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Plasma Lipid Profile, Lipid Peroxidation and Antioxidant Status in Preeclamptic and Uncomplicated Pregnancies in Bangladesh

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To investigate the changes in plasma lipid profile, lipid peroxidation and antioxidant status in Bangladeshi pregnant women and their potential involvement in the pathophysiology of preeclampsia, we performed a case-control study consisting of randomly selected women (20-30 years) with preeclampsia (PE, n = 25) as compared to uncomplicated normal pregnant (UP, n = 22) and nonpregnant (NC, n = 25) women. The study was conducted in the Clinical Biochemistry Laboratory of Dhaka University. Serum lipid profile, thiobarbituric acid reactive substances (TBARS), lipid hydroperoxide (LHP), Total Antioxidant Status (TAS) and vitamin C levels were measured using standard methods. Serum total cholesterol levels of PE and UP groups were significantly higher ($p<0.001$) compared to Nonpregnant Control (NC) group. But there was no significant difference between the total cholesterol levels of PE and UP groups. Serum TG level of PE group was significantly higher compared to UP ($p<0.01$) and NC ($<p<0.001$) groups. HDL cholesterol (HDL-C) has a lower level while LDL cholesterol (LDL-C) has a higher level in PE group compared to other two groups and these differences are also statistically significant. TBARS and LHP were significantly higher in PE group than UP and NC groups. But when compared these values between UP and NC groups, there was no significant difference. The values of TAS and serum vitamin-C levels were found to significantly decrease in PE group compared to UP and NC groups. Though there was no significant difference of TAS value between UP and NC group but vitamin-C level was significantly lower in UP group compared to NC group. Our data suggest that an abnormal lipid metabolism and particularly high triglyceride, lipid peroxides, LDL-C and low antioxidant activity and HDL-C concentrations may contribute to the promotion of oxidative stress and vascular dysfunction seen in PE and may play a significant role in its pathophysiology.

Key words: Preeclampsia, lipid profile, total antioxidant status, thiobarbituric acid reactive substances, lipid hydroperoxides

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INTRODUCTION

Preeclampsia (PE) is a pregnancy specific multisystem disorder of unknown etiology and is the leading cause of maternal and perinatal mortality and morbidity. World Health Organization (WHO) reported that preclampsia affects 2-3% of all pregnancies and is responsible for about 60 000 deaths worldwide every year, mostly in developing countries (WHO, 2005). Preeclampsia have declined substantially in developed parts of the world, but remain the major problems in the developing world due to limited progress in understanding the cause(s) and pathophysiology and thus prevention of this complex condition. In Bangladesh, preeclampsia or eclampsia is the third major cause of maternal mortality (16%) (Fauveau *et al*., 1988) preceded by hemorrhaging and sepsis.

Gratacos (2000) suggested that maternal endothelial cell dysfunction may be the key event resulting in diverse clinical symptoms of PE. A major role of the endothelium in PE has since been reported Roberts and Sargent (2005). It has been proposed that both fetoplacental and maternal factors interact in the development of endothelial cell dysfunction and its clinical and symptoms (Aydin *et al*., 2004).

Another hypothesis, which is commonly known as the oxidative stress hypothesis, suggests that placental and maternal free radical reactions promote a cycle of events that compromise the defensive functioning of the vascular endothelium in PE. There is evidence to support the hypothesis that excessive production of oxygen and nitrogen-based free radicals (oxidative stress) are involved in the pathophysiology of PE (Hubel, 1999). In both hypotheses widespread endothelial cell dysfunction seems to be the common link.

The hypothesis that free radical generation contributes to endothelial dysfunction in PE is supported by studies showing an increase in circulating lipid peroxides and a decrease in antioxidant patterns in PE patients (Gratacos *et al*., 1998). However, other studies failed to provide evidence of elevated circulating secondary products of lipid peroxidation in PE (Morri *et al*., 1998; Diedrich *et al*., 2001).

In combination with other metabolic changes, the abnormal lipoprotein metabolism in PE is considered a maternal adaptive response to placental insufficiency (Sattar *et al*., 1996). Abnormal lipid profiles and species may have a role in the promotion of oxidative stress and vascular dysfunction seen in PE (Myatt and Myodovnik, 1999). Although previous investigators have demonstrated the presence of oxidative stress in preeclampsia, our purpose in this study is to investigate the changes in plasma lipids (cholesterol, triglyceride), lipoprotein cholesterols (LDL-C and HDL-C), lipid peroxides and antioxidant status in pregnant women with and without PE (nonpregnant women as a comparison) in order to determine the potential role of oxidative stress in the pathophysiology of PE.

MATERIALS AND METHODS

Subjects and sample collection Three groups of women [nonpregnant control (n = 25); uncomplicated pregnant (n = 22) and preeclamptic pregnant (n = 25)] were recruited to participate in this study. Preeclamptic and healthy pregnant women were selected from those attending the Obstetrics and Gynecology Department of Dhaka Medical College Hospital, Dhaka, Bangladesh. The study protocol was reviewed and approved by the local Ethics Committee and all participants gave informed consent.

Preeclamtic patients met the following inclusion criteria: Systolic blood pressure >140 mmHg or a rise of at least 30 mmHg; diastolic blood pressure >90 mmHg or a rise of at least 15 mmH; proteinuria of 300 mg/24 h urine and antepartum preeclampsia. The exclusion criteria of preeclampsia patients were: postpartum eclampsia/preeclampsia, diagnosis of other complications for example HB. infection, tumor and cancer. Subjects with uncomplicated pregnancies were normotensive throughout gestation and had no proteinuria. The control subjects were healthy nonpregnant women of similar age and socio-economic status as PE and UP subjects. Blood was collected at the Dhaka Medical College Hospital and analyzed in Biochemistry and Molecular Biology Department, University of Dhaka.

Analytical methods: Serum total cholesterol, HDL-cholesterol and TG, were determined by commercially available kits by Biolabo, France. LDL-cholesterol was calculated from Friedewald Formula (Friedwald *et al*., 1972). Serum ascorbic acid was measured by Lowry method. Thiobarbituric acid reactive substances (TBARS) value was determined according to the method of (Yagi, 1998). Lipid hydroperoxide value was determined by colorimetric method based on the oxidation of ferrous to ferric ion in the presence of xylenol orange (Nourooz-Zadeh *et al*., 1994). Total antioxidant status was determined using a kit by Randox, UK (Miller *et al*., 1993). Based on the principle that ABTS^{R} (2,2′-Azino-di-[3-ethylbenzthiazoline sulphonate]) by incubating with peroxidase (metmyoglobin) and H_2O_2, produce the radical cation ABTS^{+}. This has a relatively stable blue green color, which is measured spectrophotometrically at

600 nm. Presence of antioxidant in the sample causes suppression of this color production to the degree, which is proportional to their concentration.

Statistical analysis: Data were analyzed using the Statistical Package for Social Sciences (SPSS) (version 11.0 for Windows, SPSS Inc., Chicago, USA). The statistical method used was student's t-test (Two tailed). Differences were considered significant at $p<0.05$.

RESULTS

Table 1 shows age and gestational age were not significantly different between groups. We verified preeclampsia by measuring blood pressure and comparing among the groups. As expected, both the systolic and diastolic blood pressure was significantly increased ($p<0.001$) in PE women than uncomplicated pregnant and nonpregnant women.

Lipid profiles: Total serum cholesterol of PE and UP groups was significantly higher ($p<0.001$) than the nonpregnant control group (Fig. 1). Both UP and PE groups had cholesterol greater than the reference value. TG level of PE group was significantly higher ($p<0.01$) compared to that of the UP group matched for gestational age at sampling and that of nonpregnant control group ($p<0.001$). HDL-C level of PE group was significantly decreased ($p<0.01$) as compared to UP group. In a similar fashion, significant difference was found in LDL-C level between preeclamptic (PE) and Uncomplicated Pregnant (UP) groups.

Lipid peroxidation rate in different study groups: TBARS value of PE group was significantly higher ($p<0.001$) than the UP and NC groups (Fig. 2). There were no significant differences in TBARS values between NC and UP groups. Plasma lipid hydroperoxides (LHP), the major initial reaction products of lipid peroxidation, was significantly higher in PE group ($p<0.001$) compared to UP and NC groups (Fig. 2). Lipid hydroperoxide value in UP group was also significantly higher than the NC group.

Table 1: Baseline characteristics of study subjects

Variables	Nonpregnant control (n = 25) Mean±SE	Uncomplicated pregnancy (n = 22) Mean±SE	Preeclampsia (n = 25) Mean±SE
Age (years)	23.66±0.51	24.10±0.98	25.41±0.91
Gestation at sampling (weeks)	NA	36.10±0.37	34.93±0.48
Systolic blood pressure (mmHg)	117±0.95	113±1.97	155±4.22*
Diastolic blood pressure (mmHg)	74±1.53	73±1.69	104±2.55*

Student's t-test was performed to assess group differences, *: $p<0.001$, NA: Not Available

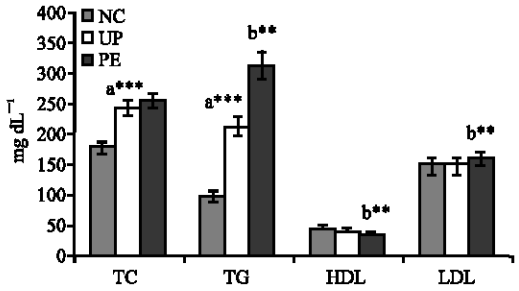

Fig. 1: Lipid profile in preeclampsia (PE) as compared to Uncomplicated Pregnant (UP) and Nonpregnant Control (NC) subjects. Values represented are means±SE. a = versus nonpregnant controls and b = versus uncomplicated pregnant subjects. TC = Total Cholesterol, TG = Triglycerides, HDL-C = High Density Lipoprotein-Cholesterol, LDL-C = Low Density Lipoprotein-Cholesterol. *: $p\leq0.05$, **: $p\leq0.01$, ***: $p\leq0.001$

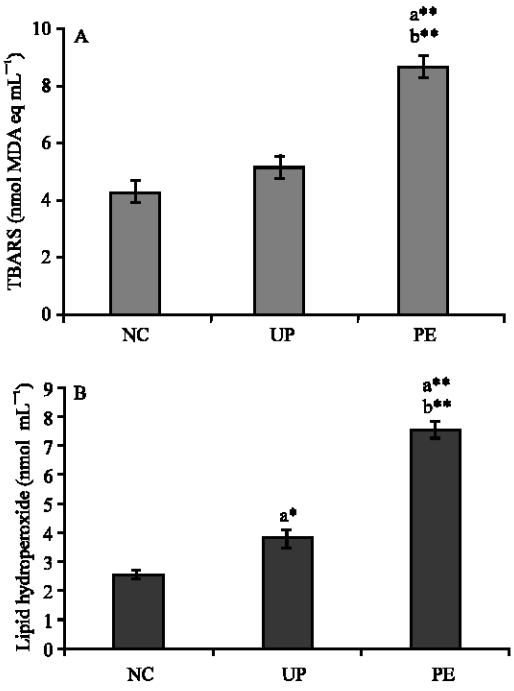

Fig. 2: Lipid peroxidation rate in preeclampsia (PE) as compared to Uncomplicated Pregnant (UP) and Nonpregnant Control (NC) subjects. (A) Thiobarbituric acid reactive substance (TRARS) and (B) Lipid hydroperoxide. Values represented are means±SE. a: versus nonpregnant controls, b: versus uncomplicated pregnant subjects. *: $p\leq0.01$ **: $p\leq0.001$ versus uncomplicated pregnant subjects

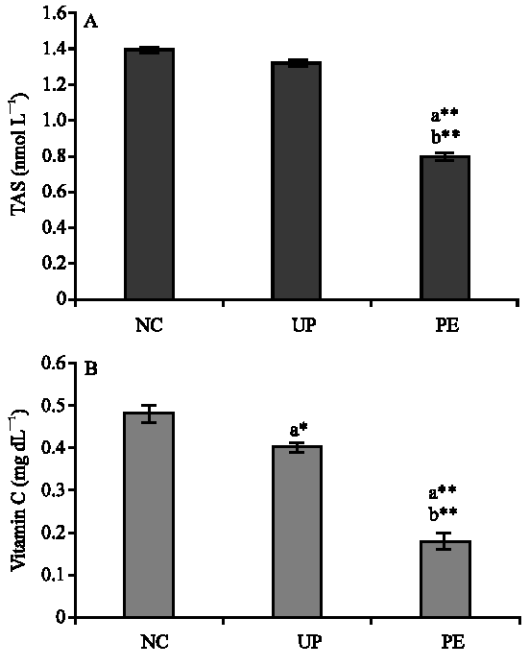

Fig. 3: Antioxidant status in preeclampsia (PE) as compared to Uncomplicated Pregnant (UP) and Nonpregnant Control (NC) subjects. (A) Total Antioxidant Status (TAS) and (B) Vitamin C. Values represented are means±SE. a: versus nonpregnant controls, b: versus uncomplicated pregnant subjects. *: $p \leq 0.01$, **: $p \leq 0.001$ versus uncomplicated pregnant subjects

Antioxidant status in different study groups: Total Antioxidant Status (TAS) of PE group was significantly lower ($p<0.01$) compared to that of the UP group (Fig. 3), which was also significantly lower than that of Nonpregnant Control (NC) group. Plasma concentrations of vitamin C was significantly decreased ($p<0.001$) in PE group compared to UP and NC groups (Fig. 3). Vitamin C was also significantly low ($p<0.05$) in UP group compared to that of NC group.

DISCUSSION

The subjects in the three study groups were matched in age and/or gestational age. Systolic and diastolic blood pressure were normal in NC and in UP groups but was high in PE group as this is one of the symptoms of preeclampsia. Normal pregnancy is characterized by a progressive increase in body fat, but the amount varies with total weight gain. During the second trimester of pregnancy, plasma lipids increase and (triglycerides, cholesterol and lipoproteins) decrease soon after delivery. The ratio of LDL to HDL increases during pregnancy.

In the present study, the plasma level of TG was increased in the PE women compared with UP women, which is consistent with the findings of previous researchers (Sattar *et al.*, 1997; Wakatsuki *et al.*, 2000). In addition, in the preeclamptic group, we found significantly lower levels of HDL-cholesterol as compared to UP and NC groups. Some studies have already reported similar results in HDL-C (Sattar *et al.*, 1997; Cekmen *et al.*, 2003; Kaaja *et al.*, 1995) as well as Apo A-1, the major protein constituent of HDL (Rosing *et al.*, 1989; Belo *et al.*, 2002) but others (Wakatsuki *et al.*, 2000; Hubel *et al.*, 1996) have failed to detect differences in HDL-C. In human gestation, there is a rise in HDL-C and apo A-1 concentrations reaching a peak in the second trimester. The increase in the number of HDL particles may help to protect the mother, counterbalancing the 'atherogenic' modifications of the apo-B containing lipoproteins during pregnancy. In preeclampsia, the reduced levels of HDL-C reveal a failure of HDL to rise, during gestation, or simply naturally occurring lower levels of HDL in these women. Further, enhanced oxidative stress in preeclamptic subjects might reduce the concentration of endogenous antioxidants, resulting in an increased susceptibility of HDL to oxidative modification. As also reported previously, we have demonstrated elevated levels of LDL-C (Sattar *et al.*, 1997; Belo *et al.*, 2002; Ogura *et al.*, 2002; Lorentzen and Henrikson, 1998) in PE compared to control women. Wakatsuki *et al.* (2000) reported that there was no difference in the levels of LDL-C between PE and UP women. We concluded that the atherogenic profile, well tolerated by the mother during UP, might somehow disrupt the normal processes in the PE mother. This abnormal lipid profile may have a potential role in the promotion of oxidative stress and vascular dysfunction seen in PE. The process of lipid peroxidation in membranes has been implicated as one of the primary events in oxidative cellular damage and has been shown to be associated with fine structure disturbance and subsequent functional loss of biological membranes.

Llurba *et al.* (2004) and Regan *et al.* (2001) reported that there is no evidence for enhanced lipid peroxidation in PE patients. Contrary to the above studies, our results showed significantly increased plasma lipid hydroperoxides, the major initial reaction products of lipid peroxidation, in PE women. This is consistent with other previously reports (Gratacos *et al.*, 1998). In our study, two products of lipid peroxidation such as thiobarbituric acid reactive substances (TBARS) and lipid hydroperoxide increase in the similar way. Lipid peroxidation is closely linked to antioxidants and polyunsaturated fatty acids present in lipoprotein particles.

Shaarawy *et al.* (1998) and Atamer *et al.* (2005) observed that serum total antioxidant status in mild and severe preeclampsia and eclampsia were significantly lower than that of healthy pregnant women. The results of our study also suggest that in patients with PE there is an increase in free radical generation as indicated by an increase in the levels of lipid peroxides and a decrease in the concentrations of antioxidants such as total antioxidant status and vitamin C (Fig. 2 and 3). The lower concentrations of vitamin C in plasma during gestation in those who did, than in those who did not develop preeclampsia leads support to the findings of earlier study (Redman and Sargent, 2005) which suggest that oxidative stress is associated with the disorder. Llurba *et al.* (2004) also reported significant decreased in plasma concentrations of ascorbic acid in PE women compared to healthy pregnant women, although low vitamin C values were not observed in any case.

This is consistent with other studies which suggested that, in patients with PE, ascorbate may be utilized to a greater extent to counteract free radical-mediated cell disturbances (Hubel *et al.*, 1999; Mutlu-Turkoglu *et al.*, 1998; Roberts and Lain, 2002) and with studies by others who advocate vitamin C and E supplementation for the prevention of PE in women at increased risk of the disease (Chappell *et al.*, 1999, 2002). The results of this study would suggest that intake of water-soluble antioxidant nutrients may initially be recommended. Vitamin C, present in aqueous compartments-cytosol, plasma and other body fluids-is able to trap most Reactive Oxygen Species (ROS) present therein and functions as a first-line defense mechanism against free radicals. The interaction between vitamin C and E in the antioxidant defense of biochemical systems is well established because ascorbic acid can reduce tocopheroxyl radicals directly or indirectly and thus support the antioxidant activity of vitamin E.

These results are also supported by Sagol *et al.* (1998) who demonstrated that serum antioxidant activity and ascorbic acid level were significantly decreased in mild and severe preeclampsia compared with normal pregnancies. Based on these results, it was suggested that the enhanced lipid peroxidation products may cause peroxidative damage to vascular endothelium and result in clinical symptoms of preeclampsia (Sagol *et al.*, 1998). However, no data pertaining to endothelial dysfunction in the form of altered levels of nitric oxide, prostacyclin, or Von-Willebrand factor was presented in this study. On the other hand, Mutlu-Turkoglu *et al.* (1998) showed a significant increase in TBARS, an indication of increase in lipid peroxidation secondary to enhanced free radical generation, significant decreases in total thiol (t-SH) content and superoxide dismutase (SOD) activity. However, they found unchanged vitamin C levels and Glutathione Peroxidase (GPx) activity in the plasma of preeclamptic women compared to women with normal pregnancies. Following delivery, the elevated TBARS decreased and the reduced SOD activity and t-SH contents increased significantly. These results suggested that PE is associated with an imbalance between lipid peroxides and the anti-oxidant system. Shaarawy *et al.* (1998) in agreement suggested that serum total antioxidant status in mild and severe PE were significantly lower than that of healthy pregnant women.

Though these studies (Mutlu-Turkoglu *et al.*, 1998; Atamer *et al.*, 2005; Sagol *et al.*, 1998; Madazli *et al.*, 1999) and other investigations (Wang and Walsh, 1996; Uotila *et al.*, 1993) are in support of an alteration in the prooxidant and antioxidant status in patients with preeclampsia, concomitant supplementation of antioxidant vitamins E (800 IU day^{-1}) and C (1000 mg day^{-1}) in a randomized placebo-controlled trial study does not prevent preeclampsia in women at risk (Poston, 2006). Although in a previous (Chappell *et al.*, 1999) smaller trial study with an identical regimen were found to be of some benefit in the prevention of PE in women who were at increased risk. This suggests that once the PE occurs, antioxidant supplementation is of less benefit. Though the exact reason for this increase in free radical generation and lipid peroxidation is not known, there is reasonable evidence to suggest that circulating neutrophils of patients with PE release an excess of ROS (Crocker *et al.*, 1999) and that neutrophils remain in an activated state (Barden *et al.*, 1997; Tsukimori *et al.*, 1993). This increased activity of neutrophils could be due to an enhancement in the production of cytokines such as interleukin-1 β (IL-1b), IL-10 and tumor necrosis factor α (TNF α) (Rinehart *et al.*, 1999; Saito *et al.*, 1999) though some studies do not support this view (Kupferminc *et al.*, 1999; Hennessy *et al.*, 1999; Heyl *et al.*, 1999).

On the basis of our study and the data available in the literature, it is clear that PE is associated with increased oxidative stress, low antioxidant activity and increased lipid peroxidation. Our data suggest that an abnormal lipid metabolism and particularly high triglyceride, LDL-C and lipid peroxides and low antioxidant activity and HDL-C concentrations may contribute to promotion of oxidative stress and vascular dysfunction seen in PE.

However, it remains to be determined whether these changes in the prooxidant and antioxidant status are the causes of PE or the consequence of the disease. It is also not clear, which is the primary event that triggers the onset of increased blood pressure in PE.

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