

The Role of Some Clinical and Laboratory Tests in the Prediction of Preeclampsia

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Abstract

Eighty eight healthy primigravid women studied in the period between 14-24 weeks and in the period between 28-32 weeks of gestation to predict the later development of preeclampsia. Urine evaluated for microalbuminuria and calcium excretion (calcium/ creatinine ratio), also plasma fibronectin and isometric hand grip exercise test (IHET) were measured. Preeclampsia developed in 17 women (19.3%). Plasma fibronectin was found to have the best sensitivity positive and negative predictive values while IHET had the best specificity in the period between 14-24 weeks. In the period between 28-32 weeks plasma fibronectin showed the best sensitivity, specificity positive and negative predictive values. The best results were obtained in the two periods when plasma fibronectin was combined with calcium/creatinine ratio, yet this combination is not superior to the results of plasma fibronectin alone.

Introduction

PREECLAMPSIA is a complex clinical syndrome with hypertension representing but one manifestation pathologically important events in the development of preelampsia include poor trophoblastic perfusion elaboration of endothelial cell

toxins activation of coagulation, impairment of vasopressor function and altered endothelial permeability, the primary immunologic genetic and biochemical bases of preeclampsia remain speculative [1].

Treatment of preeclampsia remained suboptimal because of the unknown etiolo-

gy of the disease. Until the etiology of the disease is revealed the main goal would be prevention [2].

Prevention of preeclampsia does not only require knowledge of the pathophysiologic mechanism of the disease, but also availability of methods of early detection and means of intervention and correction of pathophysiologic changes. The signs and symptoms of preeclampsia become apparent at a relatively late stage of pregnancy, usually in the third trimester. However, the underlying causes that are thought to be responsible for the disease process appear to occur much earlier in pregnancy, between 8th and 10th weeks of gestation [3].

The availability of simple predictors of the subsequent development of preeclampsia might allow prevention treatment and further improve outcome. Early recognition and treatment with bed rest, low-dose aspirin and calcium supplementation favorably influence this outcome [4].

The aim of this study was to show the value of the presence of microalbuminuria, hypocalcemia increased plasma fibronectin and positive IHET, separately or in combination in the prediction of preeclampsia. This is in order to find an easy and practical screening test to predict the development of preeclampsia.

Material and Methods

In this study, one hundred healthy primigravid women of the attendants of

the Antenatal Care Clinic of El-Minia University Hospital were prospectively recruited into the study between september 1991 and september 1992.

Women recruited in the study fulfilled the followed criteria:

1. Healthy primigravidae
2. No past history of cardiovascular or renal diseases.
3. Gestational age when included into the study ranged between 14 and 24 weeks.
4. Blood pressure at the beginning of the study was less than 140/90 mm.Hg.

All the subjects were asked to refrain from taking aspirin, other antiprostaglandins or big doses of calcium.

On admission into the study the following was done for all subjects:

1. A complete medical and obstetric / gynecological examinations
2. Ultrasonographic examination for estimation of gestational age and detection of any abnormality such as congenital malformations or low lying placenta which if present the women would be excluded from the study.
3. Isometric hand grip exercise test was performed to each subject by the same individual [5].

Laboratory Investigations:

The following laboratory investigations were done for all subjects on admission into the study between (14-24 weeks) and

repeated in the early third trimester (28-32 weeks) which included:

1. Complete urine analysis using total screen urine strips obtained from Behringwerke AG, Marburg, West Germany, to exclude cases with gross albuminuria.
2. Urine culture (cases giving positive results were excluded from the study) to avoid false positive test for microalbuminuria.
3. Microalbuminuria on the morning sample of urine determined using immunodiffusion technique [8] .
4. Selectivity index of albuminuria which is the ratio between IgG clearance and albumin clearance and comprises in addition to microalbuminuria, measurement of serum albumin, serum IgG and urine IgG using immunodiffusion technique [8]
5. Calcium / creatinine ratio in urine which comprises estimation of calcium and creatinine concentrations in urine.
6. Plasma fibronectin estimation using immunodiffusion technique [8]

All samples kept at - 70°C till the time of assay.

Evaluation of the Predictive Tests:

The predictive values of the different tests are evaluated using the following parameters:

I-Sensitivity =

$$\frac{\text{No. of true positive cases (TP)}}{\text{No. of true Positive cases (TP)+ No. of false negative cases (FN)}}$$

$$\text{II-Specificity} = \frac{\text{TN}}{\text{T N + F P}}$$

$$\text{III- Positive predictive value} = \frac{\text{TP}}{\text{T P + F P}}$$

$$\text{IV- Negative predictive value} = \frac{\text{TN}}{\text{T N + F N}}$$

N.B.

T P = The test is positive in women who developed preeclampsia

T N = The test is negative in women who do not developed preeclampsia

F P = The test is positive in women who do not developed preeclampsia

F N = the test is negative in women who developed preeclampsia.

Statistical Analysis:

For qualitative characteristics including the clinical parameters, blood pressure changes and values of laboratory predictive tests in the preeclamptic and normotensive groups. Means and standard deviations were calculated and compared using unpaired t-test. *p* value of < 0.01 was taken as the level of statistical significance.

For qualitative characteristics including the different predictive values of the predictive tests. The χ^2 test was used to

compare the predictive values of the tests in the two estimations (between 14-24 weeks) and (between 28-32 weeks) and on comparing the predictive values of the different combination of tests.

Results

Eighty eight women of the one hundred women included at the beginning of the study, were successfully followed up till the time of delivery.

Preeclampsia developed in 17 (19.3%) of those who completed the study. One woman of the preeclamptic group delivered prematurely at 28 weeks gestation due to severe preeclampsia.

On admission to the study, there was statistically significant difference between the preeclamptic group and the normotensive group as regards the weight and quetelet index but there was no statistically significant difference between the two

groups as regards age, height, gestational age, systolic, diastolic or mean arterial blood pressure.

The cut off points of the calcium/creatinine ratio in the periods between 14-24 weeks gestation and 28-32 weeks gestation for subsequent development of preeclampsia were taken as one standard deviation below the mean of normotensive cases i.e (0.07 and 0.06 respectively). While the same points for microalbuminuria and plasma fibronectin in the two estimations were taken as one standard deviation above the mean of normotensive cases i.e. (10 ug/ml and 11 ug/ml) for microalbuminuria and (293.02 ug/ml and 344.68 ug/ml) for plasma fibronectin (Tables 1 & 2).

On comparing the predictive values of the different tests both in the periods between 14 - 24 weeks gestation and 28 - 32 weeks gestation. There were no statistically significant differences among the different

Table (I): Comparison Between the Mean Values of the Laboratory Predictive Tests in the Normotensive Group and Preeclamptic Group on Admission into the Study (Between 14-24 Weeks Gestation).

	Normotensive group n= 71 Mean \pm SD	Preeclamptic group n= 71 Mean \pm SD	p value
Calcium/creatinine ratio	0.12 \pm 0.05	0.07 \pm 0.04	0.0001
Microalbuminuria ug /ml	7.67 \pm 2.33	8.42 \pm 2.02	0.103
Plasma Fibronectin ug /ml	240.72 \pm 52.30	332.70 \pm 53.07	0.0001

predictive tests as regards the preeclamptic group "true positive cases" but there were statistically significant differences as regards the normotensive group "false positive cases" due to high value of false positive cases obtained with microalbuminuria. The sensitivity, positive and negative predictive values improved in the second estimation (between 28 - 32 weeks), although the specificity remained the same for calcium / creatinine ratio and IHET. Yet, the sensitivity, specificity, positive and negative predictive values improved in the second estimation for microalbuminuria and plasma fibronectin (Tables 3 & 4).

In the period between 14-24 weeks gestation, plasma fibronectin was found to have the best sensitivity, positive and negative predictive values. While, IHET had the best specificity (Table 3).

In the period between 28-32 weeks gestation, plasma fibronectin was found to

have the best sensitivity, specificity, positive and negative predictive values (Table 4).

On using the different combination of the predictive tests both in the periods between 14-24 weeks gestation and 28-32 weeks gestation, there were no statistically significant differences among the different combination of the predictive tests performed. Yet the best results were obtained when plasma fibronectin was combined with calcium/creatinine ratio (Tables 5&6). However, this combination is not superior to the use of plasma fibronectin alone (Tables 3&4).

Selectivity index was used to assess the selectivity of albuminuria. It is low in cases with significant microalbuminuria which indicates that microalbuminuria is a selective albuminuria.

$$S.I. = \frac{\text{Clearance of IgG}}{\text{Clearance of albumin}}$$

Table (2): Comparison Between the Mean Values of the Laboratory Predictive Tests in the Normotensive Group and Preeclamptic Group in the Period Between 28-32 Weeks Gestation.

	Normotensive group n= 71 Mean ± SD	Preeclamptic group n= 71 Mean ± SD	p value
Calcium/creatinine ratio	0.10 ± 0.04	0.05 ± 0.03	0.0001
Microalbuminuria ug /ml	8.17 ± 2.33	9.58 ± 2.64	0.06
Plasma Fibronectin ug /ml	289.49 ± 55.19	397.58 ± 37.66	0.0001

Table (3): Predictive Value of the Different Tests in Preeclamptic and Normotensive Groups (Between 14-24 Weeks Gestation).

	Calcium / creatinine ratio ≤ 0.07	Microalbuminuria $\geq 10 \text{ lg / ml}$	Fibronectin $\geq 293.03 \text{ lg / ml}$	Isometric hand grip exercise test
Women with preeclampsia*	9 / 17	7 / 17	11 / 17	6 / 17
Women with normal blood pressure**	4 / 71	20 / 71	4 / 71	3 / 71
Sensitivity (%)	53	41	65	35
Specificity (%)	94	72	94	96
Positive predictive value (%)	69	26	73	67
Negative predictive value (%)	89	84	92	86

* $\chi^2 = 4.722$

$p = 0.1933$

** $\chi^2 = 29.071$

$p = 0.0001$

Table (4): Predictive Value of the Different Tests (Between 28-32 Weeks Gestation).

	Calcium / creatinine ratio ≤ 0.07	Microalbuminuria $\geq 10 \text{ lg / ml}$	Fibronectin $\geq 344.68 \text{ lg / ml}$	Isometric hand grip exercise test
Women with preeclampsia *	12 / 17	8 / 17	13 / 17	9 / 17
Women with normal blood pressure **	4 / 71	18 / 71	3 / 71	3 / 71
Sensitivity (%)	70	47	76	53
Specificity (%)	94	75	96	96
Positive predictive value (%)	75	33	81	75
Negative predictive value (%)	93	85	94	89

* $\chi^2 = 3.732$

$p = 0.2919$

** $\chi^2 = 25.679$

$p = 0.0001$

Table (5): Predictive Value of the Different Combinations of Predictive Tests (Between 28-32 weeks gestation).

	Calcium/ creatinine ratio + Micro- albuminuria	Calcium/ creatinine ratio + Fibro- nectin	Calcium/ creatinine ratio + IHET	Microal- buminuria + Fibro- nectin	Micro- albuminuria + IHET	Fibro- nectin + IHET
Women with preeclampsia*	6 / 17	8 / 17	4 / 17	6 / 17	4 / 17	5 / 17
Women with normal blood pressure**	4 / 71	3 / 71	3 / 71	3 / 71	3 / 71	3 / 71
Sensitivity (%)	35	47	24	35	24	29
Specificity (%)	94	96	96	96	96	96
Positive predictive value (%)	60	73	57	67	57	63
Negative predictive value (%)	86	88	84	86	84	95

* $\chi^2 = 3.091$
 ** $\chi^2 = 0.275$

$p = 0.686$
 $p = 0.998$

Table (6): Predictive Value of the Different Combinations of Predictive Tests (Between 28-32 Weeks Gestation).

	Calcium/ creatinine ratio +	Calcium/ creatinine ratio +	Calcium/ creatinine ratio +	Microal- buminuria +	Micro- albuminuria +	Fibro- nectin +
	Micro- albuminuria	Fibro- nectin	IHET	Fibro- nectin	IHET	IHET
Women with preeclampsia*	6 / 17	8 / 17	4 / 17	6 / 17	4 / 17	5 / 17
Women with normal blood pressure**	4 / 71	3 / 71	3 / 71	3 / 71	3 / 71	3 / 71
Sensitivity (%)	41	59	53	41	41	53
Specificity (%)	94	69	96	96	96	96
Positive predictive value (%)	64	77	75	70	70	75
Negative predictive value (%)	87	91	92	87	87	92

* $\chi^2 = 2.082$ $p = 0.8377$ ** $\chi^2 = 0.275$ $p = 0.998$

Discussion

The ideal predictive test should be simple and easy to perform early in pregnancy and be reproducible and non invasive with high sensitivity and high positive predictive value. Such an ideal predictive test is not existing at this moment.

The predictive values of the IHET performed in the third trimester obtained in this study are in concordance with those obtained by Degani et al. [5] and Mary et al. [9], as regards the specificity, positive and negative predictive values but not in concordance with them as regards the sensitivity of the test. These authors were performing the roll over test followed by the IHET and they did not report the interval between performing the two tests. This may affect the sensitivity of the test. The sensitivity reported by both of them was not exactly the same. Degani et al. [5] who were the first to recommend the use of IHET as a predictor of preeclampsia, reported a higher sensitivity.

The predictive values for microalbuminuria tested early in the third trimester obtained in this study are in concordance with those reported by Rodriguez et al. [10] and Mostafa and Mostafa [11]. However, the results of this study are slightly less favorable than those reported by the last author.

The findings of this study although showed low predictive value of microalbu-

minuria, yet, it is not in concordance with that of Lopez-Espinoza et al. [12] and Konstantin-Hansen et al. [13]. The former reported that proteinuric preeclampsia, as defined by relatively insensitive routine laboratory measurements, is not preceded by a phase of increasing albumin loss which can be detected by more sensitive assay. The latter stated that microalbuminuria can not be used to predict women in whom preeclampsia will develop among normal women.

The predictive values obtained by early estimation of calcium/creatinine ratio reported in this study is in concordance with that reported by Sanchez-Ramos et al. [14] who stated that urinary calcium excretion can be used as a predictor of preeclampsia as early as the period between 20-24 weeks of gestation.

The predictive value of calcium/creatinine ratio obtained in this study in the period between 28-32 weeks of gestation are in concordance with those obtained by Rodriguez et al. [10] and Mostafa and Mostafa [11].

The use of calcium/creatinine ratio as a test of hypocalciuria adopted in this study and those of Rodriguez et al. [10] and Mostafa & Mostafa [11], instead of the cumbersome use of 24-hour urine collection to test for hypocalciuria is more simple and gave the same results obtained by Sanchez-Ramos et al. [14] who were using a 4-hour urine method.

Fibronectin levels may change in association with several disease status. Levels decrease in cases of liver insufficiency, disseminated intravascular coagulation, respiratory distress syndrome, sepsis and polytrauma and increase in patients with rheumatoid arthritis [15].

In this study, although thorough investigations of these conditions were not done to women that showed high levels of fibronectin, non of these women showed the clinical manifestations of these conditions.

The predictive values of fibronectin (between 14-24 weeks and between 28-32 weeks gestation) reported in this study are in concordance with what have been previously reported by Ballegeer et al. [4] and Lockwood and Peters [15]. Also, Mostafa and Mostafa [11] reported the same results between 28-32 weeks gestation.

On comparing the different predictive tests used in this study between 14-24 weeks gestation, plasma fibronectin was found to have the best sensitivity Positive and negative predictive values. While, IHET was found to have the best specificity.

On comparing the different tests between 28-32 weeks fibronectin was found to have the best predictive values.

Although there is no available study which compared the predictive tests used in this current study especially in the peri-

od between 14-24 weeks gestation (midtrimester). However, these findings are in accordance with what has been deduced by Bailegeer et al. [4] who compared the predictive value of plasma fibronectin with other predictive tests and concluded that increased plasma fibronectin level is the best predictor of gestational hypertension with or without proteinuria and that its level in plasma increases several weeks before the development of hypertension.

In this study when using different combination of the predictive tests as suggested by Rodriguez et al. [10] both between 14-24 weeks and 28-32 weeks gestation, the best combination was that obtained with plasma fibronectin and calcium/creatinine ratio. But when this combination was compared with the results obtained with plasma fibronectin alone it was not found to be superior. This finding is not in accordance with the findings reported by Rodriguez et al. [10] and Mostafa & Mostafa [11]. However, these authors were trying to find a better predictive test than the use of microalbuminuria alone. So, they recommended the use of microalbuminuria in combination with calcium/creatinine ratio. And although in this study this combination gives a better predictive value than the use of microalbuminuria alone, yet, this finding could not be generalized to the other tests particularly those with high predictive value as plasma fibronectin.

Selectivity index was performed between 14-24 weeks and repeated between 28-32 weeks of gestation and showed microalbuminuria obtained in the preeclamptic women to be selective, this is in accordance with what was stated by Hindmarsh [16].

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