INTERNATIONAL JOURNAL
OF ADVANCED RESEARCH

RESEARCH ARTICLE

Correlation between plasma fibronectin level and renal function in pregnant women with Preeclampsia.

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Manuscript Info

Abstract

Background:- Worldwide, pre-eclampsia and eclampsia contribute to the death of a pregnant woman every three minutes((Emillja, 2011). Preeclampsia is one of the leading causes of maternal and perinatal morbidity and mortality. Although the exact pathogenesis of preeclampsia still remains to be unrivalled and is most likely multifactorial; it is increasingly clear that pathological processes at the interface of the fetal and maternal circulation leading to generalized endothelial cell dysfunction contribute to the spectrum of the disease . The signs and symptoms of the disease are well recognized and they characteristically manifest in the second to third trimester, although the underlying pathology is present at earlier stages of pregnancy. The identification of reliable screening markers that could predict the subsequent onset of preeclampsia before maternal clinical manifestations become apparent would permit major improvements in obstetric care through better targeting of antepartum surveillance.

Objectives:- The purpose of this study was to examine plasma fibronectin levels and serum renal function test throughout normotensive pregnancy and preeclampsia and to analyze their predictive values for the detection of preeclampsia within the second and third trimester of pregnancy.

Methods:- Case control study in which Blood samples were collected from 50 healthy pregnant women and 50 Preeclamptic women. Plasma samples were assayed for fibronectin by enzyme-linked immunosorbent assay and measurement of uric acid, uria nitrogen and serum creatinine by continuous segmented flow analyzer

Results:- In both groups, fibronectin levels rose as pregnancy advanced, but in women with preeclampsia, this increase was significantly higher ($P = 0.0001$). Throughout pregnancy, patients with preeclampsia exhibited significantly higher serum uric acid, than did control subjects. A difference was established (preeclampsia, 7.5±0.9; control, 3.2±0.44mg/dl [mean ± SEM]; $P = . 0.001$. The best cutoff point and time interval to calculate predictive values for plasma fibronectin were 444 mg/dl. Sensitivity, specificity, and positive and negative predictive values were 98%, 100%, 100%, and 98%, respectively.

Conclusion:- In women in whom clinical preeclampsia developed, endothelial damage seemed to be present since early gestation through early changes in some biochemical indicators during early pregnancy . Plasma fibronectin levels of ≥444 μg/mL may help in the early detection of preeclampsia in healthy nulliparous women. Also serum uric acid could help in early detection of preeclampsia.

Introduction:-

Preeclampsia is a specific state of pregnant women which involves an increase of arterial blood pressure, accompanied by proteinuria, oedema or both.The incidence of preeclampsia is 5-7% in all pregnancies (Smith,1993) .Preeclampsia is one of the leading causes of maternal and perinatal morbidity and mortality(R. Madazli et al ,2005) .

The association of elevated plasma fibronectin in preeclampsia have been documented in previous studies indicating an endothelial cell dysfunction(Itemobong etal,2011) .An association between uric acid and preeclampsia has been acknowledged since the early 1900s, and increased levels of plasma uric acid have frequently been associated with severe pregnancy-related disease and poorer pregnancy outcomes(Annabel,2010).

This study was performed to assess the variation or alterations in plasma fibronectin in both patients and control and to evaluate and compare the clinical utility of various biological markers in predicting preeclampsia. . This study was the first study in Iraq and Arab countries .

Modern obstetric care has reduced the incidence of eclampsia in high income countries. In Scandinavia the incidence of eclampsia is 0,05%(Andersgaard,2006). In low-income countries the incidence varies but a figure from WHO is 2,8%(WHO,2005). Pre-eclampsia and eclampsia are still among the most important causes of maternal mortality, both in high- and low-income countries(WHO,2005; Khan,2006).

Aim of study:-

1-To determine the validity of plasma fibronectin as a marker of preeclampsia in women with preeclampsia .
2-To evaluate and compare the clinical utility of plasma fibronectin and serum uric acid for predicting preeclampsia
3-To evaluate whether serum measurement of urea and creatinine would contribute to evaluate preeclampsia.
5- To determine the demographic risk factors and values of blood pressure to predict preeclampsia.

Methods:-

This is a **case control study** in which Blood samples were collected from 50 healthy pregnant women and 50 Preeclamptic women. Plasma samples were assayed for fibronectin by enzyme-linked immunosorbent assay and measurement of uric acid, urea nitrogen and serum creatinine by continuous segmented flow analyzer . All these measurement were compared between groups. In the second and third trimester of pregnancy.

Results:-

Demographic and clinical features :

The results presented in this study were based on the analysis of 50 patients with preeclampsia, compared with 50 apparently healthy pregnant considered as controls .

Distribution of patients According to Age :

In the present study, the age of preeclampsia patients ranged between 15 to 38 years with a mean age of 28±3 years With (p value = 0.001) as shown in table (2).

Renal function test:

Blood urea, serum creatinine and serum Uric acid were found to be highly significantly in preeclampsia and in different types of preeclampsia (p 0. 001) as seen in table(3)

Correlation coefficient between total plasma fibronectin with renal function tests , blood pressure and demographic characteristics of preeclampsia.

There was positive   relationship between total plasma fibronectin and serum uric acid(p 0.044)   among preeclampsia women but this relationship was not found with other renal function tests

There was positive   relationship between total plasma fibronectin and diastolic blood pressure (p 0.045) among preeclampsia women but this relationship was not found with systolic blood pressure.

There was positive relationship between total plasma fibronectin and BMI, gestational age (p 0. 031, 0.002respectively) among preeclampsia women but this relationship was not found with maternal age as shown in table (4)

Correlation coefficient of total plasma fibronectin between the preeclampsia and normal pregnancy groups
The Plasma fibronectin was found to be highly significantly different between the preeclampsia and normal pregnancy groups (p 0.001). As shown in table(5).

The best cut-off values of plasma fibronectin based on ROC curve analysis:
The best cut-off values of plasma fibronectin to diagnosis preeclampsia based on ROC curve analysis were 440 µg/ml and the areas under the curve equal to 0.98.as shown in table (6).

The sensitivities and false-positive rates (receiver operating characteristic curve Sensitivity =98% ,Specificity =100% ,Positive predictive value=100% Negative predictive value =98%

The sensitivities and false-positive rates (receiver operating characteristic (ROC) curve analysis for the detection of preeclampsia by measurement of plasma fibronectin concentration .The areas under the curve equal to 0.98 was determined for the prediction of preeclampsia

Discussion:-
Serum uric acid,blood urea and serum creatinine in preeclampsia:
The current study showed that serum uric acid, serum creatinine and blood urea of preeclampsia women were significantly higher than those with normal pregnancy. Also showed higher significance between preeclampsia groups as preeclampsia progress.This is agreement with other study conducted by (Hidajet,2012).suggests that Creatinine, urea and uric acid are non-protein nitrogenous metabolites that are cleared from the body by the kidney following glomerular filtration. Measurements of plasma or serum concentration of these metabolites are commonly used as indicators of kidney function and other conditions.

Therefore, their determination in serum during pregnancy is of a major importance to diagnose kidney function especially at women with preeclampsia signs. This would be used to evaluate kidney function as well as the possibility of a secondary source of urea or of the nitrogen part of urea increase (Blood urea nitrogen) in plasma(Stillman,2007). This can be explained with the occurrence of microangiopathic haemolysis, which is related to the injury of endothelium in the group with preeclampsia changes.

As a consequence, urea synthesis in liver would be increased as well as the incapability of kidneys to excrete urea from blood with such a high concentration(Myatt,2009).

Relation of level of plasma fibronectin with preeclampsia:
Alterations in the concentrations of placental markers of poor placentation may precede the clinical onset of preeclampsia(Madazli,2005).

Indeed, as shown in the present study, highly significant increased plasma levels of fibronectin in patients who developed preeclampsia as compared with healthy pregnant women. Also this study shows highly statistically difference between mild and sever preeclampsia.

The interpretation of this result may be related to fact that Fibronectin is synthesized in the endothelial cell and its elevated level may be an indicator of endothelial damage and continuously increased as the preeclampsia progressed . Fibronectin as a valuable predictor of subsequent preeclampsia has been demonstrated by other investigators(Bolin,2012; Lee,1997)).

Increased plasma fibronectin levels, even before the clinical onset of preeclampsia, confirms the concept of preeclampsia as an endothelial cell dysfunction disease(Itemobong,2011). Based on ROC curve in the current study, fibronectin was potentially clinically useful test in establised preeclampsia.

Fibronectin had highest predictive value (AUC= 0.98). As to the differential validity between two groups (control vs preeclampsia), using cutoff value of 444 mg/dl, sensitivity was 98 %, specificity was100 %,positive predictive value was 100 %.

This differential validity between two groups (control vs preeclampsia)shows highly statistically difference (p= 0.001).There have been only one study used ROC curve not consistent ; indicated that fibronectin was less effective (Madazli et al,2005).

Corelation between plasma fibronectin and blood urea ,serum creatinine and serum uric acid:
This study showed moderate positive correlation between serum uric acid level and plasma fibronectin level in preeclampsia (r=0.286, p=0.04) and weak negative correlation between serum creatinine , and blood urea with plasma fibronectin in preeclampsia (r=-0.07,p=0.6 ,r=- 0.103,p=0.4) respectively, this is agreement with (Gersch *et al.,* 2009) suggests that in women with pre-eclampsia, serum uric acid levels are increased compared with levels in healthy pregnant women.

The proposed reasons for hyperuricemia in pre-eclampsia include decreased renal tubular excretion and increased oxidative stress, caused mainly by the ischemic placenta. Another mechanism that may be involved after the development of preeclampsia may be the reduction in gfr that occurs in many, but not all, cases of preeclampsia.

In the setting of ischemia, xanthine dehydro genase is converted to xanthine oxidase, which metabolizes purines into uric acid, superoxide anions and hydrogen peroxide. These compounds have been implicated in ischemia–reperfusion injury, and therefore potentiate uric acid production. This result can be explained the positive correlation between serum uric acid level with plasma fibronectin level .Similar results are reported by (Fieg*et al.*, 2004 ; Anker, s. D. *Et al.* , 2003) , there have been studies not consistent ; one indicated a significantly negative correlation (Homer*et al.,*2008).

Suggests one explanation for this apparent discrepancy could be that for some women, worsening placental ischemia with pre-eclampsia ultimately results in decreased placental cell numbers and a subsequent reduction in uric acid production. Where two showed no association (Cnossen *et al* , 2009; Koopmans. *Et al.,* 2009) .suggests lacking sensitivity and specificity for routine clinical use.

Table 1. A categorization of risk factors for pre-eclampsia (Dildy,2007).

Maternal-Specific risk Factors	Partner-Related risk Factors	Presence of specific underlying disorders	Pregnancy-Associated risk Factors
1-History of previous pre-eclampsia, 2- Maternal age, long interval between pregnancies 3- Family history	1Nulliparity/primipa ternity 2-Limited sperm exposure, donor insemination	1-Chronic hypertension and renal disease. 2- Obesity, insulin resistance, low maternal birth weight 3- Gestational diabetes, type-1 diabetes mellitus 4-Activated protein C resistance (factor V Leiden), protein S Deficiency. 5- Antiphospholipid antibodies	1- Multiple pregnancy 2-Foetus with chromosomal anomalies (trisomy 13) 3- Hydatidiform moles

Table (2): Descriptive statistic of age in preeclampsia and control .

Age (years)	Range	Mean ±S.D.	P value
Control	20- 35	27±5.7	0.001
Preeclampsia	15- 38	28±3	

Table 3: relation between preeclampsia, types of preeclampsia and control group according to renal function tests .

Renal function tests	Control	Preeclampsia	P-value	Type of preeclampsia		
				Mild	Sever	P-value
Blood urea(mg/dl)	**28.4±5.3**	**40.2±5.9**	**0.000**	**37.6 ± 0.8**	**46± 0.9**	**0.001**
Creatinine(mg/dl)	**0.52±0.12**	**0.72±0.13**	**0.001**	**0.6643±0.08**	**0.89 ±0.038**	**0.001**
Uric acid (mg/dl)	**3.2±0.44**	**7.5±0.9**	**0.001**	**7.0 ± 0.7**	**11.54 ± 0.3**	**0.001**

Table 4: shows correlation coefficient between total plasma fibronectin with renal function tests , blood pressure and demographic characteristics of preeclampsia.

Total plamsa fibronectin	Blood urea	Serum creatinine	Serum uric acid	DBP	SBP	BMI	Maternal age	Gestational age
R-value	0.074	-0.103	0.286	0.285	0.057	0.305	-0.426	0.011
P-value	0.608	0.476	0.044	0.045	0.693	0.031	0.940	0.002

Table 5: shows plasma fibronectin levels in control and preeclampsia groups**.**

	Control	Preeclampsia	P-value	Type of Preeclampsia		
				Mild	severe	p-value
Fibronectin (µg/ml)	265.3±30.8	852±208.8	0.0001	795. ±185	1004. ±192	0.001

Table 6: sensitivity and specificity of fibronectin in study groups.

Cutoff point	Control(50)	Preeclampsia(50)	Area under curve	P-value
≥444	0	49	0.98	<0.001
≤444	50	1		
Total	S0	50		

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