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RESEARCH ARTICLE

LEVELS OF FREE FATTY ACID AND ROLE OF LIPID-PEROXIDATION IN PRE-ECLAMPSIA AS COMPARED TO NORMOTENSIVE PREGNANT WOMEN

***Shweta Dwivedi and Dharmveer Sharma**

Department of Biochemistry, M.L.N. Medical College, Allahabad

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ABSTRACT

Preeclampsia is a hypertensive disorder and is one of the most leading cause for maternal and fetal mortality in developing countries.

Objective: To evaluate the levels of free fatty acid and lipid-peroxidation levels in pre-eclampsia.

Methods: This study was carried out in 100 patients with pre-eclampsia and 100 healthy pregnant women (control group) during the third trimester of pregnancy. The serum free fatty acid was determined by Estimation of serum free fatty acids by NEFA C diagnostic kit (wako pure chemicals. Richmond VA). Lipid-peroxidation was determined by utley's method.

Results: In the present study the level of free-fatty acid and MDA level are significantly increased in pre-eclamptic pregnancy compared with normal pregnancy

Conclusion: Higher level of Free-fatty acid and lipid-peroxidation in serum is a marker of oxidative stress which play important role in the etiopathaogenesis of preeclampsia in pregnancy.

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INTRODUCTION

Preeclampsia is the most common major medical complication of pregnancy. It represents the leading cause of both fetal and maternal morbidity and mortality, affecting 5-10% of all pregnancies (Baumwell and Karumanchi, 2007). The etiology of pre-eclampsia remains largely unknown. It has been hypothesized that abnormal trophoblast invasion, inflammatory responses, oxidative stress and endothelial dysfunction are all potential contributing factors in this disorder (Sibai *et al*., 2005; James *et al*., 2010). Many theories have attempted to explain why preeclampsia arises (Courtney *et al*., 2006). The mechanism causing preeclampsia is not totally understood. Much attention has been focused on the actual physiological changes of preeclampsia which may provide a better understanding of the disease process. Poorly functioning endothelial cells, the cells lining the inside of blood vessels, may be responsible for the physiologic changes of preeclampsia as it can become dysfunctional altering lipid peroxidation which is the process of converting unsaturated fatty acids in cells and tissues.

****Corresponding author: Shweta Dwivedi,***
Assistant Professor, Department of Biochemistry, M.L.N. Medical College Allahabad.

Lipid peroxidation plays a role in the development of cardiovascular disease. There is increase in the oxidative stress during pre-eclampsia and as a consequence it leads to increased creation of lipid peroxides, reactive oxygen species and leading to endothelial injury and dysfunction. There is some evidence that preeclampsia patients have higher amounts of the by-products of lipid peroxidation (Kashinakunti *et al*., 2010; Hubel *et al*., 1996). Free fatty acids which also called non-esterified fatty acids (NEFAS) are fatty acids that are not esterified to glycerol or another alcohol such as choline or cholesterol. In blood plasma or serum, FFAs are really not free but bound to plasma albumin. Circulating free fatty acids (FFAs) are key regulators of glucose metabolism and have been shown to be increased in preeclamptic patients during and before the clinical onset of the disease (Kashinakunti *et al*., 2010; Hubel *et al*., 1996; Murai *et al*., 1997). It was hypothesized that alterations in the circulating lipids contribute in inducing endothelial dysfunction in patients with preeclampsia. Preeclampsia, a pregnancy specific syndrome, is a major cause of maternal and perinatal morbidity and mortality. The exact mechanism underlying etiology of preeclampsia remains elusive (Abbasalizadeh *et al*., 2007; Ghazavi *et al*., 2008; Moslemizadeh *et al*., 2008; Savvidou *et al*., 2008). It has been proposed that excess oxidative stress and exaggeration of a maternal inflammatory response are involved in the pathogenesis of preeclampsia. Endothelial dysfunction, insulin

resistance and inflammation are demonstrated features of preeclampsia which share with atherosclerosis (Shakour-Shahabi *et al*., 2010; Shenoy *et al*., 2010). Oxidative stress may mediate endothelial cell dysfunction and contribute to the pathophysiology of preeclampsia as there is evidence of increased pro-oxidant activity formation along with decreased anti-oxidant protection in preeclampsia. Superoxide dismutase (SOD) levels are decreased and reduced SOD activity reported in neutrophils and placentas of preeclamptic women (Walsh, 1998). Due to metabolic changes and low grade inflammation, pregnancy is a condition of increased susceptibility to oxidative stress (Rusterholz *et al*., 2007; Challis *et al*., 2009). Several organs in pregnancy show increased basal oxygen consumption and changes in substrate energy use resulting in increased mitochondrial mass and production of reactive oxygen species (ROS) (Toescu *et al*., 2002). The placenta is another local source of free radicals. It produces nitric oxide (NO), but also, because it's so rich with free radical producing macrophages, it can contribute to the development of oxidative stress (Dotsch *et al*., 2001). In the present study we evaluated the levels of free fatty acid, lipid-peroxidation and non enzymatic antioxidant (Vitamin E and Vitamin C)

MATERIALS AND METHODS

This study was performed in 100 pregnant women (in their IIIrd trimester pregnancy) age group between 20-35 years. All the subjects were categorized under 2 groups viz, control group (Normotensive pregnant women) and study group (Pre-eclamptic pregnant women). For the biochemical parameters to be analysed, blood samples were collected after an overnight fast from the anticubital vein avoiding venostasis in all subjects. EDTA Vials were used for the estimation of anti-oxidant Vitamin (E & C). For the determination of plasma levels of Vitamin blood was collected between 7-10 a.m. from fasting subjects in EDTA vials. The samples were kept in ice and protected from light. Blood samples were immediately centrifuged at 3000 rpm for 10 minutes. Plasma was collected and kept at 4°C till analysis, which was done immediately after collection. Plasma vitamin C levels was determined spectrophotometrically by Carl A Burtis's method, Plasma vitamin E levels was determined by the method of Emmeric-Engel. Free fatty acids levels in serum were estimated by commercially available NETA-C kt.

Statistical analysis

Values are expressed as Mean ± SD. The significant mean difference between groups were assessed by the "student t" test and distribution of 't' probability (p).

RESULTS

The observation revealed the changes in Free Fatty Acid, Lipid-peroxidation, anti-oxidants (Vitamins C & E) in Normotensive and preeclaamptic pregnant women in their third trimester pregnancy.

- The mean serum free fatty acids (S.FFA) was found to be 0.48 ± 0.13 (m.mol/L) in normotensive subjects and 0.79 ± 0.21 (mmol/L) in pre-eclamptic subjects. The 64.6% increase levels of S.FFA in pre-eclamptic group were found to be highly significant ($p < 0.001$) as compared to Normotensive group.
- The changes in lipid per oxidation levels are represented in Table. It reveals a general trend (preeclamptic group). The percentage increase in MDA levels in preeclamptic group. 31.62% ($p<0.001$).
- The percentage decrease in Vitamin E levels as compared to control was 28.3%. Statistically the changes observed were highly significant ($P < 0.001$) in study group as compared to controls.
- Vitamin C levels in study group (pre-eclamptic group) showed significant decrease ($P < 0.001$, 40.3%).

Levels of Free Fatty Acid, MDA, Vitamin C & E Preeclamptic women compared with normal pregnancy

S.N.	Particulars	Normal Pregnancy	Pre-eclamptic
1	Free Fatty Acid	0.48±0.13	0.79±0.21
2	Lipid-peroxidation	2.91±0.26	3.83±0.33
3	Vitamin C	0.82±0.41	0.49±0.23
4	Vitamin E	0.92±025	0.79±0.21

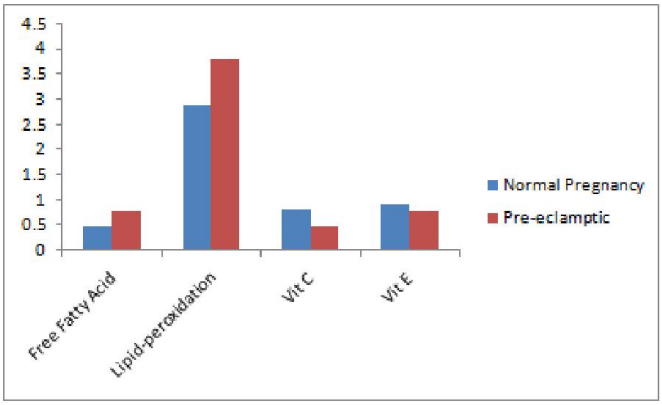

Figure. Levels of Free Fatty Acid, MDA, Vitamin C & E Preeclamptic women compared with normal pregnancy

DISCUSSION

Oxidative stress in placental tissue increased in pre-eclampsia and these free radicals play an important role in pathophysiology of the disorder, & evidence accumulates that oxidative stress is a mediator of endothelial dysfunction (Var *et al*., 2003; Sikkema *et al*., 2003) Various important anti-oxidants are significantly decreased in women with preeclampsia (Noris *et al*., 2004). Levels of ascorbic acid, MDA and the activities of two antioxidant enzymes SOD and GSH-Px were taken as markers of oxidative stress. Antioxidant levels in PE are found to be uniformly low in almost all the studies on this subject (Kaur *et al*., 2008; Llurba *et al*., 2004). Low ascorbic acid and vitamin E levels found in most of the studies were seen as good indicators of the antioxidant/pro oxidant imbalance that characterizes oxidative stress. Low ascorbic acid levels were also a logical basis for supplementation with vitamin C, but as we have shown earlier there is still no clear evidence for that (Rumbold and Crowther, 2010). The results of the present study were in line with

Harsem *et al*. (2006) study reporting the increased lipid peroxidation in preeclamptic patients compared with normal pregnant women. In the present study, maternal serum levels of malondialdehyde were significantly increased in preeclamptic patients compared with normal pregnant women. This finding was in concordance with earlier reports (Sharma *et al*., 2006; Biri *et al*., 2007; Howlader *et al*., 2007; Mehendale *et al*., 2008; Uboh *et al*., 2008). Nicola *et al*. (2009) found that plasma from women with preeclampsia had increased lipid accumulation and endothelial apoptosis compared with plasma from women with uncomplicated pregnancies. They provide evidence that these changes potentially result from elevated concentrations of free fatty acids and increased its molar ratio to albumin. Also, they had shown that plasma from women with preeclampsia had a significant impact on endothelial cellular metabolism and apoptosis compared with normal pregnant controls. They confirmed that exposure of endothelial cells to the 'preeclampsia' fatty acid/albumin combination, in comparison to the 'normal pregnant' cocktail of fatty acids and albumin, mimicked these impaired outcomes, which justify suggesting that circulatory levels of fatty acids in women with preeclampsia may be capable of affecting the properties of vascular endothelial cells. Lipid-peroxidation has been blamed to be the main causative factor for oxidative stress in pre-eclampsia. Free radicals initiate lipid-peroxidation by attacking polyunsaturated fatty acid in cell membrane (Madazilik *et al*., 1999). Uncontrolled peroxidation of fatty acids and cholesterol alter membrane fluidity and permeability as lipid peroxides are toxic compounds that damage endothelial cells, increase peripheral vasoconstriction and increase thromboxane synthesis and decrease prostacyclin synthesis (Alexa *et al*., 1996). Once steady state levels of blood lipid peroxides begin to rise, the stage would be set for self-perpetuating chain-reaction processes to take place. Endothelial contact with lipid peroxides would allow peroxidative damage of endothelial cell membrane lipids. This could ultimately reduce the ability of the endothelium to act as a permeability barrier to plasma components. Exposure of the vascular endothelium to lipid peroxides would begin to shut off production of prostacyclin, increasing the propensity for vasoconstriction and platelet aggregation (Hubel *et al*., 1989).

In this study, we found that the levels of malondialdehyde (a lipid peroxidation product) increased significantly increased in preeclampsia compared to normal pregnant females. This increase signifies the excessive ongoing lipid peroxidation in preeclampsia and this may well be a marker of oxidative stress. This result correlates well with numerous studies undertaken at many institutes. In India, studies conducted by Adiga, Patil *et al*. (2007) and Krishna Menon (2007) at different institutes showed significant elevations in the levels of malondialdehyde in preeclampsia compared to normal pregnancy and non-pregnant females. Outside India also, various studies like those by Elesa Llusla (2004), Madazli *et al*., and Chamy *et al*. (2003) have all found significantly increased MDA levels in preeclampsia as compared to normal pregnancy and also in pregnancy as such compared to non-pregnant females.

Conclusion

Increased FFA in maternal serum and high levels of oxidative damage in placental mitochondria may be involved in the pathogenesis of preeclampsia. Increased FFA in serum and decreased activity of antioxidant enzyme in placenta may contribute to oxidative damage levels in placental mitochondria in women with PE.

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