Taiwanese Journal of Obstetrics & Gynecology 54 (2015) 350–354

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Maternal serum copeptin concentrations in early- and late-onset pre-eclampsia

Abdullah Tuten [a,*], Mahmut Oncul [a], Mine Kucur [b], Metehan Imamoglu [a], Ozlem Balcı Ekmekci [b], Abdullah Serdar Acıkgoz [a], Fatma Selcen Cebe [c], Cengiz Yesilbas [a], Rıza Madazlı [a]

[a] Department of Obstetrics and Gynecology, Cerrahpasa School of Medicine, Istanbul University, Istanbul, Turkey
[b] Department of Medical Biochemistry, Cerrahpasa School of Medicine, Istanbul University, Istanbul, Turkey
[c] Cerrahpasa School of Medicine, Istanbul University, Istanbul, Turkey

ARTICLE INFO

Article history:
Accepted 18 October 2013

Keywords:
copeptin
early-onset pre-eclampsia
gestational age
late-onset pre-eclampsia
pre-eclampsia

ABSTRACT

Objective: Early-onset pre-eclampsia is primarily associated with placental dysfunction, whereas late-onset pre-eclampsia is defined as a maternal constitutional disorder. As a protein cosynthesized with vasopressin, copeptin is a potential marker of metabolic syndrome and insulin resistance, which shares similar risk factors with pre-eclampsia. The aim of this study was to investigate the copeptin levels in patients with early-onset and late-onset pre-eclampsia.

Materials and methods: A total of 80 pregnant women receiving antenatal and obstetric care were recruited. The patients were subdivided into four groups: Early-onset pre-eclampsia ($n = 20$), late-onset pre-eclampsia ($n = 20$), and two control groups of similar gestational ages for both pre-eclamptic groups ($n = 20$ in each group). The maternal serum copeptin levels were measured using an enzyme-linked immunosorbent assay.

Results: The mean copeptin levels were 0.92 ± 0.57 ng/mL and 1.65 ± 0.95 ng/mL in the early-onset and late-onset pre-eclampsia groups, respectively. These values were higher compared with the control groups (0.54 ± 0.25 ng/mL and 1.15 ± 0.94 ng/mL, respectively). However, the difference was only statistically significant in the early-onset pre-eclampsia group ($p = 0.011$). Copeptin levels were associated only with gestational age and systolic–diastolic blood pressure.

Conclusion: Our results suggest that copeptin levels might be useful in the evaluation of the severity of pre-eclampsia. However, copeptin might be involved in early- rather than late-onset pre-eclampsia.

Introduction

Pre-eclampsia is a multisystem disease of pregnancy, characterized by new-onset hypertension and proteinuria, which develops after 20 weeks of gestation in previously normotensive women, complicating 3–5% of all pregnancies [1]. Although the exact cause of pre-eclampsia remains unknown, this disease is characterized by inadequate placentation, oxidative stress, inflammation, and widespread endothelial dysfunction [2]. Pre-eclampsia can be classified as early onset and late onset, according to the development of symptoms before or after 34 weeks of pregnancy, respectively [3,4]. Early-onset pre-eclampsia associated with placental dysfunction is markedly severe, frequently leading to deliveries of growth-retarded premature babies or poor outcomes for mothers [5].

Women affected with pre-eclampsia have significantly increased risks of metabolic and cardiovascular diseases following pregnancy [6,7]. Pre-eclampsia, metabolic syndrome, and cardiovascular diseases share the same risk factors, including obesity, hypertension, dyslipidemia, hypercoagulability, and insulin resistance, and these conditions are characterized by endothelial dysfunction [8–10]. Recently, the activation of the stress-mediated hypothalamic–pituitary–adrenal (HPA) axis, regulated through copeptin, was implicated in the pathophysiology of metabolic

* Corresponding author. Department of Obstetrics and Gynecology, Cerrahpasa School of Medicine, Kocamustafapasa St No. 53, Cerrahpasa, Istanbul 34098, Turkey.
E-mail address: drabdtuten@gmail.com (A. Tuten).

http://dx.doi.org/10.1016/j.tjog.2013.10.045

syndrome and cardiovascular diseases [11]. Corticotropin-releasing hormone and copeptin-regulated stress-mediated HPA axis activation are involved in the endocrine stress response [12–14]. Copeptin is superior to cortisol in the determination of the stress level, because cortisol has a strong circadian rhythm, and the measurement of cortisol as a free hormone in serum remains challenging [15].

Zulfikaroglu et al [16] reported that increased maternal levels of copeptin might be involved in the pathogenesis of pre-eclampsia, and copeptin might be a clinically useful biomarker for the assessment of disease severity in early-onset pre-eclampsia. Similarly, as an indicator of inadequate placentation in pre-eclampsia, copeptin levels have been associated with abnormal uterine and umbilical artery Doppler velocimetry values. Inadequate placentation is primarily associated with early-onset rather than late-onset pre-eclampsia, whereas late-onset pre-eclampsia results from an underlying maternal constitutional disorder. However, the outcomes of late-onset pre-eclampsia resemble those of normal pregnancies compared with early-onset pre-eclampsia. Therefore, we hypothesized that copeptin might be an important biomarker of early- rather than late-onset pre-eclampsia.

Copeptin, a 39-amino acid glycopeptide, is cosynthesized in the hypothalamus with vasopressin, which is also an antidiuretic hormone. Copeptin can be used as an indicator of serum vasopressin levels, because the levels of this hormone in serum are more stable in plasma and serum compared with vasopressin [17]. In addition to reflecting individual stress levels, vasopressin also has hemodynamic and osmoregulatory effects. Interestingly, copeptin has been shown to act identically with vasopressin during the course of disorders of the osmoregulatory system, and copeptin levels have been directly correlated with the plasma vasopressin levels in both healthy volunteers and critically ill patients [18]. In addition, copeptin levels have been demonstrated as independent predictors of survival in patients suffering from hemorrhagic and septic shock and have shown prognostic implications in diseases other than infections [19].

In this study, we evaluated the copeptin levels in normal pregnancy and pregnancies complicated by early-onset and late-onset pre-eclampsia. We also investigated the association between maternal serum copeptin levels and umbilical and uterine artery Doppler velocimetry values in pre-eclamptic patients.

Materials and methods

A total of 80 pregnant women, comprising 40 women with normal pregnancies and 40 women diagnosed with pre-eclampsia, receiving antenatal and obstetric care at the Department of Obstetrics and Gynecology, Istanbul University Cerrahpasa Faculty of Medicine Hospital (Istanbul, Turkey), from May 2012 to July 2012, were recruited for this case-control study. Pre-eclampsia was defined according to the criteria of the American College of Obstetrics and Gynecology (ACOG practice bulletin) [20]. Pre-eclampsia was determined through increased blood pressure (>140/90 mmHg) occurring in a pregnant woman after 20 weeks of amenorrhea, accompanied by proteinuria (≥0.3 g/24 h), as defined according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.

The patients with pre-eclampsia were divided into two groups as follows: 20 patients diagnosed before 34 weeks of gestation were defined as having “early-onset pre-eclampsia,” and those diagnosed and delivered at 34 weeks of gestation or later were defined as having “late-onset pre-eclampsia.” For each patient with pre-eclampsia, one control woman was randomly matched according to weeks of gestation among normotensive patients with uncomplicated pregnancies who delivered healthy babies weighing >2500 g at term. This group was divided into two subgroups based on the gestational weeks (early and late control groups). The early control group comprised 20 healthy pregnant women recruited during a routine visit to the antenatal clinic at 24–34 gestational weeks; only those women whose pregnancies continued normally remained in this group. The late control group comprised 20 healthy pregnant women recruited during a routine visit to the antenatal clinic following the completion of 34 gestational weeks. Therefore, the control groups were appropriately structured for statistical evaluation in terms of gestational weeks for both early-onset and late-onset pre-eclamptic patient groups. The mean ages, gestational weeks, and body mass index (BMI) were evaluated. The BMI was calculated using the following formula: weight (kg)/height $(m)^2$.

The following exclusion criteria were used: multiple pregnancies, pregestational or gestational diabetes mellitus, smoking, chronic hypertension, polyhydramnios, prior renal diseases, and evidence of acute or chronic inflammation. The diagnosis of pregnancy was based on a positive serum beta-human chorionic gonadotropin test and the presence of fetal heart beat in the uterine cavity on ultrasonographic evaluation. The gestational ages were evaluated according to the last menstrual period and confirmed through ultrasound performed until 14 gestational weeks, based on the crown rump length values of the embryos.

Blood samples were collected from each participant before administration of any medication and before any medical or surgical intervention. None of the patients was in labor at the time of sampling. The serum was separated by centrifuging the samples at 4000*g* for 10 minutes and freezing at −80°C for later analysis. The serum copeptin concentrations were measured in duplicate using a competitive enzyme immunoassay (Catalog No. EK-065-32 copeptin-human EIA kit: Phoenix Pharmaceuticals, Inc., CA, USA). The assay sensitivity was 0.12 ng/mL, and the interassay and intra-assay calculation values were 5–10% and <15%, respectively.

The umbilical artery and uterine artery blood-flow velocity values were obtained using transabdominal color and pulsed Doppler velocimetry measurements of the uterine and umbilical arteries, performed by the same physician (A.T.) for all study patients. Voluson 730 Pro ultrasound machines (GE Healthcare, UK), equipped with pulsed and color Doppler technologies, were used, and uterine and umbilical artery Doppler velocimetry values were measured. Informed consent was obtained from all women, and the study protocol was approved through the Human Ethics Committee of Istanbul University.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 18.0, SPSS Inc., Chicago, IL, USA. The data are presented as the arithmetical means, and the standard deviations were calculated for each group. Student *t* test was used for comparison of the parametric variables, and chi-square test was used for comparison of the nonparametric variables. The relationship between a particular biochemical parameter and the stage or grade was evaluated using Pearson correlation test. A p value < 0.05 was considered statistically significant.

Results

The clinical characteristics, uterine and umbilical artery Doppler velocimetry findings, and mean maternal serum copeptin levels of the subgroups (early-onset pre-eclampsia, late-onset pre-eclampsia, and 2 control groups) are summarized in Table 1. Pre-eclamptic patients in both early-onset and late-onset groups were compared with their gestational age-matched controls.

No statistical differences were observed between the patients with early-onset pre-eclampsia and their respective controls in terms of mean maternal ages, BMI values, mean gestational ages at

Table 1
Baseline characteristics of the patients.

	Early-onset controls ($n = 20$)	Early-onset pre-eclampsia ($n = 20$)	p	Late-onset controls ($n = 20$)	Late-onset pre-eclampsia ($n = 20$)	p
Maternal age (y)	30.4 ± 3.44	29.1 ± 6.1	NS	30.9 ± 3.4	31.1 ± 4.1	NS
Nulliparity, *n* (%)	3 (15)	9 (45)	0.01	3 (15)	5 (25)	NS
Previous pre-eclampsia, *n* (%)	0 (0)	5 (25)	0.03	0 (0)	0 (0)	NS
Gestational age at sampling (d)	28.65 ± 0.48	28.8 ± 2.0	NS	36.0 ± 0.9	35.8 ± 1.2	NS
BMI (kg/m^2)	29.8 ± 1.9	30.2 ± 2.3	NS	29.4 ± 0.6	29.5 ± 4.5	NS
SBP (mmHg)	104 ± 7.5	160 ± 20.2	0.001	110.5 ± 8.5	153.5 ± 23.9	0.001
DBP (mmHg)	67.5 ± 7.1	105.5 ± 13.9	0.001	71.6 ± 76	101.3 ± 17.1	0.001
Birth weight (g)	3184 ± 421	1398 ± 357	0.001	3059 ± 328	2288 ± 740	0.001
IUGR, *n* (%)	0 (0)	15 (75)	0.001	0 (0)	11 (55)	0.001
Uterine artery PI	0.88 ± 0.10	0.99 ± 0.18	0.029	0.82 ± 0.11	1.00 ± 0.19	0.003
Uterine artery RI	0.54 ± 0.07	0.56 ± 0.09	NS	0.51 ± 0.06	0.55 ± 0.83	NS
Umbilical artery PI	0.86 ± 0.10	1.04 ± 0.24	0.004	0.80 ± 0.12	1.13 ± 0.35	0.001
Umbilical artery RI	0.56 ± 037	0.58 ± 0.06	NS	0.55 ± 0.05	0.67 ± 0.08	NS
Copeptin (ng/mL)	0.54 ± 0.25	0.92 ± 0.57	0.011	1.15 ± 0.94	1.65 ± 0.95	NS

All values are presented as means ± standard deviation, unless otherwise indicated differently.
*$p < 0.05$ is considered statistically significant.
BMI = body mass index; DBP = diastolic blood pressure; IUGR = intrauterine growth restriction; NS = not significant; PI = pulsatility index; RI = resistivity index; SBP = systolic blood pressure.

the sampling time, and uterine and umbilical artery resistance index (RI) values. The percentage of nulliparity was higher in the pre-eclampsia group ($p = 0.01$), and there were five patients with a history of previous pre-eclampsia in the pre-eclampsia group, whereas the control group had none ($p = 0.01$). The birth weights of the newborns were significantly different between the groups ($p = 0.001$), and 75% of the patients with pre-eclampsia delivered babies with intrauterine growth retardation (IUGR), whereas no babies with IUGR were delivered in the control group ($p = 0.001$). The mean systolic and diastolic blood pressures and both umbilical and uterine artery Doppler velocimetry pulsatility index (PI) values were significantly higher in the pre-eclampsia group ($p = 0.001$, $p = 0.001$, $p = 0.029$, and $p = 0.004$, respectively).

No statistically significant differences were observed in patients with late-onset pre-eclampsia when compared with their control groups in terms of mean maternal ages, percentage of nulliparity, number of patients with previous pre-eclampsia diagnosis, BMI values, uterine and umbilical artery RI values, and gestational age at sampling time. The birth weights of the newborns were significantly different between the groups ($p = 0.001$). Approximately 55% of the patients with pre-eclampsia delivered babies with IUGR; however, no babies with IUGR were delivered in the control group ($p = 0.001$). The mean systolic and diastolic blood pressures and both umbilical and uterine artery Doppler velocimetry PI values were significantly higher in the pre-eclampsia group ($p = 0.001$, $p = 0.001$, $p = 0.003$, and $p = 0.001$, respectively).

The mean maternal serum copeptin levels were higher in both early-onset and late-onset pre-eclamptic patients compared with their control groups (Figure 1). However, this difference was only statistically significant in patients diagnosed with early-onset pre-eclampsia ($p = 0.011$).

As shown in Table 2, the maternal serum copeptin levels did not correlate with the maternal BMI values, birth weights of the newborns, and the umbilical and uterine artery PI and RI Doppler velocimetry values. However, there was a correlation between maternal serum copeptin levels, gestational age, and systolic and diastolic blood pressures ($p = 0.001$, $p = 0.047$, and $p = 0.038$, respectively).

Discussion

The major findings of this study are as follows: (1) maternal serum copeptin levels were markedly increased in patients diagnosed with pre-eclampsia in the third trimester compared with women with normal, ongoing pregnancies of similar gestational age. The increase of copeptin levels in patients with early-onset pre-eclampsia was statistically significant compared with the control group. However, a similar difference in patients with late-onset pre-eclampsia was not statistically significant. (2) Although maternal serum copeptin levels were positively correlated with gestational age, and systolic and diastolic blood pressure, the levels did not correlate with maternal age, BMI, birth weight, and uterine and umbilical artery Doppler values in both early-onset and late-onset pre-eclampsia.

Early-onset pre-eclampsia is primarily considered a fetal disorder, typically associated with placental dysfunction, a reduction in placental volume, intrauterine growth restriction, abnormal uterine and umbilical artery Doppler evaluation, low birth weight, multiorgan dysfunction, perinatal death, and adverse maternal and neonatal outcomes [21,22]. By contrast, late-onset pre-eclampsia is considered a maternal disorder, resulting from an underlying maternal constitutional disorder, associated with a normal placenta, larger placental volume, normal fetal growth, normal

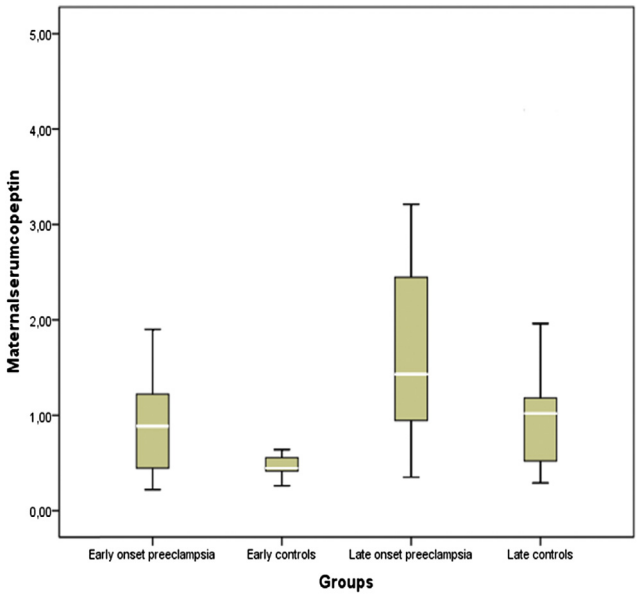

Figure 1. Serum copeptin concentrations in women with pre-eclampsia and normal controls.

Table 2
Correlations between serum copeptin levels and all the other parameters assessed in all groups.

	Copeptin	
	r	*p*
Maternal age	0.129	0.253
BMI	0.141	0.212
Gestational week	**0.401**	**0.001***
Birth weight	−0.134	0.237
SBP	**0.223**	**0.047***
DBP	**0.242**	**0.038***
Umbilical artery PI	−0.110	0.925
Umbilical artery RI	0.161	0.165
Uterine artery PI	−0.009	0.937
Uterine artery RI	0.630	0.537

*$p < 0.05$ is considered statistically significant.
BMI = body mass index; DBP = diastolic blood pressure; PI = pulsatility index; *r* = correlation coefficient; RI = resistivity index; SBP = systolic blood pressure.

uterine and umbilical artery Doppler evaluation, normal birth weight, and more favorable maternal and neonatal outcomes [21,23–25].

Zulfikaroglu et al [16] documented the elevation of serum copeptin levels in patients diagnosed with pre-eclampsia. Consistent with these data, the serum copeptin levels were higher in both early-onset and late-onset pre-eclampsia compared with the control groups in this study. The elevation of the serum copeptin levels in pre-eclamptic patients might reflect the fact that arginine vasopressin directly stimulates cortisol release in humans through the activation of V_{1a} receptors on adrenal cortex cells [26], resulting in salt and water retention, causing pre-eclampsia. In addition, arginine vasopressin activates the receptors on the chromaffin cells in the adrenal medulla, leading to an increase in the vasoconstrictive epinephrine levels, which might subsequently contribute to hypertension in pre-eclampsia [27].

The pre-eclamptic patients included in the Zulfikaroglu et al [16] study were compatible with the diagnosis criteria of early-onset pre-eclampsia. However, in our study, the elevation of serum copeptin levels was only statistically significant in the early-onset pre-eclampsia group. Because the copeptin levels have been associated with individual stress levels [18], and early-onset pre-eclampsia is presumed to be a considerably severe condition compared with late-onset pre-eclampsia, this significant difference in the copeptin levels in early-onset pre-eclampsia might reflect a relatively stressful condition.

Zulfikaroglu et al [16] concluded that the increase in serum copeptin levels was correlated with the severity of the disease and abnormal uterine and umbilical Doppler velocimetry results. In our study, we observed no correlation between maternal serum copeptin and uterine and umbilical artery Doppler velocimetry values in patients with pre-eclampsia. This finding is in contrast to the results reported by Zulfikaroglu et al [16]. Therefore, we suggest that the relation between copeptin and impaired uteroplacental perfusion remains controversial. Moreover, in this study, regardless of the onset of the disease, maternal serum copeptin levels were positively associated with elevated systolic and diastolic blood pressure, considered as diagnostic criteria for pre-eclampsia and a poor prognostic factor. This correlation might reflect the activation of the receptors on chromaffin cells in the adrenal medulla, as described earlier [27].

Previous studies have reported that normal human pregnancy dramatically affects the HPA axis, in which copeptin has been shown to act as a regulative factor [28,29]. Increased placental estrogen production stimulates hepatic corticosteroid-binding globulin production [30,31], eventually depleting the levels of free cortisol, and thereby activating the HPA axis and increasing serum levels of free cortisol [32–35]. In this study, the maternal serum copeptin levels were also positively associated with gestational age in all groups, presumably reflecting increased individual stress levels during pregnancy. This increase in serum copeptin levels was also exaggerated in patients diagnosed with both early-onset and late-onset pre-eclampsia, likely reflecting the extra chronic physical stress caused by the disease itself. The small patient population contributed to the limitations of this study. Future studies with larger populations are needed to obtain a relatively elaborate definition of copeptin secretion, metabolism, and action in patients with pre-eclampsia.

In conclusion, early-onset pre-eclampsia has been associated with impaired maternal and fetal outcomes compared with late-onset pre-eclampsia. The results obtained in this study have shown that serum copeptin levels are positively correlated with early-onset pre-eclampsia, potentially reflecting the presence of relatively increased physiological stress. In addition, the serum copeptin levels were associated with elevated systolic and diastolic blood pressure. Moreover, these results have revealed a positive correlation between maternal serum copeptin levels and gestational age, suggesting a gradual increase in HPA axis activation.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

References

[1] Young BC, Levine RJ, Karumanchi SA. Pathogenesis of preeclampsia. Annu Rev Pathol 2010;5:173–92.
[2] Eiland E, Nzerue C, Faulkner M. Preeclampsia 2012. J Pregnancy 2012;2012:1–7.
[3] von Dadelszen P, Magee LA, Roberts JM. Subclassification of preeclampsia. Hypertens Pregnancy 2003;22:143–8.
[4] Eastabrook G, Brown M, Sargent I. The origins and end-organ consequence of pre-eclampsia. Best Pract Res Clin Obstet Gynaecol 2011;2:435–47.
[5] Kovo M, Schreiber L, Ben-Haroush A, Gold E, Golan A, Bar J. The placental component in early-onset and late-onset preeclampsia in relation to fetal growth restriction. Prenat Diagn 2012;32:632–7.
[6] Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007;335:974.
[7] Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstet Gynecol 2009;114:961–70.
[8] Roberts JM, Bodnar LM, Patrick TE, Powers RW. The role of obesity in pre-eclampsia. Pregnancy Hypertens 2011;1:6–16.
[9] Solomon CG, Seely EW. Brief review: hypertension in pregnancy: a manifestation of the insulin resistance syndrome? Hypertension 2001;37:232–9.
[10] Hauth JC, Clifton RG, Roberts JM, Myatt L, Spong CY, Leveno KJ, et al. Maternal insulin resistance and preeclampsia. Am J Obstet Gynecol 2011;204:327.e1–6.
[11] Saleem U, Khaleghi M, Morgenthaler NG, Bergmann A, Struck J, Mosley Jr TH, et al. Plasma carboxy-terminal provasopressin (copeptin): a novel marker of insulin resistance and metabolic syndrome. J Clin Endocrinol Metab 2009;94:2558–64.
[12] Gillies GE, Linton EA, Lowry PJ. Corticotropin releasing activity of the new CRF is potentiated several times by vasopressin. Nature 1982;299:355–7.
[13] Rivier C, Vale W. Modulation of stress-induced ACTH release by corticotropin-releasing factor, catecholamines and vasopressin. Nature 1983;305:325–7.
[14] Rivier C, Vale W. Interaction of corticotropin-releasing factor and arginine vasopressin on adrenocorticotropin secretion *in vivo*. Endocrinology 1983;113:939–42.
[15] Katan M, Morgenthaler N, Widmer I, Puder JJ, König C, Müller B, et al. Copeptin, a stable peptide derived from the vasopressin precursor, correlates with the individual stress level. Neuro Endocrinol Lett 2008;29:341–6.
[16] Zulfikaroglu E, Islimye M, Tonguc EA, Payasli A, Isman F, Var T, et al. Circulating levels of copeptin, a novel biomarker in pre-eclampsia. J Obstet Gynaecol Res 2011;37:1198–202.
[17] Morgenthaler NG, Struck J, Jochberger S, Dünser MW. Copeptin: clinical use of a new biomarker. Trends Endocrinol Metab 2008;19:43–9.
[18] Szinnai G, Morgenthaler NG, Berneis K, Struck J, Müller B, Keller U, et al. Changes in plasma copeptin, the c-terminal portion of arginine vasopressin during water deprivation and excess in healthy subjects. J Clin Endocrinol Metab 2007;92:3973–8.

[19] Katan M, Müller B, Christ-Crain M. Copeptin: a new and promising diagnostic and prognostic marker. Crit Care 2008;12:117.
[20] Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. Am J Obstet Gynecol 2000;183: S1–22.
[21] Obed S, Patience A. Birth weight and ponderal index in pre-eclampsia: a comparative study. Ghana Medical J 2006;40:8–13.
[22] Ihle BU, Long P, Oats J. Early onset pre-eclampsia: recognition of underlying renal disease. Br Med J (Clin Res Ed) 1987;294:79–81.
[23] Onah HE, Iloabachie GC. Conservative management of early-onset pre-eclampsia and fetomaternal outcome in Nigerians. J Obstet Gynaecol 2002;22: 357–62.
[24] Crispi F, Llurba E, Domínguez C, Martín-Gallán P, Cabero L, Gratacós E. Predictive value of angiogenic factors and uterine artery Doppler for early- versus late-onset preeclampsia and intrauterine growth restriction. Ultrasound Obstet Gynecol 2008;31:303–9.
[25] Dissanayake VH, Samarasinghe HD, Morgan L, Jayasekara RW, Seneviratne HR, Broughton Pipkin F. Morbidity and mortality associated with preeclampsia at two tertiary care hospitals in Sri Lanka. J Obstet Gynaecol Res 2007;33:56–62.
[26] Gallo-Payet N, Guillon G. Regulation of adreno-cortical function by vasopressin. Horm Metab Res 1998;30:360–7.
[27] Grazzini E, Breton C, Derick S, Andres M, Raufaste D, Rickwaert F, et al. Vasopressin receptors in human adrenal medulla and pheochromocytoma. J Clin Endocrinol Metab 1999;84:2195–203.
[28] Lindsay JR, Nieman LK. The hypothalamic-pituitary-adrenal axis in pregnancy: challenges in disease detection and treatment. Endocr Rev 2005;26:775–99.
[29] Lindsay JR, Jonklaas J, Oldfield EH, Nieman LK. Cushing's syndrome during pregnancy: personal experience and review of the literature. J Clin Endocrinol Metab 2005;90:3077–83.
[30] Wilson EA, Finn AE, Rayburn W, Jawad MJ. Corticosteroid-binding globulin and estrogens in maternal and cord blood. Am J Obstet Gynecol 1979;135: 215–8.
[31] Scott EM, McGarrigle HH, Lachelin GC. The increase in plasma and saliva cortisol levels in pregnancy is not due to the increase in corticosteroid-binding globulin levels. J Clin Endocrinol Metab 1990;71:639–44.
[32] Carr BR, Parker Jr CR, Madden JD, MacDonald PC, Porter JC. Maternal plasma adrenocorticotropin and cortisol relationships throughout human pregnancy. Am J Obstet Gynecol 1981;139:416–22.
[33] Cousins L, Rigg L, Hollingsworth D, Meis P, Halberg F, Brink G, et al. Qualitative and quantitative assessment of the circadian rhythm of cortisol in pregnancy. Am J Obstet Gynecol 1983;145:411–6.
[34] Nolten WE, Lindheimer MD, Rueckert PA, Oparil S, Ehrlich EN. Diurnal patterns and regulation of cortisol secretion in pregnancy. J Clin Endocrinol Metab 1980;51:466–72.
[35] Nolten WE, Rueckert PA. Elevated free cortisol index in pregnancy: possible regulatory mechanisms. Am J Obstet Gynecol 1981;139:492–8.