ± 5.3	0.061
Weight (kg)	53.0 ± 5.8	55.0 ± 6.7*	56 ± 7.4*	58.7 ± 9.2*	<0.001
BMI (kg/m2)	20.6 ± 2.1	21.2 ± 2.4*	21.7 ± 2.8*	22.6 ± 3.4*	<0.001

*SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; BMI: body mass index. Values are expressed as mean ± standard deviation for continuous variables and percentage for categorical variables. P-trend was analyzed by a linear-term of one-way ANOVA for normally distributed continuous variables and a linear-by-linear association for categorical variables. *p < 0.05 when compared to 1Q of MBP using Bonferroni post-hoc analysis of one-way ANOVA for normally distributed continuous variables and chi-square test for categorical variables.*

Table 3. — *Risk factors for the development of preeclampsia.*

	Univariate		Multivariate	
	OR (95% CI)	*p*	OR (95% CI)	*p*
MBP (mm Hg)	1.08 (1.04–1.11)	<0.001	1.07 (1.03–1.10)	<0.001
Age (years)	1.02 (0.96–1.09)	0.530	1.00 (0.93–1.07)	0.905
Nulliparity (yes *vs*. no)	1.20 (0.70–2.07)	0.504	1.00 (0.55–1.80)	0.995
Twin pregnancy (yes *vs*. no)	4.34 (2.48–7.60)	<0.001	3.92 (2.19–7.03)	<0.001
Height (cm)	1.00 (0.95–1.05)	0.971	0.98 (0.93–1.04)	0.528
Weight (kg)	1.03 (1.01–1.06)	0.020	1.02 (0.99–1.05)	0.241

OR: odds ratio; CI: confidence interval; MBP: mean blood pressure. OR and its CI were calculated using logistic regression analysis. In multivariate analysis, all above variables were chosen as covariates. The reference of continuous variables was per 1 unit increase.

only statistically significant in comparing 4Q *vs*. 1Q (OR 2.92, $p = 0.012$), suggesting a non-linear relationship. This relationship was confirmed by using penalized smoothing splines (Figure 3). The odds of developing preeclampsia were increased from MBP of 91 mm Hg. The OR of MBP ≥ 91 mm Hg for the preeclampsia development was 2.60 (95% CI 1.42-4.77, $p = 0.002$) after adjusting for age, nulliparity, twin pregnancy, height, and weight. Increased age, nulliparity, decreased height, and increased weight were all associated with increased odds of MBP ≥ 91 mm Hg (Table 4).

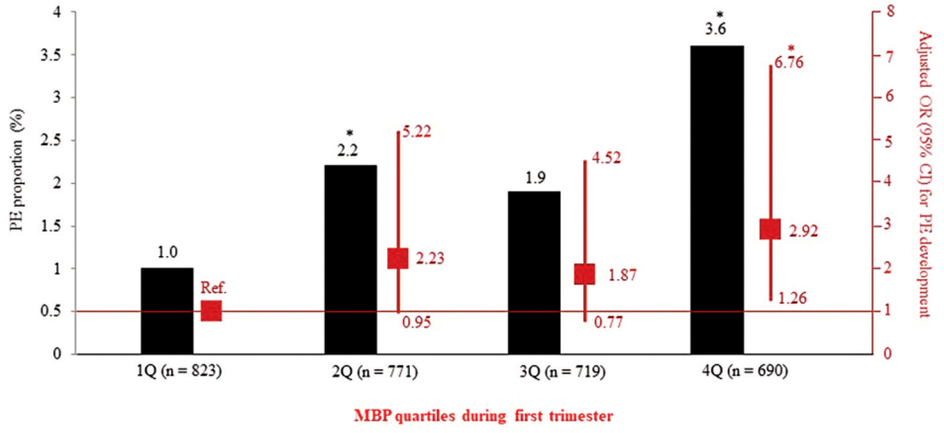

Figure 2. — Association between quartiles of MBP and preeclampsia development. Q: quartile; PE: preeclampsia; OR: odds ratio; CI: confidence interval; MBP: mean blood pressure. Adjusted OR and its CI were calculated using multivariate logistic regression analysis entering age, nulliparity, twin pregnancy, height, and weight as covariates. *$p <$ 0.05 when compared to 1Q of MBP.

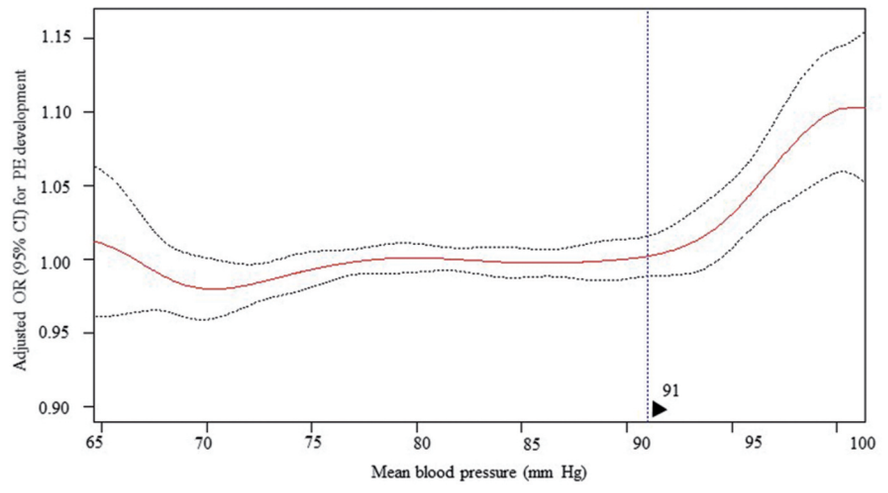

Figure 3. — Penalized smoothing splines showing the relationship between mean blood pressure and preeclampsia development. PE: preeclampsia; OR: odds ratio; CI: confidence interval. Upper and lower 1% of mean blood pressure were truncated. The red vertical line indicates the adjusted OR of multivariate analysis and the black dotted line indicates the associated 95% CI. The multivariate analysis was adjusted for age, nulliparity, twin pregnancy, height, and weight. The blue vertical dotted line indicates the threshold as suggested by visual inspection.

Table 4. — *Factors associated with high mean blood pressure.*

	Univariate		Multivariate	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (years)	1.06 (1.02–1.09)	0.001	1.05 (1.01–1.08)	0.011
Nulliparity (yes vs. no)	1.04 (0.81–1.34)	0.751	1.33 (1.01–1.77)	0.043
Twin pregnancy (yes vs. no)	1.51 (1.04–2.19)	0.031	1.39 (0.94–2.05)	0.098
Height (cm)	1.00 (0.97–1.02)	0.840	0.96 (0.94–0.99)	0.002
Weight (kg)	1.07 (1.05–1.08)	<0.001	1.07 (1.06–1.09)	<0.001

OR: odds ratio; CI: confidence interval; MBP: mean blood pressure. High mean blood pressure was defined as mean blood pressure ≥ 91 mmHg. OR and its CI were calculated using logistic regression analysis. In multivariate analysis: all above variables were chosen as covariates. The reference of continuous variables was per 1 unit increase.

Discussion

According to the current study, MBP during the first trimester in previously healthy women was independently associated with the development of preeclampsia in a nonlinear fashion, after adjusting for age, nulliparity, twin pregnancy, height, and weight. A few studies conducted during the 1980s and early 1990s reported that BP during the second trimester was significantly associated with preeclampsia [20-22]. Using AUROC analysis, Conde-Agudelo *et al.* suggested that the best cutoff points of mean arterial BP for preeclampsia at 20, 26, and 31 weeks of gestation were 81, 85, and 89 mm Hg, respectively [23]. However, the use of these data values is inappropriate because BP after 20 weeks of gestation is a diagnostic criterion of [12], not a predictive factor. Furthermore, elevated BP before 20 weeks of gestation has consistently been suggested to be a

risk factor for preeclampsia in healthy nulliparous women [11, 24]. For example, Sibai *et al.* analyzed 4,314 healthy nulliparous women who participated in the Calcium for Preeclampsia Prevention Study Group [25]. After adjusting for various confounding factors, systolic BPs ranging from 101 to 119 mm Hg and 120 to 136 mm Hg were associated with an increased risk of preeclampsia [adjusted ORs, 1.93 (95% CI, 1.37-2.72) and 2.66 (95% CI, 1.66-4.26), respectively] compared to systolic BP below 101 mm Hg. A similar finding was also observed among overweight nulliparous women [26]. However, these studies did not further explore the possibility of a non-linear association between BP and preeclampsia.

Thus, the present authors divided MBP into quartiles to further analyze the association between MBP and preeclampsia development. Compared to the first quartile, the risk of developing preeclampsia was only statistically significant in the fourth quartile for MBP, suggesting a non-linear association.

In a study by Odegard *et al.*, systolic BP before 18 weeks of gestation was significantly associated with a subsequent risk of preeclampsia ($p < 0.0001$), but the statistical significance was only valid in groups with systolic BPs ranging from 120 to 129 mm Hg and greater than or equal to 130 mm Hg, but not with a systolic BP between 110 and 119 mm Hg [27]. However, the authors did not further explore the possibility of a non-linear relationship.

In the present study, the authors used penalized smoothing splines to confirm the non-linear association between MBP and preeclampsia development. With visual inspection, the risk of preeclampsia development increased when MBP increased beyond 91 mm Hg, which was similar to the mean of the highest MBP quartile. The current study has several strengths. First, to the present authors' knowledge, this is the first study on the association of BP in the early pregnancy period with the development of preeclampsia in Asian women. Second, the results are easily applicable to the clinic, especially considering that BP measurements are already a part of routine practice in prenatal care. According to the present study results, a woman with an MBP greater than or equal to 91 mm Hg during the first trimester has a 2.60-fold greater risk of the subsequent development of preeclampsia. Therefore, clinicians can warn such patients regarding the increased risk of preeclampsia, and they can recommend frequent BP checks at home and more frequent clinic visits for timely intervention. Third, the present results can be used as inclusion criteria for the future preeclampsia study.

Along with known risk factors, [13] elevated BP is usually included in patient selection [28]. However, the level of "BP elevation" is quite ambiguous and arbitrary, thus weakening the overall study results. The present authors suggest that this study's results may serve as a guide for simple patient selection in such studies. Finally, the missing study variable rates were low and the sample size was large in this study. However, it also has several limitations. First, the authors used BP measured by an automated BP monitor, not a mercury sphygmomanometer. However, they assume this had little impact on the study results, because BP measured by an automated BP monitor was shown in a previous study to predict maternal and fetal outcomes, as well as BP measured by sphygmomanometer did [29]. Thus, the concordance of the results of the current study with those of previous studies using a sphygmomanometer supports the present authors' assumption. Second, the study was retrospective in nature, which limits the ability to infer direct causal relationships from the study results. Moreover, no blood specimens were available for the measurement of supporting biomarkers. Finally, the homogenous Asian ethnicity of the study population could limit the generalizability of the results. However, this may also be a strength, considering Asian women have been poorly represented in most previous studies on the association between BP and preeclampsia, and to date, no other preeclampsia studies solely involving Asian women have been completed. In conclusion, increased MBP during the first trimester was associated with the subsequent development of preeclampsia, but the association was non-linear. Because women with an MBP above about 90 mm Hg during the first trimester are at higher risk for preeclampsia, clinicians need to care for them more intensively. Future prospective studies are needed to confirm this study's results.

References

[1] Walker J.J.: "Pre-eclampsia". *Lancet*, 2000, *356*, 1260.1.

[2] Martin J.N., Jr., Owens M.Y., Keiser S.D., Parrish M.R., Tam Tam K.B., Brewer J.M., *et al.*: "Standardized Mississippi Protocol treatment of 190 patients with HELLP syndrome: slowing disease progression and preventing new major maternal morbidity". *Hypertens. Pregnancy*, 2012, *31*, 79.

[3] Berg C.J., Callaghan W.M., Syverson C., Henderson Z.: "Pregnancy-related mortality in the United States, 1998 to 2005". *Obstet. Gynecol.*, 2010, *116*. 1302.

[4] Backes C.H., Markham K., Moorehead P., Cordero L., Nankervis C.A., Giannone P.J.: "Maternal preeclampsia and neonatal outcomes". *J. Pregnancy*, 2011, *2011*, 214365.

[5] Duckitt K., Harrington D.: "Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies". *BMJ*, 2005, *330*, 565.

[6] Salahuddin S., Lee Y., Vadnais M., Sachs B.P., Karumanchi S.A., Lim K.H.: "Diagnostic utility of soluble fms-like tyrosine kinase 1 and soluble endoglin in hypertensive diseases of pregnancy". *Am. J. Obstet. Gynecol.*, 2007, *197*, 28 e1.

[7] Kim S.Y., Ryu H.M., Yang J.H., Kim M.Y., Han J.Y., Kim J.O., et al.: "Increased sFlt-1 to PlGF ratio in women who subsequently develop preeclampsia". *J. Korean. Med. Sci.*, 2007, *22*, 873.

[8] Lee E.S., Oh M.J., Jung J.W., Lim J.E., Seol H.J., Lee K.J., *et al.*: "The levels of circulating vascular endothelial growth factor and soluble Flt-1 in pregnancies complicated by preeclampsia". *J. Korean Med. Sci.*, 2007, *22*, 94-8.

[9] Irwin J.C., Suen L.F., Cheng B.H., Martin R., Cannon P., Deal C.L., *et al.*: "Human placental trophoblasts secrete a disintegrin metalloproteinase very similar to the insulin-like growth factor binding protein-3 protease in human pregnancy serum". *Endocrinology*, 2000, *141*, 666.

[10] Tornehave D., Chemnitz J., Teisner B., Folkersen J., Westergaard J.G.: "Immunohistochemical demonstration of pregnancy-associated plasma protein A (PAPP-A) in the syncytiotrophoblast of the normal placenta at different gestational ages". *Placenta*, 1984, *5*, 427.
[11] Myatt L., Clifton R.G., Roberts J.M., Spong C.Y., Hauth J.C., Varner M.W., *et al.*: "First-trimester prediction of preeclampsia in nulliparous women at low risk". *Obstet. Gynecol.*, 2012, *119*, 1234-42.
[12] American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy.: "Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy". *Obstet. Gynecol.*, 2013, *122*, 1122.
[13] Shah D.A., Khalil R.A.: "Bioactive factors in uteroplacental and systemic circulation link placental ischemia to generalized vascular dysfunction in hypertensive pregnancy and preeclampsia". *Biochem. Pharmacol.*, 2015, *95*, 211.
[14] Brosens I., Pijnenborg R., Vercruysse L., Romero R.: "The "Great Obstetrical Syndromes" are associated with disorders of deep placentation". *Am. J. Obstet. Gynecol.*, 2011, *204*, 193.
[15] Lee C.N., Chang S.W., Cho N.H., Cho S.H.: "Nitrous oxide synthase expression in placenta of preeclampsia". *J. Korean. Med. Sci.*, 1997, *12*, 532.
[16] Jang S.H., Chea J.W., Lee K.B.: "Charlson comorbidity index using administrative database in incident PD patients". *Clin. Nephrol.*, 2010, *73*, 204.
[17] Chae J.W., Song C.S., Kim H., Lee K.B., Seo B.S., Kim D.I.: "Prediction of mortality in patients undergoing maintenance hemodialysis by Charlson Comorbidity Index using ICD-10 database". *Nephron Clin. Pract.*, 2011, *117*, c379-84.
[18] Lee S.W., Yu M.Y., Baek S.H., Ahn S.Y., Kim S., Na K.Y., *et al.*: "Glomerular Immune Deposits Are Predictive of Poor Long-Term Outcome in Patients with Adult Biopsy-Proven Minimal Change Disease: A Cohort Study in Korea". *PloS One*, 2016, *11*, e0147387.
[19] Yeung E.H., Liu A., Mills J.L., Zhang C., Mannisto T., Lu Z., *et al.*: "Increased levels of copeptin before clinical diagnosis of preelcampsia". *Hypertension*, 2014, *64*, 1362-7.
[20] Page E.W., Christianson R.: "The impact of mean arterial pressure in the middle trimester upon the outcome of pregnancy". *Am. J. Obstet. Gynecol.*, 1976, *125*, 740-6.
[21] Chesley L.C., Sibai B.M.: "Clinical significance of elevated mean arterial pressure in the second trimester". *Am. J. Obstet. Gynecol.*, 1988, *159*, 275.
[22] Villar M.A., Sibai B.M.: "Clinical significance of elevated mean arterial blood pressure in second trimester and threshold increase in systolic or diastolic blood pressure during third trimester". *Am. J. Obstet. Gynecol.*, 1989, *160*, 419.
[23] Conde-Agudelo A., Belizan J.M., Lede R., Bergel E.F.: "What does an elevated mean arterial pressure in the second half of pregnancy predict--gestational hypertension or preeclampsia?" *Am. J. Obstet. Gynecol.*, 1993, *169*, 509.
[24] Thadhani R., Ecker J.L., Kettyle E., Sandler L., Frigoletto F.D.: "Pulse pressure and risk of preeclampsia: a prospective study". *Obstet. Gynecol.*, 2001, *97*, 515.
[25] Sibai B.M., Ewell M., Levine R.J., Klebanoff M.A., Esterlitz J., Catalano P.M., *et al.*: "Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group". *Am. J. Obstet. Gynecol.*, 1997, *177*, 1003.
[26] Tuuri A.L., Jauhiainen M.S., Tikkanen M.J., Kaaja R.J.: "Systolic blood pressure and fatty acid-binding protein 4 predict pregnancy-induced hypertension in overweight nulliparous women". *Placenta*, 2014, *35*, 797.
[27] Odegard R.A., Vatten L.J., Nilsen S.T., Salvesen K.A., Austgulen R.: "Risk factors and clinical manifestations of pre-eclampsia". *BJOG*, 2000, *107*, 1410.
[28] Zeisler H., Llurba E., Chantraine F., Vatish M., Staff A.C., Sennstrom M., *et al.*: "Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia". *N. Engl. J. Med.*, 2016, *374*, 13.
[29] Brown M.A., Roberts L.M., Mackenzie C., Mangos G., Davis G.K.: "A prospective randomized study of automated versus mercury blood pressure recordings in hypertensive pregnancy (PRAM Study)". *Hypertens. Pregnancy*, 2012, *31*, 107.

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