The Role of Endothelin-1 and Oxidative Stress In Pregnancy Induced Hypertension

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Abstract

Pregnancy Induced Hypertension(PIH) is one of the most frequent complications of pregnancy , however little is known about its etiology. Endothelial dysfunction serves as a causative factor in the initiation of the maternal pathophysiological changes of PIH & is not just a result of this disorder. Endothelin-1 may play an important role in the pathophysiology of PIH, either by acting on vascular smooth muscle directly to induce contraction or by increasing the formation of angiotensin II. Pregnancy induced hypertension is associated with endothelial dysfunction & could be caused by oxidative stress. Recent evidence suggest the role of oxidative stress in PIH. The high level of malondiahyde (MDA) may reflect the excessive oxidative damage in PIH. The study sample consist of 50 normal non pregnant women, 50 normotensive pregnant women, and 50 preeclamptic pregnant women in their third trimester in Mosul city. The aim of this study was designed to evaluate the role of endothelial dysfunction and oxidative stress in pathogenesis of PIH. The results of this study showed that there was a highly significant elevation ($P<0.000$) in the serum level of endothelin-1 in the preeclamptic pregnant women in comparison with normotensive pregnant & the control group. Also there was a highly significant elevation ($P<0.000$) in the level of serum MDA in the preeclamptic pregnant women in comparison with normotensive pregnancy & the control group. The serum endothelin-1 has a significant negative correlation with both maternal age & gestational age, while endothelin-1 has a significant positive correlation with diastolic blood pressure. The MDA showed a significant negative correlation with maternal age, while there was a significant positive correlation between MDA & diastolic blood pressure.

دور الاندوثيلين -1واجهاد الاكسدة في ضغط الدم المحرض بالحمل

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الملخص

يعتبر ضغط الدم المحرض بالحمل من اكثر مضاعفات الحمل شيوعا ولكن على اية حال القليل عرف عن سببه0 ان اختلال وظيفة بطانة الشرايين يعتبر عامل مسبب في ضغط الدم المحرض بالحمل وليس فقط كنتيجة لهدا المرض0 الاندوثيلين – 1 له دور في تسبيب في ضغط الدم المحرض بالحمل اما بعمله على العضلات الملساء مؤديا الى تقلصها او بزيادة تكوين الانجيوتينسين 0 ضغط الدم المحرض بالحمل له علاقة باختلال وظيفة بطانة الشرايين وقد يكون السبب هو اجهاد الاكسدة 0 الدراسات الحديثة اكدت على دور اجه اد الاكسدة في ضغط الدم المحرض بالحمل 0 المستوى العالي للمالونديهايد قد يعكس التخرب الاكسدي الشديد في ضغط الدم المحرض بالحمل 0 عينة الدراسة شملت خمسين امراة سليمة وغير حامل 0خمسين امراة حامل لديها ضغط دم طبيعي وخمسين امراة مصابة بقبل التشنج الحملي في خلال الاشهر الثلاثة الاخيرة من الحمل في مدينة الموصل 0 الهدف من الدراسة هو تقييم دور خلل وظيفة بطانةالشرايين واجهاد الاكسدة في تسبيب ضغط الدم

المحرض بالحمل 0 اظهرت نتائج الدراسة ارتفاع معنوي شديد في مستوى الاندوثيليين في مصل الدم لدى النساء الحوامل المصابات بقبل التشنج الحملي بالمقارنة مع النساء الحوامل بالحمل الطبيعي 0 ايضا كان هناك ارتفاع معنوي شديد في مستوى المالونديهايد في مصل الدم لدى النساء الحوامل المصابات بقبل التشنج الحملي بالمقارنة مع النساء الحوامل بالحمل الطبيعي والنساء الغيرحوامل 0 اظهر الاندوثيليين -1علاقة عكسية شديدة مع كل من عمر الحامل وعمر الحمل بينما اظهر الاندوثيليين -1علاقة موجبة شديدة مع ضغط الدم الانبساطي الغيرحوامل0 اظهر المالونديهايد علاقة عكسية شديدة مع عمر الحامل بينما كانت هناك علاقة موجبة شديدة بين المالونديهايد و ضغط الدم الانبساطي .

Introduction

Pregnancy Induced Hypertension(PIH) is one of the most common complications of pregnancy and it contributes significantly to the maternal mortality, premature birth, intra uterine growth retardation and perinatal mortality.(1). Several pathophysiological mechanisms have been implicated in the developmental of PIH, These include endothelial dysfunction (2), an inflammatory pathway (3), oxidative stress(4),and the rennin-angiotensin system (RAS).(5). During early pregnancy incomplete trophoblast invasions leads to failure of conversion of thick walled tortous spinal arteries to low resistance flaccid sinsusoidal vessels, which results in impaired placental perfusion. The hypoxia /repefusion injury leads to increase generation of toxins including oxygen free radicals & lipid peroxides tilts the balance in favor of oxidation stress, These toxins enter the circulation & cause widespread endothelial dysfunction which cause an alteration in the ratio of the vasoconstrictors thromboxane & endothelin-1 to the vasodilators prostaglandin & nitric oxide.(6). So PIH is associated with endothelial dysfunction & could be caused by oxidative stress.(7). Endothelial dysfunction serves as a causative factor in initiation of the maternal pathophysiological changes of PIH & is not just a result of the disorder.(8). Endothelial changes also appear to involve a relative deficiency in the production of Nitric oxide, a vasodilator and inhibitor of platelets aggregation ,along with increased production of endothelin-1.(9). Endothelin 1- was discovered 28 years ago (in 1998). Because it is one of the most potent vasoconstrictor in vivo, a pathophysiological role for this peptide as a mediators of the hypertension has been postulated.(10). Endothelin-1 may play an important role in the pathophysiology of PIH, either by acting on vascular smooth muscle directly to induce contraction or by increasing the formation of angiotensin II, to which there is an increased vasopresser response in PIH. (11). Many studies up to now have demonstrated elevated plasma Endothelin-1 levels in PIH.(12). Recent evidence suggest the role of oxidative stress in PIH as it associated with lipid changes , and an increase in the lipid peroxidation ,both in the placenta and systemically, suggested that oxidative stress (an imbalanced between free radical synthesis and antioxidant defense)may be involved in the endothelial cell dysfunction. Malondiahyde (MDA) is the end product of lipid peroxidation & reflects the oxidative status of the biological system.(13), the high level of MDA may reflect the excessive oxidative damage in PIH.(14).

Subjects and Methods

This study represents a case control study, and it was conducted during the

period from March 2011 to March 2012 in al-Batool and al-Khansaa teaching hospitals. The subjects involved in this study were divided into three groups: Group(1) which served as a control group included 50 apparently healthy, non-pregnant, normotensive women, their ages ranged from(16-35) years. Group(2) which composed of 50 normotensive apparantly healthy pregnant women in their third trimester, their ages ranged from (16-36) years and having the following inclusion criteria:(1).Pregnant female with a singleton pregnancy. (2).Primigravida & multiparas. (3).Gestational ages were at 28-40 weeks calculated according to the date of last menstrual cycle ,clinical examination & by ultrasound findings. The exclusion criteria include the following:(1).Previous history of hypertension, diabetes mellitus, thyroid disease, blood disease, renal & hepatic disease.(2).Any associated disorders like urinary tract infection. (4).Multiple pregnancy. Group(3) **:**This group consisted of 50 preeclamptic pregnant women, in their third trimester, with the same previous inclusion & exclusion criteria. They were diagnosed to have preeclampsia according to the diagnostic criteria of this complication & were taking anti-hypertensive treatment at time of sampling. Their ages ranged from (19-39) years.All cases were selected by taking a detailed medical history and by physical examination. The Ethical and Research Committee of the Medical College and Hospital approved the study protocol and a verbal consent was obtained from the controls and the patients before the collection of the blood samples. About 5ml of fasting venous blood samples were obtained for the measurement of the biochemical parameters from all subjects included in this study by anticubital venepuncture and using disposable plastic syringe, without using elastic band tourniquet. The blood was allowed to clot and the serum was obtained by centrifugation at 3000rpm for 10 minutes. The serum was used to measure serum endothelin-1 (ET-1) concentration was determined by enzyme immunoassay (EIA), by using a kit supplied from (Enzo life sciences), and serum malondialdehyde (MDA) concentration was determined by method of Buege and Aust (1987).(15).

Statistical Analysis

The SPSS statistical package(version 19) was used for the statistic analysis of the data.The comparison between the studied groups were done by ANOVA(one way analysis of variance) followed by Duncan's multiple range test (DMRT). Pearson correlation was used to find the relation between the studied parameters.The statistical test results were considered highly significant at $P \leq 0.001$, significant at $p \leq 0.05$, and not significant at $p \leq 0.05$.

Results

Table (1):- Descriptive statistics of the serum oxidative stress marker (MDA), and the serum endothelin-1 levels among the studied groups.

Parameters	Group	No	Mean	SD	Min	Max	95% C.I	
							LB	UB
MDA (μmol/L)	G1	50	1.48	0.77	0.30	2.80	1.26	1.69
	G2	50	2.95	1.42	0.60	5.50	2.55	3.36
	G3	50	5.43	1.49	2.00	8.10	5.01	5.86
Endothelin-1 (pg/ml)	G1	50	1.59	0.32	1.00	2.00	1.50	1.68
	G2	50	1.55	0.34	1.00	2.00	1.45	1.64
	G3	50	2.97	0.46	2.00	4.80	2.84	3.10

There is a highly significant elevation (P<0.000) in the level of serum MDA in the preeclamptic pregnant women (5.43μmol/L) in comparison with normotensive pregnancy (2.95μmol/L) & the control group (1.48 μmol/L).Also there is a highly significant elevation (P<0.000) in the serum level of endothelin-1 in the preeclamptic pregnant women (2.97pg/ml) in comparison with normotensive pregnant (1.55pg/ml) & the control group (1.59pg/ml), table(2).

Table (2):- Comparison of the serum oxidative stress marker (MDA), and the serum endothelin-1 levels between the control, normotensive, and the preeclamptic pregnant women.

Parameters	Group	No.	Mean	SD	P≤ value
MDA(μmol/L)	G1	50	1.48 a	0.77	0.000
	G2	50	2.95 b	1.42	
	G3	50	5.43 c	1.49	

Endothelin-1 (pg/ml)	G1	50	1.59 a	0.32	0.000
	G2	50	1.55 a	0.34	
	G3	50	2.97 b	0.46	

Correlation of oxidative stress marker (MDA) with maternal demographic characteristics in preeclamptic pregnant women

Using Person correlation test, the MDA showed a significant negative correlation with maternal age(r=-0.624),(p<0.000), table (3). While there was a significant positive correlation between MDA & diastolic blood pressure (r=0.469) (P<0.001). In addition, MDA showed a positive correlation with gestational age (r=0.047), (P<0.747), and with systolic blood pressure (r=0.004) (P<0.979), and with BMI (r=0.246), (P<0.085).

Table (3):- Pearson correlation coefficient of serum oxidative marker (MDA) with maternal demographic characteristics in the preeclamptic pregnant group.

Characteristics	MDA (r.)	P. value
Age (Y)	-0.624**	0.000
Gestational age (w)	0.047	0.747
Systolic BP(mmHg)	0.004	0.979
Diastolic BP (mmHg)	0.469**	0.001
BMI (kg/m^2)	0.246	0.085

** .Correlation is significant at the 0.01 level.

Correlation of the serum endothelin-1 with maternal demographic characteristics in preeclamptic pregnant women.

Using pearson correlation test, the correlation between the serum endothelin-1 & maternal demographic characteristic of the preeclamptic pregnant women, table (4) revealed the following: The serum endothelin-1 has a significant negative correlation with both maternal age (r= - 0.493), (P=0.000), & gestational age (r= -0.753), (P=0.000), while endothelin-1 has a significant positive correlation with DBP (r=0.525), (P=0.000), and it has positive correlation with SBP (r=0.233), (P=0.104), & BMI (r=0.080) ,(p=0.580).

Table(4):- Correlation of serum endothelin-1 with maternal demographic characteristics of the preeclamptic pregnant women.

Characteristic	Endothelin-1	
	r	p
Maternal age (year)	-0.493**	0.000
Gestational age (week)	-0.753**	0.000
SBP (mmHg)	0.233	0.104
DBP (mmHg)	0.525**	0.000
BMI (Kg/m^2)	0.080	0.580

** Correlation is significant at the 0.01 level.

Discussion

Generalized maternal endothelial cell dysfunction may explain the multisystemic nature of preeclampsia. Pregnancy induced hypertension is accompanied by elevated endothelin-1 level with even higher levels in patients with severe PIH or HELLP syndrome(11). The present study showed a significant elevation in serum level of endothelin-1(ET-1)in the preeclamptic women as compared to the control group and normotensive pregnant women at $p \leq 0.000$. This elevation of serum endothelin-1 in preeclamptic women may support the idea that ET-1 may play an important role in the pathophysiology of preeclampsia, either by acting on vascular smooth muscle directly to induce vasoconstriction or by increase angiotensin II to which there is an increased vasopresser response in preeclampsia.(11). Hakkinnen et al., 1992 suggested that ET-1 is mainly released from the placental during delivery, because of much higher concentration of ET-1 in the retroplacental blood, in maternal plasma, and cord blood.(16). Slowinski et al., 2002, have reported increased ET-1 levels in preeclampsia in comparison to normal pregnancy.(17). Asakura et al., 2003 concluded that the main source of high plasma levels of endothelin-1 in preeclampsia is the placenta.(18).It has been shown that material plasma ET-1 levels increase in Preeclampsia & correlate with the severity of disease.(19). Oxidative stress has been implicated in the pathogenesis for several complication of human pregnancy including Preeclampsia. (20). Recent evidence suggests the role of oxidative stress in Preeclampsia. The present study showed a highly significant elevation ($P<0.000$) in the level of serum MDA in the preeclamptic pregnant women in

comparison with normotensive pregnancy & the control group . Biomarkers of lipid peroxidation are elevated in the placenta of the preeclamptic womenOxidative stress increases during Preeclampsia & result in increased production of lipid peroxide. .(21)

There is a reduced antioxidant response in patients with PIH. & reduced levels of antioxidant nutrients & increased lipid peroxidation.(22). This results may explain that the oxidative stress may play a role in pathogenesis of PIH.

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