Creatinine level as a predictor of hypertensive disorders during pregnancy

T. WOLAK*, R. SERGIENKO†, A. WIZNITZER‡, E. PARAN* and E. SHEINER‡

Hypertension Unit, Epidemiology and Health Services Evaluation† and Obstetrics and Gynaecology‡, Faculty of Health Sciences, Soroka University Medical Center, Ben Gurion University of the Negev, Be'er-Sheva, Israel*

Accepted: 7 June 2011

ABSTRACT

This study aims to examine the association between creatinine level during the first 20 weeks of pregnancy and the development of pre-eclampsia in the second half of the pregnancy. The study population included all registered births (n=9341) between 2001 and 2007 in a tertiary medical centre. Student's t-test and receiver operating characteristic (ROC) curves were used to determine any association. Significant association was documented between creatinine level in the first 20 weeks and the prevalence of hypertensive disorders. The mean plasma creatinine value in women with mild pre-eclampsia versus healthy women was 0.59 mg/dL ± 0.14 versus 0.57 mg/dL ± 0.15, respectively (P=0.023). The mean plasma creatinine value in women with severe pre-eclampsia versus healthy women was 0.61 mg/dL ± 0.17 versus 0.58 mg/dL ± 0.15, respectively (P=0.040). The mean plasma creatinine value in women with hypertensive disorders versus healthy women was 0.60 mg/dL ± 0.15 versus 0.58 mg/dL ± 0.15, respectively (P=0.003). The ROC curve demonstrated a significant association between creatinine level in the first 20 weeks of pregnancy and the development of mild and severe pre-eclampsia in the second half of pregnancy (area under the curve: 0.54, 95% confidence interval [CI]: 0.51–0.57, P=0.02, and 0.56, 95% CI: 0.50–0.62, P=0.033, respectively). Higher creatinine levels during the first 20 weeks of pregnancy are associated with a higher risk of developing mild and severe pre-eclampsia.

KEY WORDS: Creatinine.
Hypertension.
Pre-eclampsia.
Pregnancy.

Introduction

Pre-eclampsia occurs in approximately 3–14% of all pregnancies worldwide[1] and is a major contributor to maternal and fetal morbidity.[2] However, the pathogenesis and the causes of pre-eclampsia are not fully understood. One theory suggests that the major reason for the development of pre-eclampsia is a placental anomaly with abnormal trophoblast implantation,[3] although other maternal mechanisms may be involved, including increased sensitivity to angiotensin II[4] as well as a maternal genetic and immunological susceptibility.[5,6]

There has been a constant search for markers to identify women during the early stage of pregnancy who are at risk of developing pre-eclampsia (e.g., VEGF and sFlt-1); however, these markers are not specific and levels rise only a few weeks before the development of pre-eclampsia.[7]

During normal pregnancy, the renal blood flow and glomerular filtration rate (GFR) are enhanced.[8] The rise in GFR translates to a fall in the different serum markers of renal clearance, including creatinine, blood urea nitrogen and uric acid.[9] The present study aims to evaluate markers that are generally available and can be used easily in daily practice for the prediction of pre-eclampsia. In addition, the hypothesis that creatinine level during the first 20 weeks of pregnancy might serve as a marker for the development of pre-eclampsia in the second half of pregnancy is tested.

Materials and methods

A retrospective population-based study was conducted in order to examine whether different creatinine levels in the first 20 weeks of pregnancy are associated with a different prevalence of mild and severe pre-eclampsia during the second half of the pregnancy. The study was approved by the local ethics committee.

Correspondence to: Dr. Talya Wolak
Hypertension Unit, Soroka University Medical Center, P.O. Box 151
Be'er-Sheva, Israel
Email: twolak@bgu.ac.il

Study population

The study population included all registered births between 2001 and 2007. The data were retrieved from the computerised medical files of each birth, including information about the course of pregnancy and delivery. Reasons for exclusion from the study included a lack of creatinine examination in the first half of the pregnancy, multiple births, and patients with chronic hypertension and pre-gestational diabetes mellitus.

Creatinine measurement

The computerised data were compared with the biochemical laboratory data. When multiple creatinine measurements were available, the highest creatinine value during the first 20 weeks of pregnancy was used

Pre-eclampsia was defined as new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman, and eclampsia was defined as the

Table 1. Basic characteristics of the study group.

	Normotensive *n*=8890	Mild pre-eclampsia *n*=345	Severe pre-eclampsia *n*=106	*P value *vs.* normotensive group
Mother's age (years)	29.2±5.7	29.8±5.9	29.2±6.9	0.96
Gestational age (weeks)	38.8±2.2	38.3±1.9	35.6±3.6*	*0.001
Birth weight (g)	3166.1±535.7	3144.0±535.2	2304.7±776.4*	*0.001

One-way ANOVA (mean±SD)

Table 2. Basic characteristics of the study group and creatinine values.

Creatinine (mmol/L)	<35 *n*=801	35–70 *n*=7980	71–88 *n*=520	≥89 *n*=46	Total *n*=9347	*P* value
Mother's age (year)	28.1±5.7	29.3±5.7	29.8±5.7	31.3±5.8	29.2±5.7	<0.001
Gestational age (week)	38.7±2.4	38.7±2.2	38.7±2.1	38.5±1.8	38.7±2.2	0.77
Birth weight (g)	3119.3±571.3	3157.8±545.6	3168.5±530.3	3188.3±584.6	3155.0±547.2	0. 26

One-way ANOVA (mean±SD)

development of grand-mal seizures in a woman with gestational hypertension or pre-eclampsia.[1]

The hypertensive disorders were divided as follows: mild pre-eclampsia, severe pre-eclampsia, total hypertensive disorder (mild and severe pre-eclampsia). The distinction between mild and severe pre-eclampsia was made according to the recommendations of the American College of Obstetricians and Gynecologists. Pre-eclampsia was considered to be severe if one or more of the following criteria were present: systolic blood pressure >160 mmHg or diastolic blood pressure >110 mmHg, proteinuria >5 g/24 h, oliguria, visual disturbance, impaired liver function, thromobocytopenia, pulmonary oedema and fetal growth retardation.[1]

Table 3. A comparison between mean creatinine levels during the first 20 weeks of pregnancy in patients with and without mild pre-eclampsia, severe pre-eclampsia and total hypertensive disorders.

Mild pre-eclampsia		*P* value
Without mild pre-eclampsia (*n*=8890)	With mild pre-eclampsia (*n*=345)	
51 mmol/L ± 13	53 mmol/L ± 11	0.026
Severe pre-eclampsia		***P* value**
Without severe pre-eclampsia (*n*=8890)	With severe pre-eclampsia (*n*=106)	
51 mmol/L ± 13	54 mmol/L ± 15	0.043
Hypertensive disorders* (HTN)		***P* value**
Without HTN (*n*=8890)	With HTN (*n*=451)	
51 mmol/L ± 13	53 mmol/L ± 13	0.003

*Mild and severe pre-eclampsia.

Each group was compared to subjects who were free of any pregnancy-related hypertensive disorder. Only six subjects with eclampsia were found in the study population and therefore they were excluded from the analysis.

Data collection

The following data were collected for each delivery: maternal age, gestational age and birth weight. The obstetric risk factors examined were hypertensive disorders comprising mild and severe pre-eclampsia.

Statistical analysis

Statistical analysis was performed using the SPSS package. Statistical significance was calculated using Student's *t*-test for differences in qualitative variables and one-way ANOVA for differences in continuous variables. Receiver operating characteristic (ROC) curve analysis was used to describe the relationship between the sensitivity (true positive rate) and the false-positive rate for the creatinine level and the prediction of pre-eclampsia. The area under the curve was calculated to provide a summary of diagnostic accuracy. $P<0.05$ was considered statistically significant.

Results

The study population included 9341 births that met the inclusion criteria. There were 8890 healthy women, 345 with mild pre-eclampsia and 106 with severe pre-eclampsia. Basic characteristics and creatinine values are shown in Tables 1 and 2. Mean creatinine values in the first 20 weeks of pregnancy in cases with and without pregnancy complications are shown in Table 3.

The study group included 680 (7.3%) subjects with gestational diabetes (GDM). There was no significant difference in the creatinine level during the first half of the pregnancy in women who developed GDM versus women who were free of GDM (51 mmol/L ± 13 *vs.* 50 mmol/L ± 11 [$P=0.23$], respectively).

The ROC curve analysis is shown in Figure 1 and investigated the association between creatinine level during the first 20 weeks of gestation and mild pre-eclampsia, severe pre-eclampsia and total hypertensive disorders during pregnancy (including mild pre-eclampsia, severe pre-eclampsia and eclampsia). This showed a significant association, with an area under the curve of 0.54, 95% confidence interval (CI): 0.51–0.57, $P=0.02$ for mild pre-eclampsia (Fig. 1a), 0.56, 95% CI: 0.50–0.62, $P=0.033$ for severe pre-eclampsia (Fig. 1b), and 0.54, 95% CI: 0.52–0.57, $P=0.002$ for hypertensive disorders (Fig. 1c).

Discussion

The major finding of this study is that creatinine level in the first 20 weeks of pregnancy is associated with higher risk for the development of pregnancy-related hypertensive disorders during the second half of pregnancy. As pre-eclampsia is a relatively common complication associated with maternal and fetal aggravated risk, there is a constant search for a safe, simple and reliable screening tool. Currently, however, no such tool is available. Extensive research has been carried out to evaluate the role of placental angiogenic factors.[10,11] Although the results showed good correlation with the development of pre-eclampsia, they did not perform as well as predictors used in earlier pregnancy.[12] Various risk factors are recognised for the development of pre-eclampsia, including maternal age, presence of diabetes mellitus, chronic hypertension, and high body mass index.[13] Accordingly, the pathogenesis of pre-eclampsia involves not only placental aspects but also maternal factors, among which the kidney may play an important role.

During normal pregnancy there is a fall in vascular resistance, increase in renal blood flow, increase in GFR and attenuation of response to the vasoconstrictor angiotensin II (AngII).[14,15] In non-pregnant women AngII has significant influence on systemic and renal haemodynamics. It is a most potent vasoconstrictor and is able to decrease eGFR.[16,17] During normal pregnancy, reduced systemic vascular resistance leads to activation of the rennin-angiotensin system with elevation of circulating AngII levels. However, due to the physiological decrease in response to AngII seen in normal pregnancy, blood pressure remains low.[18] In pre-eclampsia the decreased response to AngII is abolished.[4] The systemic vascular structure and the kidney are exposed to high levels of circulating AngII without the protective effect of a reduced response to AngII. The net result is elevated blood pressure and a decrease in eGFR. Whether or not such changes occur to a lesser extent during the first 20 weeks of gestation in women prone to develop pre-eclampsia is unclear. These minor changes would not result in increased blood pressure or a change in eGFR but rather in subtle signs of abnormal renal function.

Such minor changes were previously described by Millar and colleagues who showed that urine kallikrein:creatinine ratio during the first half of pregnancy was significantly lower in women who developed pre-eclampsia in later pregnancy.[19] Another study that showed early changes in renal function as a predictor of pre-eclampsia used urine albumin and calcium:creatinine ratio as predictors of pre-eclampsia.[20]

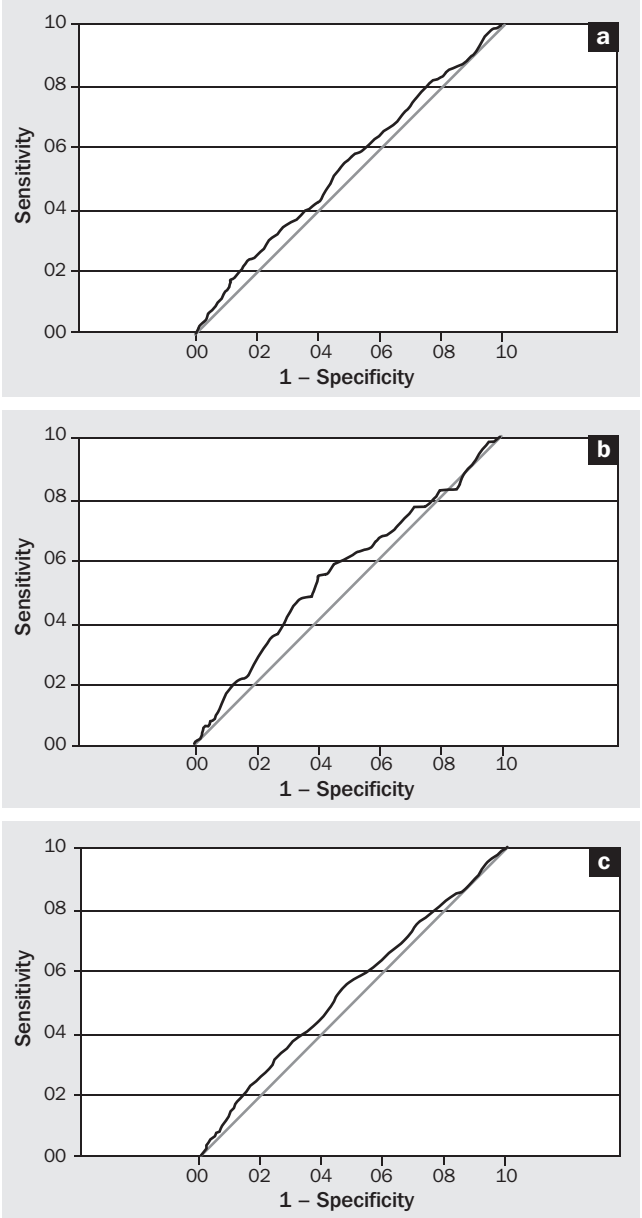

Fig. 1. Receiver operating characteristics curve analysis of creatinine level. **a)** Prediction of mild pre-eclampsia (area under the curve: 0.54, 95% confidence interval [CI]: 0.51–0.57, $P=0.021$); **b)** Prediction of severe pre-eclampsia (area under the curve: 0.56, 95% CI: 0.50–0.62, $P=0.033$); **c)** Prediction of all hypertensive disorders during pregnancy (mild and severe pre-eclampsia; area under the curve area: 0.54, 95% CI: 0.51–0.57, $P=0.002$).

Recently, the authors demonstrated an association between relatively high plasma potassium level and uric acid level in the first 20 weeks of pregnancy and the prevalence of pre-eclampsia in the second half of pregnancy.[21] These changes may reflect a suboptimal fall in vascular resistance and renal function in women prone to develop pre-eclampsia in the later course of their pregnancy. Undoubtedly, an easy and reliable marker for the prediction of pre-eclampsia is needed. Creatinine level may serve as an early indicator for the subsequent development of pre-eclampsia; however, prospective studies are needed to confirm this observation. □

References

1 ACOG Practice Bulletin. Diagnosis and management of preeclampsia and eclampsia. *Obstet Gynecol* 2002; **99** (1): 159–67.

2 Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979–1986. *Am J Obstet Gynecol* 1990; **163** (2): 460–5.

3 Moore-Maxwell CA, Robboy SJ. Placental site trophoblastic tumor arising from antecedent molar pregnancy. *Gynecol Oncol* 2004; **92** (2): 708–12.

4 Granger JP, Alexander BT, Bennett WA, Khalil RA. Pathophysiology of pregnancy-induced hypertension. *Am J Hypertens* 2001; **14** (6 Pt 2): 178S–185S.

5 Mogren I, Hogberg U, Winkvist A, Stenlund H. Familial occurrence of preeclampsia. *Epidemiology* 1999; **10** (5): 518–22.

6 Gleicher N. Why much of the pathophysiology of preeclampsia-eclampsia must be of an autoimmune nature. *Am J Obstet Gynecol* 2007; **196** (1): 5 e1–7.

7 Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. *Hypertension* 2008; **51** (4): 970–5.

8 Davison JM, Dunlop W. Renal hemodynamics and tubular function normal human pregnancy. *Kidney Int* 1980; **18** (2): 152–61.

9 Karumanchi SA, Maynard SE, Stillman IE, Epstein FH, Sukhatme VP. Preeclampsia: a renal perspective. *Kidney Int* 2005; **67** (6): 2101–13.

10 Venkatesha S, Toporsian M, Lam C *et al*. Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat Med* 2006; **12** (6): 642–9.

11 Levine RJ, Lam C, Qian C *et al*. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med* 2006; **355** (10): 992–1005.

12 Barton JR, Sibai BM. Prediction and prevention of recurrent preeclampsia. *Obstet Gynecol* 2008; **112** (2 Pt 1): 359–72.

13 Milne F, Redman C, Walker J *et al*. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. *BMJ* 2005; **330** (7491): 576–80.

14 Moran P, Lindheimer MD, Davison JM. The renal response to preeclampsia. *Semin Nephrol* 2004; **24** (6): 588–95.

15 Gant NF, Daley GL, Chand S, Whalley PJ, MacDonald PC. A study of angiotensin II pressor response throughout primigravid pregnancy. *J Clin Invest* 1973; **52** (11): 2682–9.

16 Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 1996; **334** (25): 1649–54.

17 Aizawa T, Ishizaka N, Taguchi J *et al.* Heme oxygenase-1 is upregulated in the kidney of angiotensin II-induced hypertensive rats : possible role in renoprotection. *Hypertension* 2000; **35** (3): 800–6.

18 Godard C, Gaillard R, Vallotton MB. The renin-angiotensin-aldosterone system in mother and fetus at term. *Nephron* 1976; **17** (5): 353–60.

19 Millar JG, Campbell SK, Albano JD, Higgins BR, Clark AD. Early prediction of pre-eclampsia by measurement of kallikrein and creatinine on a random urine sample. *Br J Obstet Gynaecol* 1996; **103** (5): 421–6.

20 Rodriguez MH, Masaki DI, Mestman J, Kumar D, Rude R. Calcium/creatinine ratio and microalbuminuria in the prediction of preeclampsia. *Am J Obstet Gynecol* 1988; **159** (6): 1452–5.

21 Wolak T, Sergienko R, Wiznitzer A, Ben Shlush L, Paran E, Sheiner E. Low potassium level during the first half of pregnancy is associated with lower risk for the development of gestational diabetes mellitus and severe pre-eclampsia. *J Matern Fetal Neonatal Med* 2010; **23** (9): 994–8.