Oxidative Stress Increases Activin A Secretion in Pregnancy Hypertensive States

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ABSTRACT

Introduction: *Activin A is a glycoprotein hormone produced by many tissues. During normal pregnancy the fetoplacental unit is the main source of activin A with the placenta producing the majority of secreted activin A. Oxidative stress may be the underlying mechanism for increased placental activin A production in preeclampsia.* ***Aim of Work****: To evaluate the levels of activin A and malondialdehyde (MDA) in pregnancy hypertensive states and to explore whether circulating levels of activin A are correlated to MDA levels (marker of oxidative stress).* ***Subjects and Methods:*** *The study included 75 pregnant women divided into three groups: 25 pregnant women with normal blood pressure (group1 as control), 25 pregnant women with pregnancy induced hypertension (PIH) (groupII) and 25 pregnant women with preeclampsia (groupIII). Serm levels of activin A and malondialdehyde (MDA) were measured by ELISA and by colorimetric methods respectively.* ***Results****: Serum levels of activin A and malondialdehyde were higher in patients with preeclampsia than in patients with pregnancy induced hypertension and that of control group. There was a highly significant correlation between serum levels of activin A and each of malondialdehyde and blood pressure in preeclampsia group and PIH group.* ***Conclusion****: Serum levels of activin A might be used as a marker that reflects the severity of pregnancy hypertensive states. Oxidative stress might be the mechanism of increased secretion of activin A.*

Key Words: *Preeclampsia, Oxidative stress, Activin A.*

INTRODUCTION

Pre-eclampsia is one of the most dangerous health problems of human pregnancy. It is diagnosed by the new appearance of hypertension and proteinuria after 20 weeks gestation. It is a leading cause of fetal growth restriction, premature birth, and low birth weight babies[(1)].

Preeclampsia complicates 5-7% of all pregnancies. Preeclampsia occurs with increased frequency among young, nulliparous women. However, the frequency distribution is bimodal, with a second peak occurring in multiparous women greater than 35 years of age. Among daughters of preeclamptic women, the risk of preeclampsia is significantly higher than the population risk[(1)].

Preeclampsia is a hypertensive disorder of pregnancy characterized by increased vasoconstriction leading to maternal hypertension and reduced blood flow to organs and tissues, including the kidney, uterus and placenta. Increased platelet

aggregation, disseminated intravascular coagulation, endothelial cell dysfunction, proteinuria and edema are other abnormalities associated with preeclampsia. Severe preeclampsia can lead to eclampsia,which is characterized by maternal convulsions thought to be caused by cerebral vasoconstriction. Despite of considerable research on preeclampsia,the only treatment present is removal of the fetus and placenta[2].

During uncomplicated pregnancy, there is an increased production of pro-oxidant that is balanced by the synthesis of antioxidant. In preeclampsia, there is an imbalance between pro-oxidant and antioxidant defenses. It is uncertain whether an imbalance between pro-oxidants and antioxidants (oxidative stress) precedes preeclampsia or occurs after preeclampsia has developed. Oxidative stress can cause cellular dysfunction, growth arrest or ultimately cell death[3].

Activin A is a glycoprotein hormone produced by many tissues. During normal pregnancy the fetoplacental unit is the main source of activin A, with the placenta producing the majority of secreted activin A. It belongs to Transforming Growth Factor β (TGFβ) superfamily. TGFβ superfamily is a group of proteins whose members are involved in control of cell proliferation and differentiation in many systems[4].

Maternal serum levels of activin A increase from about mid-pregnancy to a peak close to term[5], falling quickly after birth[6]. In pregnancies complicated by placental dysfunction as evidenced by intrauterine fetal growth restriction[7], or preeclampsia[8,9] maternal serum levels of activin A are significantly higher than observed in normal pregnancy.

The adaptive trophoblast proliferation in pre-eclampic placenta may be the major source of activin A. However, since activin A is a growth factor affecting cell proliferation in various tissues, the trophoblast proliferation in pre-eclampsia may be secondary to the increased production of activin A. The mechanism underlying such increased placental output remains unclear[10].

The aim of the present study is to evaluate the levels of activin A and malondialdehyde (MDA) in pregnancy hypertensive states and to explore whether circulating levels of activin A are correlated to MDA levels (marker of oxidative stress) .

SUBJECTS & METHODS

The present study was carried out at Beni Suef University, Maternity hospital. In this study 75 pregnant women were included, their age ranged from 18 to 35 years and gestational age of (26-40) weeks. They were divided into three groups: GroupI(n=25): pregnant women with normal blood pressures, no proteinuria, and no other complications, GroupII (n=25)**:** pregnancy induced hypertention (PIH) (diastolic levels above 90 mmHg after week 20 of gestation in women who reported normal blood pressure before pregnancy and presented with blood pressure under 140/90 mmHg without proteinuria) and Group III: (n=25) pre-eclamptic pregnancy-onset

hypertension along with antenatal proteinuria ≥300mg/24 h not resulting from chronic renal disease. Pre-eclampsia and PIH were diagnosed according to the criteria proposed by ***Davey and MacGillivray*** [11].

- Informed consent was obtained from all subjects before the beginning of the study. Patients with history of any medical disorders such as hypertension, diabetes mellitus, renal diseases, cardiac diseases, endocrine diseases and autiommune diseases were excluded from our study.

All pregnant females were subjected to: (a) detailed history taking, full physical examination, ulrasongraphy for determination of gestational age and to exclude intrauterine growth retardation or anomalies; (b) laboratory investigations: platelet count, P.T= prothrombin time, INR= International normalized ratio, liver enzmes (AST, ALT), Dipstick test for proteinuria and urinary creatinine,serum malondialdehyde (MDA) by colorimetric method and activin A by ELISA .

Sample collection

Blood samples were collected from the antecubital vein after at least 2 h bed rest, and allowed to clot in plastic tubes at room temperature. After centrifugation at 1000 g for 15 min, serum from the samples was separated and stored at -80 C until assayed for malondialdehyde and activin A.

Activin A assays:

The concentration of serum activin A was measured with an enzyme-linked immunosorbent assay (ELISA) according to manufacturer instructions (Oxford Bio-Innoviation, United Kingdom)[12].

Malondialdehyde assays:

Thiobarbituric acid (TBA) reacts with malondialdehyde (MAD) in acidic medium at temperature of 95°C for 30 min to form thiobarbituric acid reactive product which can be detected colorimetrically[13].

Statistical analysis

The statistical analysis of the data was done by using Excel program and SPSS program (statistical package for social sciences version 10) on Windows XP. The description of the data was done in the form of mean± SD for quantitative data and frequency and proportion for qualitative data. The analysis of the data was done to find statistical significant difference between groups for quantitative data (mean±SD). Student t-test was used to compare between two groups. One way ANOVA was used to compare more than 2 groups. Correlations were done to test for linear relations between variables. P-values less than 0.05 were considered statistically significant.

Analysis of the results

Table (1): Showing comparative study regarding demographic parameters between normal, PIH and preeclampsia groups. There was no significant difference ($p>0.05$) in age between control group and the other two groups but there was a significant difference ($p<0.05$) in parity between control group (2.12±1.30) when compared to "PIH" group **(**1.08±1.07) and preeclampsia group (1.04±1.02). Also, there was a highly significant difference ($p<0.001$) in gestational age, and a significant difference

(p<0.05) in birth weight between control group & preeclampsia group, but no significant difference (p>0.05) between control & "PIH" groups. In addition there was a highly significant difference (p<0.001) in gestational age and in birth weight between "PIH" & preeclamptic groups.

Table (2): Comparative study regarding clinical and biochemical parameters between normal, PIH and preeclampsia groups. There was a highly significant difference (p<0.001) in SBP and DBP in"PIH" and preeclampsia groups when compared to control group. Also, there was a highly significant difference (p<0.001) in SBP and a significant difference (p<0.05) in DBP of "PIH" group when compared to pre-eclamptic group.There was no significant difference (p>0.05) in serum AST,ALT,platelet count, urinary creatinine, P.T and INR levels between normal & "PIH" groups ,but there was a significant difference (p<0.05) in serum AST, ALT, urinary creatinine, P.T, and INR levels between control & pre-eclampsia groups. In addition there was a significant difference (p<0.05) between "PIH" & pre-eclampsia groups as regard the previous markers. Concerning proteinuria, a highly significant difference (p<0.001) was found between "PIH" (nil) & pre-eclamptic groups.

Table (3), figure (1) and figure (2): Showing a comparative study regarding serum levels of activin A and MDA between all studied groups. There was a highly significant difference (p<0.001) in serum activin A and MDA levels in"PIH" and pre-eclamptic groups when compared to control group. Also, there was a highly significant difference (p<0.001) in serum activin A and MDA levels between PIH and pre-eclamptic groups.

Table (1): Demographic parameters in all studied groups (n= 75).

Parameter	Normal Group I n=(25)	PIH Group II n=(25)	Preeclampsia Group III n=(25)	p
	MEAN ± SD	MEAN ± SD	MEAN ± SD	
AGE (year)	27.68±5.57	29.8±5.817	27.04±9.53	p1=0.580 p2=0.773 p3=0.915
PARITY	2.12±1.30	1.08±1.07	1.04±1.02	p1=0.003* p2=0.002* p3=0.893
GEST. AGE (week)	39.16±0.85	39.04±0.79	33.92±2.29	p1=0.608 p2< 0.001** p3< 0.001**
Birth Weight (kg)	3.02±0.30	2.96±0. 26	2.43±0.376	p1=0.383 p2=0.002* p3< 0.001**

**Significant= p< 0.05 **highly Significant= p< 0.001*
GEST. AGE=Gestational age SD=Standard deviation.
p1=Comparison between normal and PIH groups.
p2= Comparison between normal and Preeclampsia groups.
p3= Comparison between Preeclampsia and PIH groups.

Table (2): Clinical and biochemical parameters in all studied groups (n= 75).

parameters	Control Group I N=25	PIH Group II N=25	Preeclampsia Group III N=25	p
	Mean ± SD	Mean ± SD	Mean ± SD	
SBP (mmHg)	114.6±9.10	151.2±8.38	163.4±15.39	p1< 0.001** p2< 0.001** p3< 0.001**
DBP(mmHg)	75.6±8.08	98.80±5.642	103.20±7.76	p1< 0.001** p2< 0.001** p3=0.026*
AST (U/L)	30.0±6.04	32.36±7.19	37.44±9.31	p1=0.210 p2=0.002* p3=0.002*
ALT(U/L)	36.44±8.19	42.08±8.82	50.29±14.80	p1=2.880 p2=0.003* p3=0.003*
Platelet count (103/ul)	276.12±62.59	259.56±68.00	230.20±109.79	p1=3.850 p2=0.076 p3=0.062
urinary Creatinine (mg/dl)	0.88±0.166	0.86±0.153	1.25±0.63	p1=9.650 p2=0.006* p3=0.004*
Proteinuria(mg/dl)	Nil	Nil	208.4±206.2	p2< 0.001** p3< 0.001**
P.T (Sec)	12.242±0.4	12.47±0.687	14.10±3.00	p1=1.840 p2=0.008* p3=0.010*
INR	0.9972±0.06	1.00±0.104	1.31±0.57	p1=0.858 p2=0.009* p3=0.010*

**Significant= p< 0.05 **highly Significant= p< 0.001*
SBP=Systolic blood pressure. DBP= Diastolic blood pressure
AST=Aspartate transaminase. ALT=Alanine transaminase.
P.T=Prothrombin time. INR=Internatioal normalized ratio.
p1=comparison between normal and PIH groups.
p2= comparison between normal and Preeclampsia groups.
p3= comparison between Preeclampsia and PIH groups.

Table (3): Serum levels of activin A and MDA in all studied groups.

Parameter	Control Group I N=25	PIH Group II N=25	Preeclampsia Group III N=25	p
	Mean ± SD	Mean ± SD	Mean ± SD	
Activin A (ng/ml)	6.09±1.5	11.85±2.02	25.07±8.87	p1< 0.001** p2< 0.001** p3< 0.001**
MDA (nmol/ml)	4.72±1.49	11.42±1.71	29.66±5.04	p1< 0.001** p2< 0.001** p3< 0.001**

**Significant= p< 0.05 **highly Significant= p< 0.001*
MDA = Malondialdehyde.
p1 = comparison between normal and PIH groups.
p2 = comparison between normal and Preeclampsia groups.
p3 = comparison between Preeclampsia and PIH groups.

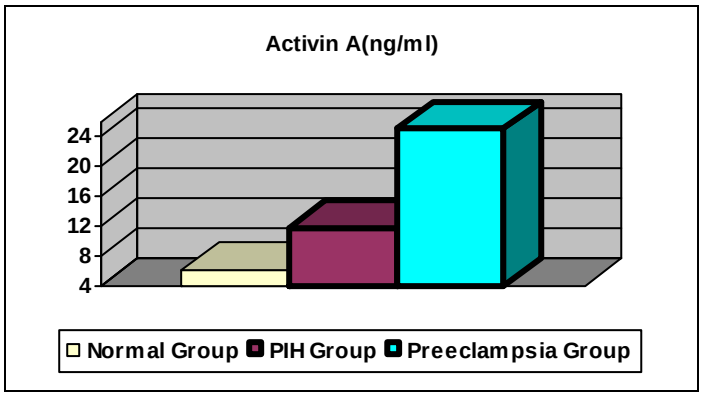

Figure (1): Serum levels of Activin A in all studied groups

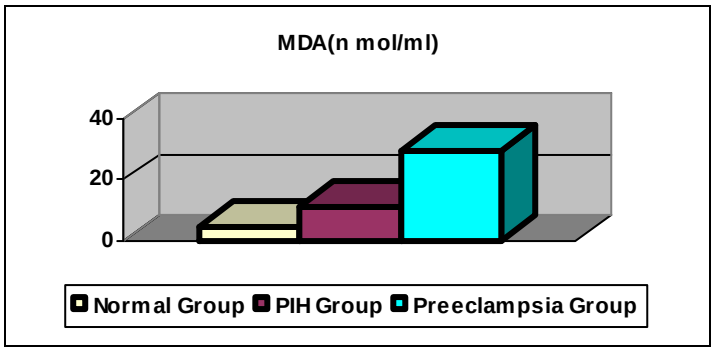

Figure (2): Serum levels of MDA in all studied groups.

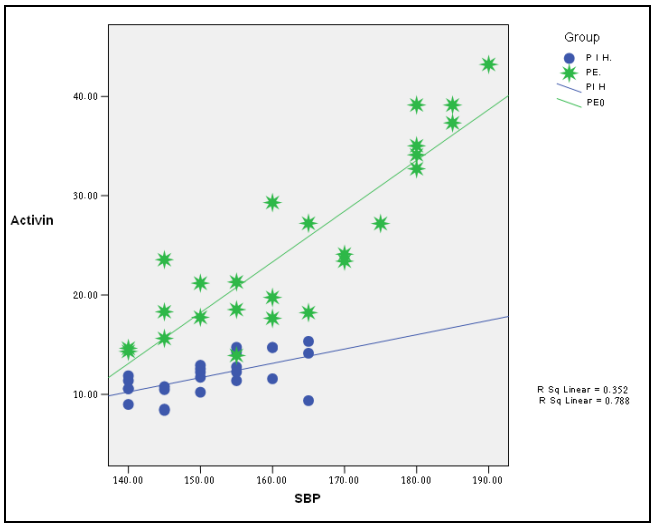

Figure (3): Correlation between serum level of activin A & SBP in PIH&preeclampsia groups.

PE=preeclampsia. PIH=pregnancy induced hypertension.

A positive correlation was found between activin A levels and SBP in preeclampsia: (r=0.888, p< 0.001) and in PIH: (r=0.429, p= 0.016)

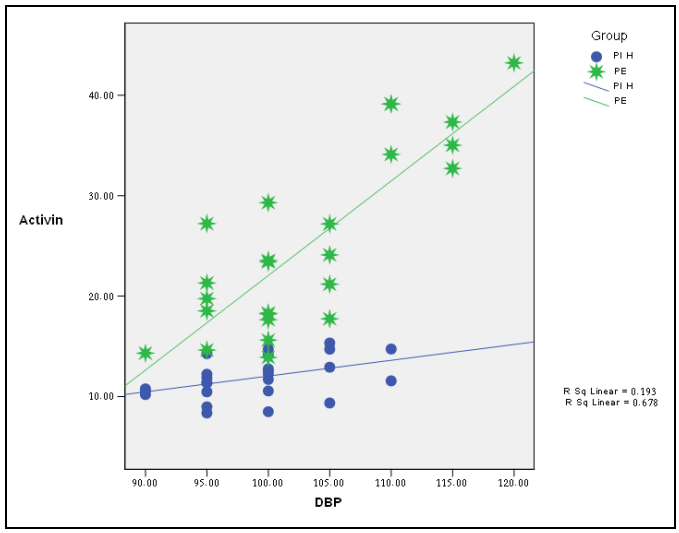

Figure (4): Correlation between serum levels of activin A & DBP in PIH & preeclampsia groups.

PE=preeclampsia. PIH=pregnancy induced hypertension.

A positive correlation was found between activin A levels and DBP in preeclampsia: (r=0.824 p < 0.001) and in PIH: (r= 0.439 p= 0.028).

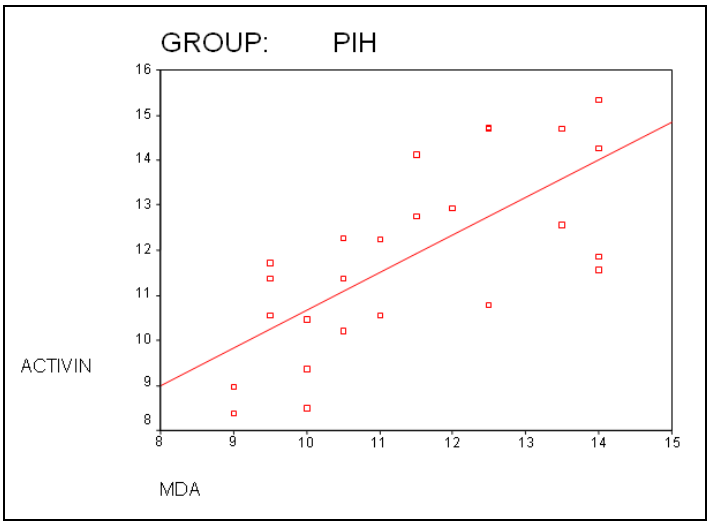

Figure (5): Correlation between serum level of activin A &MDA in PIH group.
A positive correlation was found between activin A and MDA levels in PIH group (r= 0.709, p <0.001).

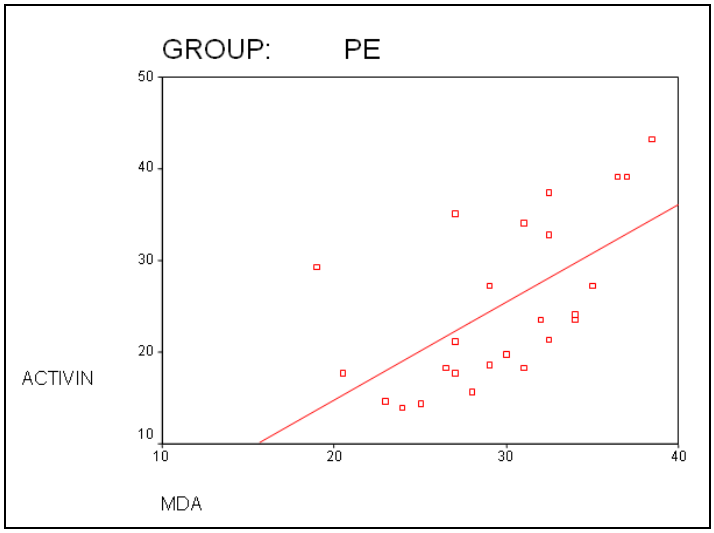

Figure (6): Correlation between serum level of activin A &MDA in preeclampsia group.
A positive correlation was found between activin A and MDA levels in Preeclampsia group (r= 0.608, p < 0.001).

DISCUSSION

Pre-eclampsia is a human pregnancy specific disorder that is diagnosed by the new onset of hypertension and proteinuria after 20 weeks gestation. It is a leading cause of perinatal morbidity and mortality and the only intervension that reverses the syndrome is delivery[(1)]. Oxidative stress of placenta is considered to be a key intermediary step in the pathogenesis of pre-eclampsia,but the cause of stress remains unknown.Hypoxia– reoxygenation (H/R) injury, as a result of intermittent placental perfusion secondary to deficient trophoplast invasion of the endometrial arteries is a possible mechanism[(14)].

Activin A is a glycoprotein hormone produced by many tissues .During the normal pregnancy the fetoplacental unit is the main source of activin A, with the placenta producing the majority of secreted activin A. It belongs to TGFβ superfamily, a group of proteins whose members are involved in control of cell proliferation and differentiation in many systems[(4)].

Accordingly, this study was undertaken to explore whether oxidative stress may be the mechanism underlying increased placental activin A production in preeclampsia and to explore whether circulating levels of activin were correlated with circulating levels of a marker of systemic oxidative stress.

In the present study,serum levels of activin A were significantly higher ($p< 0.001$) in pre-eclampsia group than "PIH" group compared to control .These results are supported by ***Mandang et al.***[(15)] who reported that circulating levels of activin A are significantly increased in women with pre-eclampsia, gestational age 26-40 weeks, when compared with those with a normal pregnancy **.**

Spencer et al.[(16)] studied the use of measurement of serum activin A level in the 1st trimester in prediction of pre-eclampsia. They concluded that although activin A is increased in the first trimester, levels of activin-A is probably too low to make a significant contribution to screening for pre-eclampsia at this time.

Aparna Reddy et al.[(17)] reported that, the levels of activin A in pre-eclamptic women were significantly higher in pre-delivery samples compared to normal pregnant women. With placental separation, the levels of circulating activin A declined rapidly and dropped significantly after 24 hours in normal pregnancy and in pre-eclampsia, suggesting the placenta is the major source of increased levels of activin A in pre-eclamptic women.

Yu et al.[(18)] concluded that in early second-trimester serum inhibin A, activin A, placental growth factor (PlGF) and second-trimester uterine artery Doppler may add further information for the prediction of pre-eclampsia. The combination of the three serum markers and uterine artery Doppler has the highest prediction value for pre-eclampsia.

The present results clearly show high concentrations of activin A in the maternal circulation of pregnant women with pre-eclampsia. The increased serum activin A level is due to decreased urinary clearance, increased placental production, or a combination of these factors. The

evidence that patients with pregnancy-induced hypertension had lower activin A plasma concentration than pre-eclamptic patients suggests that the high concentrations of activin A are not correlated with the high blood pressure but with the entity of gestational disease.. These findings also suggest that it's not the hypertensive state that induces the release of activin A, but the placental or fetal changes associated with the disease.It was reported that the putative source of activin A in maternal circulation is placenta, even though a contribution of maternal decidua cannot be ruled out[19].

On the contrary, ***Khalil et al.***[20] studied the effect of the use of the anti hypertensive α-methyl dopa, on serum activin A level in 65 women with preeclampsia and concluded that antihypertensive therapy with alpha-methyl dopa may have an effect on the synthesis and/or release of placental activin A in pregnancies complicated by preeclampsia .

In pre-eclamptic patients the proliferation of trophoblast has been proposed to explain the increased concentrations of several placental hormones in maternal circulation[21]. The adaptive trophoblast proliferation in pre-eclamptic placenta may be the major source of activin A. However, since activin A is a growth factor affecting cell proliferation in various tissues[10], the trophoblast proliferation in pre-eclampsia may be secondary to the increased production of activin A.

Recently, molecular evidence of placental hypoxia in pre-eclampsia[22] and on the in vivo observations in sheep showed that both acute[23] and chronic[24] feto-placental hypoxia increase amniotic fluid levels of activin A. Hypoxia has been explored as a possible cause of increased placental activin A production in vivo[19]. However, in contrast to the in vivo ovine data, in vitro culture of first trimester and term human placental explants under low oxygen conditions consistently reduced activin A production[25], suggesting that placental hypoxia is not a likely cause of the increased activin A observed in preeclampsia.

Also, in the present study, the circulating activin A was significantly and positively correlated with systolic and diastolic blood pressure. These results could be explained by the experimental evidence indicating that activin A modulates endothelin secretion by vascular endothelial cells and that activin-like immunoreactivity is present in vascular endothelial cells[26], suggesting a possible autocrine role of activin A on hypertension . Another organ involved in the regulation of blood pressure which produces and may be a target of activin is the kidney. In fact, recent findings have shown that TGF-ß mediates the angiotensin II-induced hypertrophy of proximal tubular cells in cultured murine kidney cells[27].

Also, in the present study, higher levels of MDA were found in both patients with preeclampsia and pregnancy induced hypertension than that of normal pregnancy group. There was further increase in MDA levels in preeclamptic group of patient

than its levels in PIH group. These findings were supported by ***Adiga et al.***[3] that reported, in preeclampstic women, lipidperoxidation products especially malondialdehyde (MDA) increase. Increased placental oxidative stress has been linked to the systemic features of preeclampsia through the release of a variety of possible mediators of endothelial cell dysfunction such as lipid peroxides**,** pro-inflammatory cytokines[28,29] and syncytiotrophoblast microparticles[30]**.**

Cytokines as tumour necrosis factor α (TNF-α) and interleukins, may contribute to the oxidative stress associated with preeclampsia. In this case, oxygen-free radicals lead to the formation of self propagating lipid peroxides[31]. Lipid peroxides are directly involved in mediating maternal endothelial dysfunction by increasing the production of thromboxane A2 and the expression of cell adhesion molecules in the utero–placental vasculature and also in the maternal peripheral vasculature[32].

Howlader et al.[33] observed that thiobarbituric acid reactive substances (TBARS), lipid hydroperoxide and protein carbonyl content were significantly increased but total anti-oxidant status and vitamin C level were significantly decreased in cord blood from pre-eclamptic mother compared to control group, suggesting that pre-eclampsia is associated with increased oxidative stress and decreased anti-oxidant status.

Also,in the present study, the circulating levels of activin A were significantly and positively correlated with MDA increased in women with preeclampsia and PIH when compared with those in a normal pregnancy. These results are consistent with ***Mandang et al.***[15] who found that maternal plasma levels of F8-isoprostane and activin A were significantly higher in women with preeclampsia when compared with controls. These data suggest that oxidative stress may be one of the mechanisms underlying increased circulating activin A in preeclampsia. The results could be explained by the work of ***Michael Cackovic et al.*** [34] who reported that women with preeclampsia have higher levels of TNF-α compared with normal pregnant women and elevated levels of TNF-α protein and mRNA have also been demonstrated in their placentas**.** TNF-α can activate the endothelial cells and upregulate the gene expression of numerous molecules such as platelet derived growth factor, cell adhesion molecules, endothelin-1 and PAI-1.These molecules have been reported to have detriminental effects on the vasculature and also characterize preeclamptic pregnancy**.** Furthermore, chronic infusion of TNF-α into rats during late pregnancy results in significant increase in renal vascular resistance and arterial pressure[35].

In conclusion**,** our study confirmed that the serum levels of activin A and MDA were elevated in preeclampia and PIH compared to normal pregnancy and this elevation is more obvious in preeclampsia than PIH indicating that activin A was involved in pathogenesis and severity of preeclampsia. Also, increased MDA levels, revealing an increase in lipidic membrane damage in pre-eclamptic patients as compared with

healthy pregnant patients. Activin A and MDA levels in serum are positively correlated in PIH and preeclampsia groups suggesting that oxidative stress may play a role in activin A production.

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شدة الأكسدة تزيد من إفراز أكتيفين أ فى أمراض ارتفاع ضغط الدم المصاحب للحمل

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أمراض ارتفاع ضغط الدم المصاحب للحمل من الأمراض الشائعه والذي يتسبب في الكثير من أمراض ووفيات الأمومه. أمراض ارتفاع ضغط الدم المصاحب للحمل يقسم الي إرتفاع الضغط المزمن ، إرتفاع الضغط الناتج عن الحمل و تسمم الحمل.

تسمم الحمل من المشاكل الأساسيه التي تعد بنسبه ٥%-٧%من كل حالات الحمل ومن الممكن ان تسبب مشاكل مثل الفشل الكلوي الحاد ، الإرتشاح الرئوي ، الإختلالات العصبيه ووفيات الأمومه .

شده الأكسده تعتبر واحده من ميكانيكات حدوث تسمم الحمل . حيث تشارك بيرو كسيدات الدهون الناتجه عن شده الاكسده بصوره مباشره في الإعتلال الوظيفي للاندوثيليام.

وقد قمنا بهذه الدراسه لتقيم دور الأكتفين أ فى الإصابة بارتفاع الضغط المصاحب للحمل واذا ما كانت شده الاكسده هي المتسببه في زياده إفراز اكتفين أ.

وقد اجريت الدراسه علي ثلاث : المجموعه الاولي (٢٥) سيده حامل غير مريضه بضغط الدم المرتفع "مجموعه ضابطه" والمجموعه الثانيه (٢٥) سيده حامل تعانين من ضغط الدم المرتفع الناتج عن الحمل والمجموعه الثالثه (٢٥) سيده تعانين من تسمم الحمل

وقد اوضحت النتائج بعد تحليلها إحصائيا أن :

إرتفاع مستوي أكتفين أ و مستوي مالون داى الدهيد في مريضات تسمم الحمل عن الحوامل اللاتي لا يعانين من ارتفاع ضغط الدم و الحوامل اللاتي يعانين من ضغط الدم المرتفع الناتج عن الحمل . هناك علاقه طرديه إيجابيه بين مستوي الأكتفين أ ومستوي مالون داى الدهيد . هناك ايضا علاقه طرديه ايجابيه بين مستوي الأكتفين أ وكل من ضغط الدم الانقباضي وضغط الدم الانبساطي.

ونستخلص من النتائج السابقه أن هناك زيادة فى افراز أكتفين أ و مالون داى الدهيد في تسمم الحمل وضغط الدم المرتفع الناتج عن الحمل بمستويات أعلي من الحمل الطبيعي ووجدت علاقه طرديه إيجابيه بين الزياده في افراز أكتفين أ و مالون داى الدهيد.

وبذلك من الممكن أن يكون مستوي أكتفين أ في الدم دلاله مفيده للتلف الأكسيدي في حالات أمراض ارتفاع الضغط المصاحب للحمل.