Associations between Homocysteine Levels and Oxidative Stress Biomarkers in Placental of Preeclampsia Iraqi Patients

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Abstract

Objective: Oxidative stress occurs when cellular levels of reactive oxygen species exceed antioxidant capabilities and has been implicated in the pathogenesis of preeclampsia.

Patients and Methods: In this study we measured the tissue levels of endogenous antioxidant proteins such as superoxide dismutase, glutathione peroxidase, glutathione reductase and in addition to the levels of homocysteine, lipid and protein oxidation in placental samples from normal and preeclamptic pregnancies.

Results: Preeclamptic tissue homogenates demonstrated significantly increased levels of homocysteine 12.31 ± 2.10 versus 2.31 ± 3.22 µmole/l, increased levels of lipid peroxidation 23.77 ± 5.26 µM/ mg protein versus 6.22 ± 2.31 µM/ mg protein ($p< 0.01$) and a significance increase in protein carbonyl concentration 250.44 ± 48.23 versus 190.24 ± 26 .46 units/mg protein when compared to controls, while levels of the other antioxidant proteins, superoxide dismutase1.55 ± 0.22 versus4.42 ± 0.32 U/mg protein $p<0.05$, Glutathionereductase12.13+ 3.3 versus 22.24 ± 7.71 U/mg protein ($P<0.05$), Glutathione68.12 ± 14.22 versus 105 ± 16ng/mg protein ($P<0.01$) and glutathione peroxidase 10. 22 ± 5.33 versus15.22 ± 4.44 nmol/min /mg protein ($P<0.05$) were all found to be significantly reduced when comparing preeclamptic placental tissue homogenates to gestational age matched control placental from non preeclamptic pregnancies.

Conclusions: The results of this study demonstrate placental oxidative stress through reduced antioxidant enzyme activities and hyperhomocystinemia which play a role in the pathogenesis of preeclampsia .These novel data further understanding the pathophysilology of preeclampsia and provides a new insight into the pathogenesis of clinical complications exhibited in this condition suggesting antioxidant therapy may be improving health of this condition.

Keywords: Homocysteine, Oxidative Stress Markers, Preeclampsia Placental.

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Introduction

Pre-eclampsia is a pregnancy-specific condition characterized by hypertension and proteinuria that remits after delivery. Preeclampsia affects between 0.4% and 2.8% of all pregnancies in developed countries and many more in developing countries, leading to as many as 8, 370, 000 cases worldwide per year. This common disorder, which is more prevalent in first pregnancies, is associated with the highest maternal and fetal morbidity and mortality of all pregnancy complications, with >90% of the most serious outcomes occurring in developing countries[(1)]. The cause of pre-eclampsia remains largely unknown, but

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poor lamentation is an important predisposing factor. This proposed role of the placenta in the pathology of preeclampsia is also strongly supported by the rapid resolution of symptoms after delivery.

Homocysteine, thiol-containing amino acid produced by the intracellular demethylation of methionine in the methylation processes is receiving a lot of attention these days as a new risk factor for a variety of disease[2].One mechanism by which increased homocysteine has been imposed to influence its pathological effects is by promoting oxidative stress[3]. Enhanced placental superoxide generation leads to the generation of free radicals[4]. Deleterious effects of free radicals include initiation of lipid peroxidation, oxidative damage of bimolecular and cellular dysfunction, and it is proposed that these may initiate maternal vascular endothelial dysfunction and leukocyte activation.

Although the precise mechanism of disorder remained elusive but according to new emerging consensus, it is a complex polygenetic trait in which maternal and fetal genes as well as environmental factors are involved. Though pathogenesis is not yet clear, several theoretical mechanisms have been proposed which result in uteroplacental insufficiency[5], this may result because of endothelial dysfunction which may be a final pathway between metabolic disturbance to clinical manifestations and is responsible for formation of various cascades for example increased procoagulant production responsible for microthrombi and formation of free oxidative radicals, leads to maternal vascular dysfunction and leucocytes activation[6], especially neutrophils which releases superoxidate and various cytokines.

Basic research during the last decade has led to an increased association of oxidative stress with homocysteine in a variety of diseases[7].

Aim of the study:

The present study was carried out to correlate the levels of oxidative stress and homocysteine in placental preeclamptic patients.

STUDY DESIGN:

Case control study, was carried out in department of gynecology and obstetrics at Al-Yarmouk teaching hospital from June 2010 to February 2011.

MATERIALS AND METHODS

Fourteenth severe preeclamptic patients with gestational age between 20-40 weeks of gestation .Criteriae of severe preeclampsia: systolic blood pressure of 160 mmHg or more and diastolic blood pressure of 110 mmHg or more on measurements at leastsix hours apart, persistent proteinuria of at least 2+by dipstick or 24 urinary excretion of 3g or more, persistent headache, visual and cerebral disturbance, oliguria, nausea-vomiting, epigastric pain, pulmonary edema, thrombocytopenia, impaired liver function testand twenty gestational age matched healthy pregnant normotensive controls were enrolled into the study. Preeclamptic patients with HELLP syndrome were excluded from the study. Multiple pieces of placental tissue from different site were collected at time of delivery from all patients.

Tissue processing:

All tissue samples were weighed and homogenized in four volumes of phosphate buffered saline (PBS) containing prolteolytic enzyme inhibitors using an ultra-homogenizer, then tissue homogenate were centrifuged for 30 min at 4000g and the supernatants collected and stored at -80C for further biochemical study.

Tissue oxidation analysis:

The level of lipid peroxidation in placental extracts was determined by measurements of malondialdehyde (MDA) generation. One volume of tissue extract was mixed thoroughly

with two volumes of stock solution of 15% trichloroacetic acid (w/v), 0.375% thiobarbituric acid (w/v), and 0.25 mol/L hydrochloric acid (w/v). The combination of the sample and the stock solution was heated for 30 min in a boiling water bath. After cooling, the precipitate was removed by centrifugation at 3200 rpm at 15 min. The absorbance of the clear supernatant is determined at 535 nm and MDA concentrations were calculated[8].

Reduced glutathione (GSH)

Placental GSH was determined with a colorimetric assay using Bioxytech GSH kit (Portland, OR, USA) based on a two-step reaction: thioethers formation followed by a β-elimination under alkaline conditions. Thioethers obtained are transformed into chromophoricthiones which have a maximal absorbance wave length at 400 nm[9].

Superoxide dismutase (SOD)

Placental SOD activity was measured at 500 nm with a commercially available kit (Randox Laboratories, kit Ransod superoxide dismutase) by testing the inhibition degree of a tetrazolium salt oxidation reaction[10].

Glutathione peroxidase (GP_X)

Placental activity GPx was measured with a commercially available kit (Ransel glutathione peroxidase, Randox) at 340 nm by measuring the decrease of NADPH absorbance).[11]

Glutathione reductase (GRx)

Placental GRx activity was measured with a commercially available kit from Randox company) by measuring the decrease of absorbance of NADPH at 340 nm according to Mannervik B and Carlberg I 1985[12].

Carbonyl protein estimation

Protein oxidation was determined through the estimation of carbonyl groups according to the Reznick method photometrically with dinitrophenylhydrazine and expressed as nmol per mg of protein (nmol/mg protein). Placental tissue homogenate samples were submitted to a reaction with 2, 4- dinitrophenylhydrazine 10mM in HCL 2.5 N, and treated with 20% trichloroacetic acid; the precipitate obtained by centrifugation was washed with a 1:1 (v/v) mixture of ethyl acetate and ethyl alcohol and dissolved in guanidine chlorhydrate 6M. In the samples thus obtained the protein concentration was determined by measuring extinction at 280 nm. The carbonyl concentration was given by the formula: C = Abs 355 x 45.45 nmol/ml[13].

Statistical Analysis

Data obtained from the study were analyzed by the use of two-way analysis of variance (ANOVA) and values for $P < 0.05$ were considered statistically significant correlation.

Results

From Table (1) the date showed that no significant difference ($p>0.05$) was found between clinical features of the preeclamptic and the normotensive pregnant control group other than hypertension, protein urea. Homocysteine and MDA levels and other oxidative stress biomarkers measurements inplacental tissue homogenates of normotensive pregnant and preeclamptic were given in Table (2) and Figure (1&2). Placental homocysteine levels of preeclamptic were higher than those of controls ($p<0.01$) as noticed in Figure (1), Likewise placental MDA levels were also higher in preeclamptic patients ($p<0.01$) as shown in Figure (2).There was a significant correlation between placenta homocysteine and MDA levels of preeclamptic patients (r: 0.74, $p<0.01$) as shown in Figure (3), whereas no correlation was found between these two of healthy pregnant subjects.

Figure (2) illustrates the significantly increased levels of Malonaldehyde ($p< 0.01$) found in preeclamptic placenta with a mean value of 23.77 ± 5.26 µmole/ mg protein in preeclamptic patients compared with 6.22 ±

2.31 µM/ mg protein in normal pregnant women. Protein carbonyl concentrations were also measured in placenta from normal and preeclamptic patients as a marker of placental oxidative stress.

Table 1. Sociodemographic features of the normotensive and preeclamptic pregnant women (Mean ± SD)

Parameters	Preeclamptic pregnancy (N=14)	Normotensive pregnancy (N=20)	P value
Age (Years)	30.0 ± 3.25	33 ± 6.50	NS
Gestational age (week)	35.03±2.50	33.50±2.60	NS
Pregnancy (number)	1± 1	1± 1	NS
Systolic blood Pressure (mmHg)	149.30±2.46	106±1.33	<0.05
Diastolic blood Pressure (mmHg)	103.40±3.11	74.70±1.45	<0.05
Proteinuria (mg/24 hr)	4800 ±800	54 ± 24	<0.001
Serum uric acid (mg/dl)	6.040±0.147	4.600±0.141	<0.01

Table 2. The placental homocysteine, malondialdehyde levels(Mean ± SD) and some laboratory parameters of the preeclamptic and normotensive pregnant women

Parameters	Preeclamptic pregnancy (N=14)	Normotensive pregnancy (N=20)	P value
MDA (µmole/ mg protein)	23.77 ± 5.26	6.22 ± 2.31	**<0.01**
Carbonyl protein (units/mg protein)	250.44 ± 48.23	190.24±26 .46	**<0.01**
GSH (ng/mg protein)	68 ± 14.22	105 ± 16	**<0.01**
GPx(nmol/min/mg protein)	10.22 ± 5.33	15. 22 ± 4.44	**<0.05**
GRx (U/mg protein)	12.13 ± 3.34	22.24+ 7.71	**<0.05**
SOD (U/mg protein)	1.55 ± 0.22	4.42 ± 0.32	**<0.05**
Homocysteine (µmole/L)	12 .11 ± 2.10	2.31 ± 3.22	**<0.01**

As shown in Table (2), an increase in protein oxidation in preeclamptic placenta (250.44±48.23 units/mg protein) was observed when compared to normal placenta (190.24 ± 26.46 units/mg protein), and there was a positive correlation between levels of homocysteine and carbonyl protein in preeclamptic pregnancy women as observed in Figure (4).

To investigate placental antioxidants status the activity of SOD in preeclamptic and normal placental were measured .From the results depicted in figure (5).SOD was shown to be signifantly reduced (P<0.05) in preeclamptic placental with a mean of 1.55 ± 0.22 U/mg protein when compared to the mean activity of 1.55 ± 0.22 U/mg/protein for the control group. GPx activity was also assessed in preeclamptic tissue and the results are presented in Table (2). Comparison of GPx activities followed a similar reduction in

antioxidant capacity as that of SOD significantly decreased placental GPx was found in preeclamptic tissue (10.22 ± 5.33versus15.22 ± 4.44nmol/min /mg protein (P<0.05) when compared to aged matched control group.

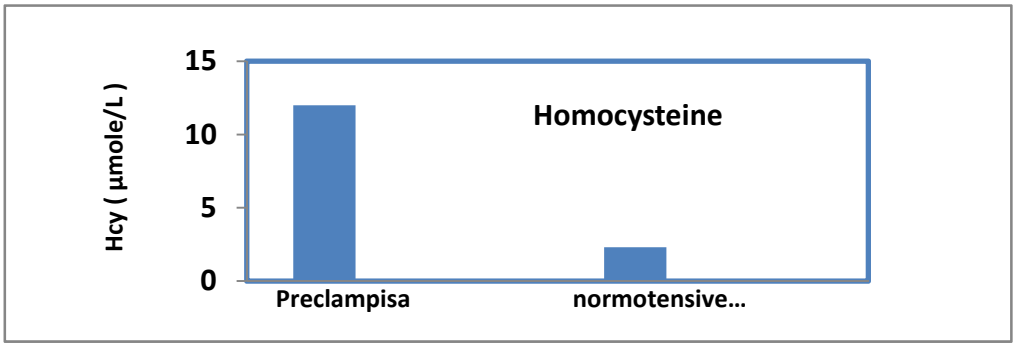

Figure 1. Levels of Placental Homocysteine (µmole/L) in normotensive and Preeclampsia pregnant women

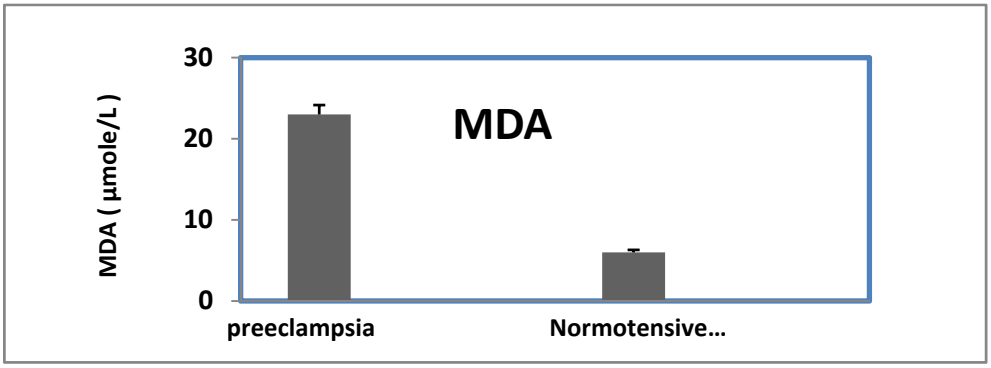

Figure 2. Levels of Placental malondialdehyde (µmole/mg protein) in normotensive and Preeclampsia pregnant women

The concentration of GSH was also measured as the final marker of non-enzymatic antioxidant and the results from Table (2), the concentration of GSH in placenta tissue homogenates was also significantly reduced (P<0.01) in preeclampsia with a mean value of 68.12±14.22 ng/mg protein when compared to a mean value of 105 ± 16ng/mg protein for age matched controls, on the other hand there is a negative correlation between levels of homocysteine and GSH in preeclampsia pregnant women (r = -0.79) as seen in Figure (6).

The placental activity of GRx was significantly reduced (p<0.05) in the placenta of pregnancies complicated with preeclampsia, with a mean activity of 12.13±3.34 U/mg protein when compared to the activity in placenta from uncomplicated pregnancies of 22.24 ± 7.71 U/mg as shown observed in Table (2). Overall, the results of this study demonstrate an increase in placental oxidation and a reduction in placental antioxidant defense mechanism in preeclampsia.

Discussion

The pathophysiology of preeclampsia is still not completely understood despite its prevalence and severity. It would appear that maternal endothelial dysfunction and hypersensitivity reaction to placental debris are central to the changes occurring within the mother and linked to increased placental apoptosis. Several reports have indicated increased apoptosis and shedding of placental fragments into the maternal circulation during preeclampsia pregnancy[14, 15], However ,the

underlying cause of increased apoptosis is not defined .Increasing oxidative stress and oxidant disequilibria have been shown to promote syncytiotrophoblast apoptosis with maternal exposure to shed membrane fragments responsible for the initiation of the systemic inflammation that plays a defying role in the development of preeclampsia[16].

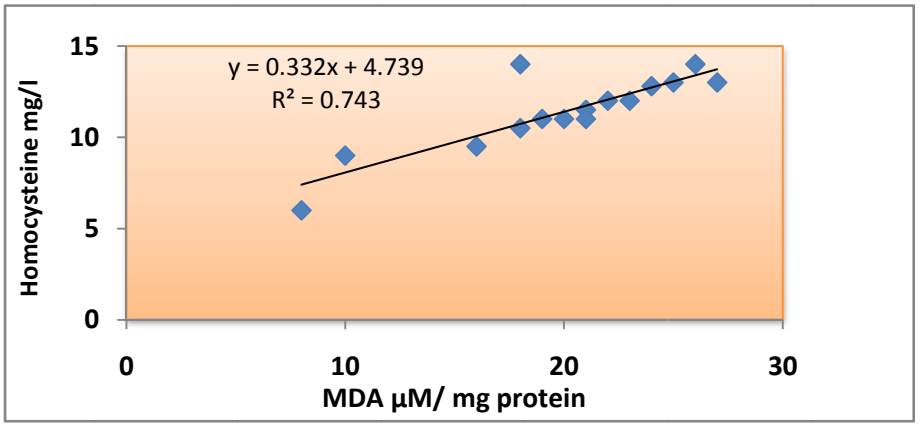

Figure 3. Correlation between placental homocysteine and malondialdehyde levels in Preeclamptic pregnant women

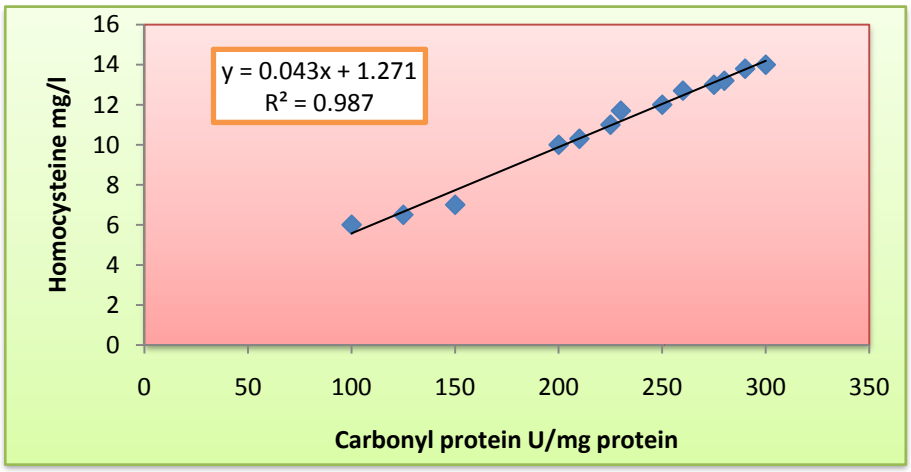

Figure 4. Correlation between placental homocysteine and carbonyl protein levels in preeclamptic pregnant patients.

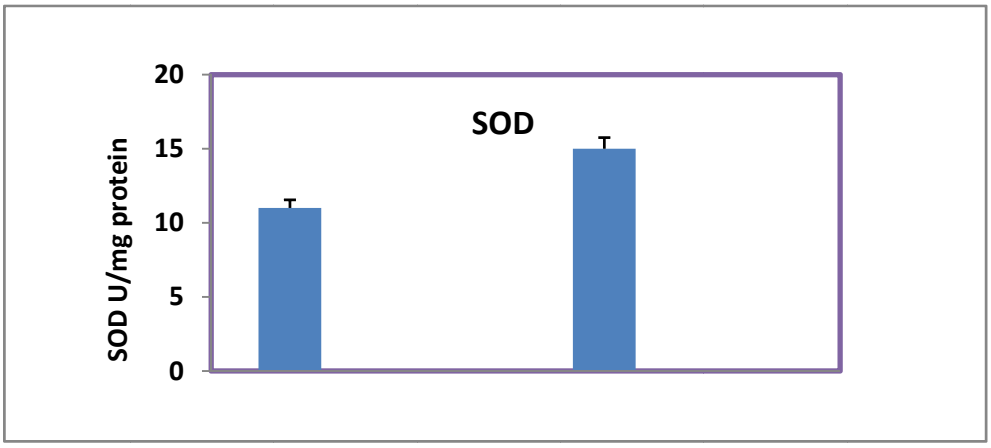

Figure 5. Levels of Placental SOD (U/mg Protein) in Normotensive and Preeclampsia pregnant women

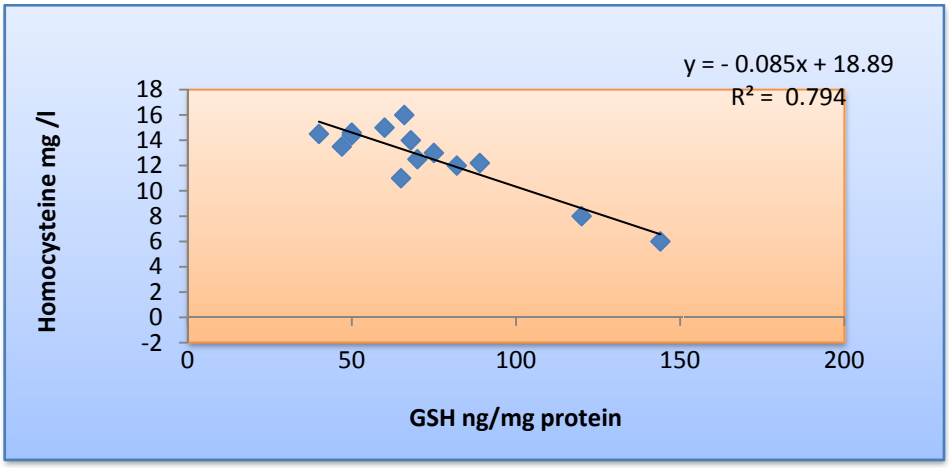

Figure 6. Correlation between placental homocysteine and GSH levels in preeclamptic pregnant patients

In this study, placental total homocysteine and MDA levels were shown to be increased and positively correlated in preeclampsia. No correlation was observed between MDA and homocysteine levels of healthy pregnant controls. Placental levels of homocysteine decrease during normotensive pregnancy parallel to the physiologic fall of albumin concentration and folic acid supplementation, but increases in preeclampsia like some other pregnancy complications[17], hyperhomocystinemia here might be a cause rather than just a marker of adverse pregnancy outcome.

In a study conducted on early pregnancy losses, hyperhomocystinemia was shown to decrease total vessel surface and hence to disrupt placental perfusion[18]. In normal endothelium, nitric oxide (NO) suppresses the smooth muscle proliferation in vessel walls. Decreased NO activity by the effect of homocysteine might contribute to the pathology in those patients.

An increased state of biological oxidation in preeclampsia placenta was observed when compared to normal which is in accordance with previous reports[19]. There was an increase in the concentrations of lipid peroxides and protein carbonyl in preeclampsia placenta; Lipid peroxides play a significant role in the oxidative stress characteristic of preeclampsia.

In normal pregnancy increasing gestational age promotes low levels of placental lipid peroxidation and increased antioxidant status conversely increased vasoconstriction and hypoxia cause significantly higher lipid peroxidation products[20] and reduced levels of antioxidants such as vitamin E, A, SOD, GPx to be associated with preeclampsia[21]. The increasing protein carbonyl and lipid oxidation products demonstrated in their investigation indicate that the preeclampsia placenta is experiencing oxidative stress that may be due to either excessive generation of ROS or a deficient antioxidant capacity.

In results from 14 preeclamptic pregnancies and 20 gestationally aged matched controls, the levels of SOD, GPx, GRx and GSH were found to be reduced significantly in preeclamptic placenta. The results for SOD concur with findings of others who have also reported decreased levels of this important antioxidant in the placental compartment during preeclampsia[22] did not observe any change in SOD immunosatining in tissue from normal and preeclampsia. This suggests that while activity may decrease, perhaps due to

SOD oxidation and inactivation the amount detected using antibodies to SOD may remain similar. The significance of a decrease in SOD activity to the progression of may directly relate to an ability to effectively inactivate the superoxide anion. Superoxide is known to stimulate the production of more highly reactive oxygen species.

The significant reduction in GPx in preeclampsia placenta demonstrated in these analyses agrees well with the findings of the majority investigations in the field[23, 24 and 25]. With the results relating directly to decrease ability for GPx to reduce the increasing levels of hydrogen peroxide and lipid peroxides generated during preeclampsia due to vasoconstriction and hypoxia. In this work we used an enzymatic assay to determine GPx activity , as such it is not possible to determine if this decrease is due to lack of production on increased protein oxidation and loss of activity. Further studies will focus on the use of real time PCR to quantitative the expression of mRNA; this will allow the determination of GPx transcriptional status in preeclamptic placenta.

From our studies on GRx activity and GSH concentrations it would appear that the regeneration system required by GPx is deficient in preeclamptic placenta. As shown in Figure (6) we found significantly less GRx activity in placenta from preeclamptic pregnancies when compared to age matched non preeclamptic controls. Similarly the tissue concentration of GSH were also significantly decreased (Figure 7). This finding is in agreement with a report published by Sahlin *et al*.[26] demonstrating reduction in mRNA expression of GSH but Shibita*et al*.[27] who found 3 fold increases in placental GSH accompanied by an increase in GSH mRNA expression in preeclamptic patients when compared to control pregnancies

The GSH enzyme system has an antiapoptoic effect though the binding of GR_X to apoptosis signal regulating kinase and the activity of GPx in the protection against hydrogen peroxide induced apoptosis[28]. In conclusion the results of this data demonstrate an increased placental oxidative state and decreased antioxidant enzyme capacity of preeclamptic placental tissue that may be important in the pathophysiology of preeclampsia. Regardless of whether these reductions are due to increased protein oxidation or reduced mRNA expression, the decreased endogenous activity of key antioxidant enzymes may lead to oxidative stress within the placenta and may contribute to the increased apoptosis which is characteristic of this disease.

Conclusion

The results of investigations included in this paper confirm the involvement of increased placental oxidative stress and decreased antioxidant enzyme capacity in the progression of preeclampsia, as well as a positive correlation between homocysteine levels with lipid peroxidation markers was investigated.

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العلاقة بين مستوى الهيموسستين وموشرات الإجهاد التأكسدي في مشيمة مرضى طليعة الارجاج

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الملخص

الخلفية: تحدث حالة الإجهاد التأكسدي عندما تتغلب مستويات أجزاء الاوكسجين الفعالة عن مستويات مضادات الأكسدة في الخلية التي يعتقد أن لها دوراً في حدوث طليعة الارجاج.

الهدف من البحث: التحري عن مستويات الهيموسستين ومؤشرات الإجهاد التأكسدي في أنسجة مشيمة المرضى الحوامل المصابات بحالة طليعة الارجاج مقارنة بالحوامل الاصحّاء، ومعرفة دورهما في آلية حدوث ذلك.

المرضى وطرق العمل: تم في هذه الدراسة قياس مستويات مضادات الأكسدة الانزيمية في أنسجة المشيمة الحوامل المصابات بطليعة الارجاج، والحوامل الطبيعيات. شملت انزيم السوبر دايميوتيز، الكلوتاثايون بيروكسديز، والكلوتاثايون ردكتيز، بالإضافة إلى مستويات الهيموسستين، ومستويات المواد الناتجة من أكسدة الدهون والبروتينات.

النتائج: أظهرت خلاصة نسيج المشيمة لمرضى طليعة الارجاج زيادة معنوية في مستويات الهيموسستين، إذ بلغت 22.31 ± 3.22 ضد 12.11± 2.10 ملغم/لتر، ومستويات بيروكسيدات الدهون بلغت 5.26 23.77± ضد 6.22± 2.31 مايكرمولر/ملغم بروتين، زيادة معنوية في تراكيز كربونيل البروتين إذ بلغت 250.44± 48.23 ضد 190.24± 46.26 حده/ملغم بروتين مقارنة بمجموعة السيطرة، فيما انخفضت بصورة معنوية مستويات مضادات الأكسدة الأنزيمية، إذ بلغت مستويات السوبر دايميوتيز إذ بلغت ±0.22 1.55ضد 4.42 ± 0.32 وحده/ملغم بروتين ومستويات الكلوتاثيون ردكتيز 12.13+ 3.3 ضد 22.24 ±7.71 وحدة/ملغم بروتين ومستويات الكلوتاثيون بيروكسديز 22.10 ±5.33 ضد 15.22 ±4.44 نانو مول/دقيقة/ملغم بروتين في المرضى ومجموعة السيطرة على التوالي. كذلك لوحظ انخفاض معنوي في تركيز مضادات الأكسدة غير الانزيمية مثل الكلوتاثيون، إذ بلغت مستوياته في المرضى 68.12± 14.22 ضد 105± 16 نانوغرام/ ملغم بروتين في مجموعة السيطرة.

الاستنتاجات: أثبتت نتائج الدراسة وجود حالة الإجهاد التأكسدى، وانخفاض فعاليات أنزيمات مضادات الأكسدة الانزيمية، بالإضافة إلى زيادة مستوى الهيموسستين التي يعتقد انها تؤدي دوراً هاماً في حدوث طليعة الارجاج عند الحوامل. ان هذه البيانات الجديدة ربما تساعدنا في فهم آلية حدوث الحالة المرضية ومحاولة استخدام تناول مضادات الأكسدة التي ربما تحد من مضاعفات المرض.

الكلمات الدالة: الهيموستين، الإجهاد التأكسدي، المشيمة.

