Original Research Article

Role of oxidative stress, Antioxidant and trace elements during Preeclampsia and Eclampsia

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Abstract

Preeclampsia (PE) is one of the most common gestational complications, being clinically characterized by a systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mmHg or higher, or both systolic and diastolic blood pressure above ≥140/90 mmHg.**Material and Methods:** In this study investigation was done to determine the contribution of different biochemical parameters of females suffering from preeclampsia and Eclampsia. The present study was carried out in the Department of Biochemistry in association of Department of General Medicine. Biochemical parameters included: Iron, Zinc, Copper, Malondialdehyde (MDA), Glutathione, Vitamin C, Vitamin E, Uric acid. The study was carried out on Case group - 100 pre-eclampsia and eclampsia patients compare to Control group - 100 normal pregnant females. **Results:**The mean systolic and diastolic blood pressure showed statistically significant difference ($p < 0.001$) between cases and controls. In case group Serum Copper level was 18.6 ± 6.2 µmol/L and in control group was 8.2 ± 2.7 µmol/L ($p < 0.001$). Serum iron level in case group was 18.92 ± 8.29 µmol/L and control group was 15.43 ± 5.49 µmol/L ($p < 0.05$). The mean serum concentrations of copper and iron showed statistically significantly difference ($p < 0.05$) in pre-eclampsia and eclampsia patients in comparison to the control group. The mean Serum Zinc levels showed no statistically significant difference ($p = 0.07$) between cases and controls. Serum Zinc level in case group was 8.3 ± 1.7 µmol/L and in control group was 9.0 ± 2.1 µmol/L. Oxidative marker between Case and control group was statistically significantly difference ($p < 0.05$). MDA in case group was 3.17 ±0.32 nmol/ml and Control 1.54± 0.21 nmol/ml ($p < 0.001$). Antioxidant marker between Case and control group was statistically significantly difference. In case group Glutathione 9.53 ± 2.46 µmol/ml and control group 11.68 ± 3.63 µmol/ml ($p < 0.001$). **Conclusion:**The results obtained support our initial hypothesis that common differences between all pregnant women and controls could be revealed, while preeclampsia and the other pregnancies would further differ indicating specific misbalance of the oxidative stress in preeclampsia.

Keywords: Oxidative stress, Antioxidant, Preeclampsia, Eclampsia

Introduction

Preeclampsia (PE) is one of the most common gestational complications, being clinically characterized by a systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mmHg or higher, or both systolic and diastolic blood pressure above ≥140/90 mmHg, measured twice with a four-hour interval, with proteinuria in 24 h or protein/ creatinine. Preeclampsia (PE), a pregnancy-specific syndrome characterized by hypertension, proteinuria, and edema, is one of the leading causes of maternal mortality and preterm delivery, and is associated with adverse long-term outcomes for both mother and child. [1]Eclampsia is a condition in which one or more convulsions occur in a pregnant woman suffering from high blood pressure, often followed by coma and posing a threat to the health of mother and baby. Most cases of eclampsia present in the third trimester of pregnancy with about 80% of eclamptic seizure occurring intrapartum or with in the first 48 hours following delivery. [2] Pathophysiological mechanisms of PE remain obscure, it is known that placental changes occur early in pregnancy, associated with an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defence system, characterizing oxidative stress. There is also a generalized inflammatory process, as well as the presence of progressive vascular endothelial damage, which culminates in placental dysfunction. [3] Despite this, it is not well established if the oxidative stress is the result of generalized oxidative cellular damage, which can affect proteins, lipid membranes, and deoxyribonucleic acid (DNA), caused by the disease already established, or if it precedes the clinical establishment of PE, being involved in its pathogenesis. [4]

Oxidative stress and preeclampsia

In preeclampsia, evidence of oxidative stress can be seen both in the maternal circulation and in the placenta. Placentas from women with preeclampsia have reduced antioxidant capacity compared to normal placentas. Furthermore, levels of antioxidants in blood from women with preeclampsia have been shown to be reduced, as well as levels of oxidative modifications of proteins and lipoprotein particles. [5]

Antioxidant protective systems

The human body relies on several antioxidant protective systems. Uric acid is a powerful antioxidant in the human plasma and is a scavenger of free oxygen and radicals. It reduces the oxo-heme oxidant formed by peroxide reaction with Hb and protects erythrocytes from peroxidative damage leading to lysis. The uric acid level both predicts and correlates with the development of conditions associated with oxidative stress and is suggested to be a marker for oxidative stress. Therefore, the concentration of serum

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uric acid in pregnant women with preeclampsia has been suggested to be associated with disease severity. [6]In the present prospective study, we hypothesized that maternal plasma trace elements, and specifically the ratios of oxidant versus antioxidant factors, may act as markers for the subsequent onset of PE and eclampsia. Thus, we sought to determine concentrations of plasma copper, iron and zinc at PE and eclampsia stage, and related it to the subsequent development of PE and eclampsia. We also examined the ratios of copper, iron, and zinc, based on their inter-relationships in regulating the antioxidant defence system. Our aim of the study is to investigate trace elements, antioxidant and oxidative stress during pregnancy in preeclampsia and eclampsia.

Aim and Objective

Aim: The aim of the study is to investigate trace elements, antioxidant, vitamins and oxidative stress during pregnancy in preeclampsia and eclampsia.

Objective

In this research we were estimate the level of different biochemical parameters in preeclampsia and Eclampsia.

Trace element likes Zinc (Zn), Copper (Cu), and Iron (Fe).
Antioxidant: Vitamin-C, Vitamin-E, uric acid, Glutathione.
In oxidative stress: Malondialdehyde (MDA).

Material and Methods

In this study investigation was done to determine the contribution of different biochemical parameters of females suffering from preeclampsia and Eclampsia. The present study was carried out in the Department of Biochemistry in association of Department of General Medicine.Biochemical parameters included: Iron, Zinc, Copper, Malondialdehyde (MDA), Glutathione, Vitamin C, Vitamin E, Uric acid.The study was carried out on Case group - 100 pre-eclampsia and eclampsia patients compare to Control group - 100 normal pregnant females.

Selection criteria

1. Control: Normal pregnant females randomly selected from the hospital who is not suffering from any other medical disorder.
2. Cases: All the patients of preeclampsia and Eclampsia will be admitted in the hospital.

Inclusion criteria: Pregnant female suffering from preeclampsia and eclampsia

Exclusion criteria: Pregnant females suffering from any other medical disorder.

Results

Physical parameters

Table 1: Distribution of Anthropometric parameters between Case and control group

Parameters	Age in years	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)
Case -(mean ± SD)	29.3	25.2 ± 2.7	169.13 ± 13.4	97.32 ±7.3
Control(mean ± SD)	31.2	25.3 ± 2.6	128.21 ± 9.7	78.62 ± 5.1
t-value	1.32	1.43	28.29	17.01
p-value	p = 0.38	p = 0.93	p < 0.001	p < 0.001

SD = Standard deviation; Kg/m^2 = kilogram per meter square; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; mmHg = millimetre mercury.

In table 1, the mean age of the case and control pregnant women was 29.3 years and 31.2 years respectively which was statistically not significantly different from those of control group (P > 0.05). Whereas, BMI between case and control group 25.2 ± 2.7 kg/m^2 versus 25.3 ± 2.6 kg/m^2 respectively which was statistically not significantly different from those of control group (P > 0.05). The systolic blood pressure in case group was 169.13 ± 13.4 mmHg and control group was 128.21 ± 9.7 mmHg. On the other hand, diastolic blood pressure in case group was 97.32 ± 7.3 mmHg and control group was 78.62 ± 5.1 mmHg.

Table 2: Distribution of Biochemical parameters between Case and control group

Parameters	Fe (µmol/L)	Zinc (µmol/L)	Copper (µmol/L)
Case (mean ± SD)	18.92 ± 8.29	8.3 ± 1.7	18.6 ± 6.2
Control(mean ± SD)	15.43 ± 5.49	9.0 ± 2.1	8.2 ± 2.7
t-value	14.9	3.6	15.82
p-value	p < 0.05	p = 0.07	p < 0.001

SD = Standard deviation; µmol/L = micromole per litre.

Biochemical parameters-In case group Serum Copper level was 18.6 ± 6.2 µmol/L and in control group was 8.2 ± 2.7 µmol/L. Serum iron level in case group was 18.92 ± 8.29 µmol/L and control group was 15.43 ± 5.49 µmol/L. The mean serum concentrations of copper and iron showed statistically significantly difference (P < 0.05) in pre-eclampsia and eclampsia patients in comparison to the control group. The mean Serum Zinc levels showed no statistically significant difference (P = 0.07) between cases and controls. Serum Zinc level in case group was 8.3 ± 1.7 µmol/L and in control group was 9.0 ± 2.1 µmol/L.

Table 3: Distribution of Oxidative marker between Case and control group

Parameters	Malondialdehyde (nmol/ml)
Case (mean ± SD)	3.17 ± 0.32
Control (mean ± SD)	1.54 ± 0.21
t-value	13.46
p-value	p < 0.001

SD = Standard deviation; nmol/ml = nanomoles per millilitre.

In table 3, Oxidative marker between Case and control group was statistically significantly difference. MDA in case group was 3.17 ±0.32 nmol/ml and Control was 1.54± 0.21 nmol/ml.

Table 4: Antioxidant marker between Case and control group

Parameters	Glutathione (µmol/ml)
Case (mean ± SD)	9.53 ± 2.46
Control (mean ± SD)	11.68 ± 3.63
t-value	17.62
p-value	p < 0.001

SD = Standard deviation; µmol/ml = micromole per millilitre.

In table 4, Antioxidant marker between Case and control group was statistically significantly difference. In case group Glutathione 9.53 ± 2.46 µmol/ml and control group 11.68 ± 3.63 µmol/ml.

Table 5: Antioxidant marker between Case and control group

Parameters	Vitamin C (mg/dl)	Vitamin E (mg/L)	Uric acid (mg/dl)
Case (mean ± SD)	0.52 ± 0.10	8.72±1.83	7.21 ± 1.32
Control (mean ± SD)	1.41 ± 0.14	11.52±2.61	4.82 ± 0.83
t-value	6.64	11.62	16.51
p-value	p < 0.001	p < 0.001	p < 0.001

SD = Standard deviation; mg/dl = milligram per decilitre. mg/L = milligram per litre.

In table 5, Antioxidant marker between Case and control group was statistically significantly difference. In case group Vitamin C was 0.52 ± 0.10 mg/dl and control group 1.41 ± 0.41 mg/dl/ml. In case group Vitamin E was 8.72 ± 1.83 mg/L and control group 11.52 ± 2.61 mg/dl/L. In case group of Uric acid was 7.21 ± 1.32 mg/dl and control group 4.82 ± 0.83 mg/dl/ml.

Discussion

Hypertensive disorder of pregnancy named preeclampsia can be related to an oxidative stress disorder. [7] There is enough relevant evidence that excessive imbalance between ROS and body antioxidant defense forces found in this pathological condition of pregnancy lead to damaging modifications of cell functions and intracellular compartments caused by oxidative stress. [8] The precise cause of preeclampsia is not known. Published evidence of oxidative stress presence in normal pregnancies suggests that redox imbalance serves beneficial events in pregnancy. [9] Moreover, detectable antioxidant system activity in pregnancy is stimulated by increased oxidant activity comparing to women out of pregnancy. [10] Inadequate trophoblast invasion, placental suboptimal perfusion and ischemia present in preeclampsia lead to initiating changes that can be documented in maternal circulation as intensifying oxidative stress. [11]In light of the results in this study regarding Total oxidant capacity (TOC) and total antioxidant capacity (TAC) values, we can conclude the following. In normal pregnancies, TOC was significantly higher than in women out of pregnancy. At the very beginning of pregnancies with hypertensive disorders that were evaluated, there were no significant differences in TOC between them and healthy pregnancies indicating physiological increase of the oxidative status in pregnancy in general, as was recently described for the process of birth in general, in particular for mothers with the babies small for gestational age. [12] On the other hand, TAC in group with preeclampsia showed statistically significant higher values in comparison to normal pregnancies. This reveals that certain redox imbalance compared to normal pregnancies is present even at the very beginning of the disorder and that protecting antioxidant capacities of the body are additionally activated. Nevertheless, although these serum capacities may not represent oxidant or antioxidant activities in maternal circulation they are sensitive and reliable detectors of oxidative stress in vivo. [13] Evaluated trace elements as antioxidant nutrients or, on the other hand, as participants in redox processes involved as components of metaloenzymes or as cofactors in chemical reactions, they could be easily manipulated by diet or by supplementation therapy. [14] Significant changes in serum concentrations of Zn in normal pregnancies were already observed. [15] Serum Cu levels in normal pregnancy increase accordingly to the rising concentrations of its main transport protein ceruloplasmin induced by high estrogen levels of pregnancy. [16] Zn levels tend to get lower in normal pregnancies as a result of higher demands of mother and fetus and pregnancy correlated hemodilution. [17] There are some published studies that show statistically significant higher levels of Cu and lower levels of Zn in circulation of women with preeclampsia in comparison to healthy pregnant women. [18] This study did not show difference between groups of pregnant women regarding serum concentrations of Zn. Cu serum levels were significantly higher in cases and Zn levels not significantly lower in cases compared to controls groups.It is well known that Fe deficiency is a risk factor for premature delivery, stillbirth and low birth-weight of children. [19] Increased Fe requirements and subsequent Fe deficiency in pregnancy can hardly be overcome by changes in diet. [20] In practice, Fe supplementation during pregnancy is recommended and has been mostly a standard care. Ideally, low Fe status should be determined before or at the beginning of the pregnancy. However, Fe excess can mediate formation of highly reactive-free radical OH in the presence of oxygen according to Fenton and Haber-Weiss reactions. [21] Thus, induced oxidative stress confirms that Fe as a catalyst of free radical reactions can be toxic. [22,23] In addition, previous studies came to conclusion that important source of circulating Fe can be placental thrombotic and necrotic tissue of women with preeclampsia where certain amounts of red blood cells are defragmented. [24] The fact that in this study significantly higher serum concentrations of Fe were found in women with preeclampsia compared to uncomplicated pregnancies implements that Fe may be involved in pathogenesis of preeclampsia. Positive correlation was found between Fe and TAC in group with preeclampsia that connects the potential Fe induced oxidant formation or oxidative stress with activation of body antioxidant protection mechanism in preeclampsia. There was significant positive correlation between Cu and TOC in all groups and negative correlation between Cu and TAC in controls. In light of that, this study showed that Cu may be the related to circulating oxidant production forces. Differences of ratios between trace elements in groups were consistent with their absolute values, with highlight to Cu and Fe values. Vitamin C and E are known as antioxidant vitamins that are suggested to decrease oxidative damage and lowering the risk of certain chronic diseases. Studies show that vitamin C may be protective against development of pre-eclampsia. Supplementation with vitamin C and E reduces oxidative stress and endothelial dysfunction and, pre-eclampsia. Vitamin C and E have scavenged free radicals in aqueous solution and may have a role in the management of pre-eclampsia. Supplementation with antioxidants may modify the women's response to oxidative stress and therefore limit the systemic and utero-placental endothelial damage observed in pre-eclampsia. [25]Hyperuricemia is a common finding in preeclamptic pregnancies. The elevation of uric acid in preeclamptic women often precedes hypertension and proteinuria, the clinical manifestations used to diagnose the disorder. Outside of pregnancy, hyperuricemia is considered a risk factor for hypertension, cardiovascular and renal disease. [26] This evidence, as well as the observation that severity of preeclampsia increases with increasing uric acid, questions whether uric acid may play a role in the pathophysiology of preeclampsia. Though uric acid is an antioxidant our study results indicates increase of uric acid levels when all other antioxidant parameter levels are decreased. This paradoxical antioxidant-prooxidant switch happens once local antioxidants like superoxide dismutase, glutathione and catalase levels are depleted. This is known as urate redox shuttle. [26,27] Furthermore ischemia itself causes increased generation of xanthine oxidase explaining the increased levels of uric acid in ischemic stroke patients. [27,28]

Conclusion

The results obtained support our initial hypothesis that common differences between all pregnant women and controls could be revealed, while preeclampsia and the other pregnancies would further differ indicating specific misbalance of the oxidative stress in preeclampsia. Namely, the normal pregnancies were characterized by increased levels of Cu and ROS production and enhanced antioxidant protection, while preeclampsia is associated with increase of Fe and imbalance in oxidative homeostasis. Such an imbalance can be detected even in the beginning of the preeclampsia disorder inducing a significant increase of total serum antioxidant capacities. It has still to be revealed whether significantly higher serum Fe levels are associated with preeclampsia as a cause or as a consequence of this disorder. In both cases, the results of this study indicate that the Fe supplementation for non-anaemic pregnant women might have harmful effects as a risk of developing preeclampsia. Vitamin C and vitamin E are common powerful antioxidants. Vitamin E, an important lipid-soluble antioxidant, is responsible for protecting cells against inflammatory response and lipid peroxidation. While elevated concentrations of circulating uric acid can be seen in woman with preeclampsia, they do appear to identify a subset of preeclamptic women who are at greater risk for maternal and fetal morbidities.

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