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The Predictive Value of Urinary Calcium to Creatinine Ratio, Roll-Over Test and BMI in Early Diagnosis of Pre-Eclampsia

[1]Azita Fath Negad Kazemi, [1]Fahime Sehhatie, [1]Nilofar Sattarzade and [2]Mehrangiz Ebrahimi Mameghani
[1]Department of Gynecology and Obstetrics, [2]Department of Scientific Research Center,
Tabriz University of Medical Science, Tabriz, Iran

Abstract: Pre-eclampsia is a common complication of pregnancy and a major cause of maternal and perinatal morbidity and mortality. Therefore, predicting of pre-eclampsia would help achieving better results of midwifery care. Several biophysical and biochemical tests have been investigated for early detection of PE; however, none of them combines have shown accuracy and simplicity necessary to predict PE. The purpose of this study was to use a combination of tests for early prediction of pre-eclampsia. This study was performed at healthy centers of Tabriz in 1386. This was a prospective study that performed on 400 nulliparous women between the 28 and 32 weeks of gestation. At first weight, height, blood pressure on left position and supine position was measured and their sample of urine was catches for calcium and creatinine measuring. These women were followed until delivery. Of total 400 women 23 women developed pre-eclampsia.Using the ROC, urinary calcium-creatinine a <0.068 showed a sensitivity 35% and specificity 93%. BMI >28.88 showed a sensitivity 61% and specificity 92%. Roll-over test >20 mm Hg showed a sensitivity 52% and specificity 95%. When all of them were positive, they showed a sensitivity 17% and specificity 99.5%. The combination of three tests has low sensitivity, however it has high specificity for refusing of pre-eclampsia.

Key words: Predictive value, pre-eclampsia, calcium to creatinine ratio, roll-over test, body mass index, Iran

INTRODUCTION

Pre-eclampsia is a common complication of pregnancy (Cunningham *et al*., 2005; Szmidt *et al*., 2006) and occurs in about 5-10% of all pregnancies (Cunningham *et al*., 2005; Kazerooni and Hamze-Nejadi, 2003). Pre-eclampsia is defined as the development of hypertension (140/90 mm Hg) and proteinuria (>300 mg of urinary protein in 24 h) after 20 weeks of gestation and unfortunately is a major cause of maternal and fetal morbidity and mortality especially in growing countries (Barker and Kingdom, 2004; Roiz-Hernandez *et al*., 2006). In this, we have two major problems: delaying in early diagnosis and evaluating accuracy of severity of this disease (Barker and Kingdom, 2004). But because of starting of clinical process of pre-eclampsia from the beginning of pregnancy, so it is important to early diagnosis before progressive of disease (Cunningham *et al*., 2005). With early prediction and diagnosis the accurate, obstetrics supports will be done. So using of methods for early diagnosis of pre-eclampsia is very important (Szmidt *et al*., 2006). In 2 post decays >100 biochemical and clinical diagnostic methods have been developed but unfortunately, there is no test with >95% accuracy, for early diagnosis of pre-eclampcia (Gunasheela *et al*., 2004). Roll Over Test (ROT) is one of the prediction method of pre-eclampsia that firstly used by Grant (Cunningham *et al*., 2005). This test is safe and cheap. Positive roll over test is associated with an approximately three fold increased risk of developing Pregnancy Induced Hypertension. In this test, the patient is made to rest in lateral position for a while and blood pressure is recorded. She is then made to roll over to supine position and BP is recorded again 5 min later (Gunasheela *et al*., 2004). A rise in diastolic pressure of 20 mm of Hg is thought to be predictive of the person developing high blood pressure later during pregnancy (Gunasheela *et al*., 2004; Kaypour *et al*., 2006). In other hand on many studies have reported an hypercalciuria in pre-eclamptic women (Gilbert and Harmon, 2003; Taufield *et al*., 1987). In pregnancy physiological changes leads to increasing of Glomerular Filtration Rate (GFR) (Cunningham *et al*., 2005; Kazerooni and Hamze-Nejadi, 2003) that finally result in increasing of creatinine clearance and calcium secretion in urine . But in women's that developing pre-eclampsia because of vasospasm and decreasing of renal blood flow, creatinine clearance was decreased and they will have increasing of serum

Corresponding Author: Azita Fath Negad Kazemi, Department of Gynecology and Obstetrics,
Tabriz University of Medical Science, Tabriz, Iran

creatinine level (Barker and Kingdom, 2004; Saudan *et al*., 1998). One of the safe and easy methods for evaluating of calcium level is accidental sampling of urine for survey of urine calcium to creatin fraction (Kazerooni and Hamze-Nejadi, 2003).

On the other hand, other studies were shown that fat women more affected by pre-eclampcia (Hacker and Moor, 2004) and those people have 7 times more predisposition to hypertension than normal people (Gilbert and Harmon, 2003). In recent studies, Sibai were claimed the relation between Body Mass Index (BMI) and pre-eclamplia (Barker and Kingdom, 2004).

A lot of studies were done in different races and society about the predictable value of a lot of tests and different results were recorded (Wong *et al*., 2002). Absolutely paradoxical result's is consequences of sample size, prevalence rate of eclampcia, evaluating method and the race of peoples were studies.

Because of different predictable values and meddling of several factors in pre-eclampsia incidence and absences of good test for early diagnosis and prediction of pre-eclampsia, the researchers prepared this study for finding of coincidence prediction value among three tests in Tabriz.

MATERIALS AND METHODS

This prospective study was conducted from March up to November 2008 with attention to z value (1.96) in confidence level of 95%. The sample size were detected 400 women among 76 medical site 28 site were selected and sampling were done from 400 women.

All women who were nulliparas, between 28-32 weeks of gestation and being Tabriz province resident were included. All woman who had history or evidence of Aspirin and Calcium usage in pregnancy, Diabetic, renal disease, hypertension before pregnancy and early delivery except pre-eclampsia were excluded from the study.

After referring of patient to research center the mother weight were recorded (±100 g in accuracy) and the mother height were recorded (0.5 cm difference accuracy). Then the researchers calculated BMI (as weight in kilograms divided by the square of height in meters). In this study all days, before recording of weight, the bar of weight recorder adjusted with standard weight and the mother weight were recorded without shoes and minimum clothes. For recording of mother blood pressure in left lateral and supine position with wearing of manometer cuff in right arm, systolic and diastolic blood pressure were recorded by hearing of first and fifth krutocof sound. Then the researchers recorded the dorsal supine blood pressure after 5 min. An increase of >20 mm Hg in diastolic BP was considered a positive test result.

In same times the patient urine sample was collected and analyzed for total urine calcium, creatinine levels and a quantitative determination of total calcium and creatinine was performed by Danesh Laboratory (the specific laboratory for the study). After that blood pressure was recorded each 2 weeks if blood pressure was 140/90 and upper, the urine protein was recorded and with +1 proteinuria and upper, pre-eclampsia was detected. In statistical analysis, the researchers used Student's t-test. The receiver-operator curve analytic technique was used to determine the best cut-off level for prediction of pre-eclampsia. The sensitivity, specificity, positive and negative predictive value was calculated according to this cut-off value.

RESULTS

Of the 400 women included in this study, 23 developed pre-eclamcia before labor. Data concerning maternal and gestational age are shown in Table 1. Comparison between these data did not show any significance difference between gestational age, maternal age, height, left lateral supine blood pressure and urine creatinine level ($p>0.05$). However, the mean weight, BMI, dorsal supine diastolic blood pressure and left lateral

Table 1: Clinical and laboratory characteristic of study groups

Characteristics	Normotensive group (N = 377)	Pre-eclamptic group (N = 23)
Mean maternal age (years) (±SD)	23.78±0.69	22.6±0.188
Mean gestational age when joining the study, weeks (±SD)	29.46±1.58	28.57±1.37
High (±SD)	158.23±5.22	158.91±5.78
Weight (±SD)	65.76±7.94	75.54±11.01
BMI (±SD)	26.24±2.72	29.93±4.20
Left lateral diastolic blood pressure (±SD)	54.62±13.86	62.17±14.21
Dorsal supine diastolic blood pressure (±SD)	59.81±13	77.17±13.21
Difference of diastolic blood pressure in two position (±SD)	5.2±8.2	15±9
Mean urine calcium level (±SD)	14.12±5.57	9.93±5.28
Urine creatinine level (±SD) Mean	109.15±56.42	110.64±41.53
Mean calcium to creatinine ratio (±SD)	0.155±0.084	0.106±0.077

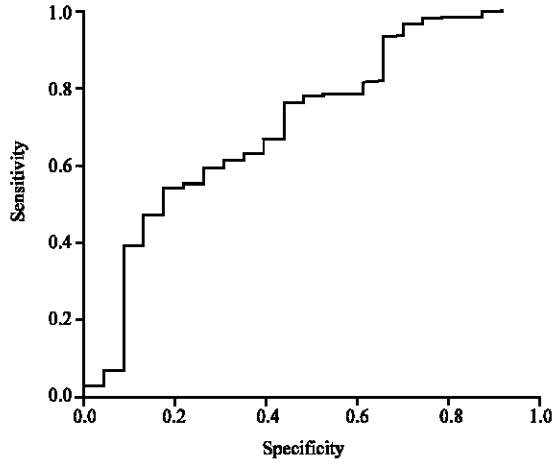

Fig. 1: Receiver-operator curve for calcium to creatinine ratio (cut-off level set at 0.068)

supine diastolic blood pressure, urine calcium level and calcium to creatinine ratio were significant difference between two groups. The mean of urine calcium to creatinine ratio was significantly lower in the pre-eclamptic group (0.106±0.077 mg dL^{-1} in the pre-eclamptic group and 0.155±0.084 in the normotensive group ($p<0.007$).

Using the receiver operator curve (Fig. 1), a cut-off level of 0.068 for calcium to creatinine ratio was chosen for predicting of pre-eclampsia. In 8 pre-eclamptic women and 26 normotensive women the calcium to creatinine ratio was equal or <0.068. This level thus yielded a sensitivity of 35% and specificity of 93%. Positive and negative predictive values of 24 and 96% were collected (Table 2). The mean difference of diastolic blood pressure in dorsal supine and left lateral position in pre-eclamptic women were high (15±9 mm Hg in the pre-eclamptic group and 5.2±8.2 in normal, $p<0.0001$). About 12 people of patient group and 19 person of normal group had 20 mm Hg differences in diastolic blood pressure, however a sensitivity of 52% and specificity of 95% negative and positive predictive values of 97 and 39% were calculated (Table 2). Also the mean of BMI in pre-eclamptic women were high (2.93±1.20 kg m^{-3} in patient and 26.24±2.72 kg m^{-2} in normal person, $p<0.0001$). Using the receiver operator curve (Fig. 2), a cut-off point of 28.88 for BMI was chosen for predicting of pre-eclampsia. About 44 pre-eclamptic women and 99 normotensive women, the BMI was equal or >28.88. This level thus yielded a sensitivity of 61% and specificity of 92%. Positive and negative predictive values of 33 and 97% were collected (Table 2). With attention to accumulation of three aforementioned test 4 person of pre-ecliptic group and 2 person of normal group were positive in 3 tests. So the

Table 2: Prediction of pre-eclampsia using urine calcium to creatinine ratio, roll-over test results and BMI

Marker	Sensitivity	Specificity	PPV	NPV
Calcium to creatinine ratio	35	93.0	24	96.0
Roll-over test	52	95.0	39	97.0
BMI	61	92.0	33	97.0
Combination of three tests	17	99.5	67	95.2

NPV: Negative Predictive Value; PPV: Positive Predictive Value

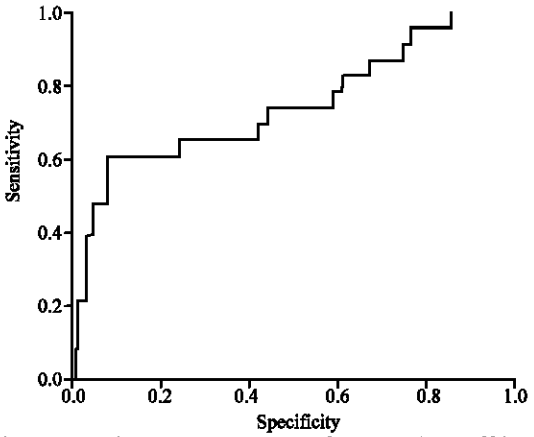

Fig. 2: Receiver-operator curve for BMI (cut-off level set at 28/88)

sensitivity, specificity, positive and negative predictive values of combination of three tests, sequence were 17, 99.5, 67 and 95.2% (Table 2).

DISCUSSION

The results of this study were shown that the mean of urine calcium to creatinin ratio between patient and normal group was significant, also similar result were shown by Kazerooni and Hamze-Nejadi (2003). They showed that if the urine calcium to creatinine level was equal or <0.229 the sensitivity, specificity, positive and negative predictive value sequentially were 75, 77, 21 and 97%. In addition Izumi *et al.* (1997) in own study with detecting of 0.08 as cut off point for urine calcium to creatinine ratio, the numbers lower that cut off point can predict pre-eclampsia. In this study, the researchers found significant difference between diastolic blood pressure in lateral and dorsal supine position in two groups. This results were similar to Kaypour *et al.* (2006) but Andersen (1980) were shown that position charge test do not have enough sensitivity and specificity for predicting of pre-eclampsia.

In the study, the body condition score mean difference was significant between normal and patient group. This result were similar to Kaypour *et al.* (2006) studies. They were shown that cut off point of 29 in BCS had 41% sensitivity, 95% specificity, 34 and 93% positive and negative predictive value for predicting of

pre-eclampsia. Also Cedergren (2006) in Swede. In his study was approved that increasing of Body weight and body condition score during pregnancy can increase pre-eclampsia risk and other probable pregnancy consequences that similar to the study.

May be the difference among the study and the surveys depend to difference in sampling, sample size and the time of sampling.

CONCLUSION

In the study, researchers observed that if three tests were positive in a patient or normal person, despite of low sensitivity, it will have the minimum specificity (99.5%) and positive predictive value for screening and predicting of preeclampsia.

Calcium to creatinine ratio, BMI and ROT test did not accurate if done. As a separate test for predicting of pre-eclampsia but the clinical usability of those test are significanctin pre-eclampsia control so it is advised the use of these cheap and low risk tests specially in 28-32 weeks of pregnancy for screening of patient then with predicting of patient it can be administered Aspirin and undervisionig of high risk patients and doing of on time labor, it can be controled the thousand death of neonatal and mothers.

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