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# Maternal serum lipid levels, oxidative stress and antioxidant activity in pre-eclampsia patients from Southwest India

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ABSTRACT

*Objective:* A study was carried out to evaluate the effects of metabolic syndrome components and oxidative stress factors among preeclamptic women from South West India.
*Study design:* A case-control study was carried out by enrolling fifty pre-eclampsia cases and hundred low-risk pregnant women within the age group of 18–40 years, at 28–34 weeks of pregnancy. The fasting glucose level, fasting insulin level, insulin resistance, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), malondialdehyde, the ferric reducing ability of plasma (FRAP assay), cardiac output and aortic wall distensibility were measured.
*Main outcome measures:* There was a significant rise in the fasting blood glucose, fasting insulin, insulin resistance levels, total cholesterol, triglycerides, LDL, and antioxidant levels in pre-eclamptic women ($p < 0.001$). The cardiac output and aortic wall distensibility were observed to be low in the cases.
*Conclusion:* We conclude that abnormal lipid metabolism and high lipid peroxide concentrations observed in pre-eclampsia may result in oxidative stress and vascular dysfunction.

## 1. Introduction

The etiopathogenesis of pre-eclampsia, one of the commonest pregnancy specific complications is still elusive. Pregnancy results in remarkable maternal metabolic adjustments and the presence of metabolic syndrome components were perceived to be an important risk factor for pre-eclampsia. The oxidative stress owing to hyperlipidemia of pregnancy also contributes to pregnancy-related hypertensive disorders. The toxaemia theory remains the favoured hypothesis in pre-eclampsia which explains the role of the compromised placenta. Metabolic syndrome is a group of conditions such as hypertension, raised cholesterol, hyperglycemia, and excess body fat around the waist, which double the risk of cardiovascular disorders (CVD). By 2020, cardiovascular disorders will be the largest cause of disability and death in India, with 2.6 million Indians predicted to die due to CVD [1]. During pregnancy, women with pre-eclampsia are more likely to exhibit relative hypertriglyceridemia, hypercholesterolemia and gestational diabetes. These women continue to demonstrate elevated risk factors for CVD such as impaired endothelial function, impaired glucose tolerance, insulin resistance and diabetes mellitus [2].Women with pre-eclampsia should be counselled regarding the future cardiovascular risks and risks for renal disorders. Pre-eclampsia foretells at least a two-fold higher rate occurrence of cardiovascular diseases in later life [3].

Metabolic syndrome comprises a group of metabolic and physical conditions with increased risk of diabetes mellitus and cardiovascular disorders. The components of the metabolic syndrome mainly insulin resistance, inflammation and dyslipidemia in pregnancy lead to maternal endothelial cell dysfunction and pre-eclampsia syndrome. The research strategies in preventing pre-eclampsia related complications and cardiovascular sequelae should mainly focus on the prevalence of metabolic syndrome in pregnant women. Obesity and physical inactivity are currently considered the major factors in the aetiology of metabolic syndrome. Meanwhile, genetic susceptibility, race, ageing, and endocrine disorders also play a vital role in the development of metabolic syndrome. Insulin resistance was identified as the dominant cause of metabolic syndrome by the World Health Organization Task Force on Diabetes [4]. In order to diagnose metabolic syndrome in pregnancy, WHO and National Cholesterol Education Program – Adult Panel III [NCEP-ATP III] definitions were commonly used [5].

The physiologic cardiovascular changes occurring during pregnancy ensure sufficient uterine blood flow, oxygenation, and nutrient delivery to the fetus. A significant increase in the maternal cardiac output occurs in normal pregnancy by the eighth week of pregnancy. Pre-eclampsia is

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not manifested in all cases as a state of decreased intravascular volume, lower cardiac output and vasoconstriction. Oxidative stress was defined as a biochemical imbalance between free radical damage and antioxidant properties. Pregnancy itself may contribute to increased oxidative stress leading to endothelial dysfunction and pre-eclampsia. An established method for measuring the end products of increased oxidative stress is to quantity the level of malondialdehyde [MDA] which is a lipid peroxidation end product. Similarly, the ferric reducing ability of plasma [FRAP] assay is one of the several methods developed to assess the "total antioxidant capacity" of plasma. Metabolic syndrome results in increased aortic stiffness which is often assessed by measuring the aortic wall distensibility. Aortic elastic properties help in assessing the function of large arteries and systemic vascular vasomotion.

This hospital-based study was carried out to evaluate the role of metabolic syndrome components and oxidative stress factors among pregnant normotensive women and preeclamptic women from South West India. The main objectives were to compare the fasting blood glucose, fasting insulin, insulin resistance, total cholesterol, Triglycerides, HDL (high-density lipoprotein), LDL (low-density lipoprotein), malondialdehyde, Ferric Reducing Ability of Plasma (FRAP assay), cardiac output and aortic distensibility in normotensive and preeclamptic women.

## 2. Methodology

A case-control study was carried out by enrolling pregnant women attending the outpatient department, at the Obstetrics and Gynecology Department, Dr T MA Pai Hospital, Manipal Academy of Higher Education between March 2014 and October 2015. Fifty pregnant women within the age group of 18–40 years with blood pressure ≥140/90 mmHg and proteinuria > 300 mg or ≥ +1 dipstick at 28–34 weeks of pregnancy were included as cases. Women with severe pre-eclampsia, gestational diabetes mellitus, pre-gestational diabetes, chronic hypertension, chronic renal disorders, women receiving aspirin and multiple pregnancies, were excluded from the study. Care was taken to collect blood samples for analysis prior administering corticosteroids. Hundred low-risk pregnant women, matched for age and gestational age, without any medical or obstetric complications were enrolled as controls. Women not willing to participate, women developing pre-eclampsia in the control group, smokers or women with a history of illicit drug use, women with renal or lipid disorders, and preeclamptic patients with HELLP syndrome [Hemolysis, elevated liver enzymes, lowered platelet count] were excluded. All the subjects were informed about the study in the local language and informed written consent was obtained. The sample size was determined by anticipating a standard deviation of 24.5 mg/dl of triglycerides among normotensive pregnant women and 20 mg/dl difference in preeclamptic pregnant women for a power of 80% at 95% confidence level with 1:2 ratio for pre-eclamptic to normotensive pregnant women. The study was reviewed and approved by the Institutional Ethics Committee, Kasturba Medical College, Manipal (IEC No: UEC/30/2013-14). The outcome variables studied were fasting blood glucose, fasting insulin, fasting Cholesterol, Triglycerides, HDL, LDL, Malondialdehyde, FRAP assay, cardiac output and aortic wall distensibility. In the present study, fasting blood glucose levels ≥105 mg/dl was considered hyperglycemia. The fasting plasma triglyceride value ≥291 mg/dl and fasting plasma HDL value ≤34 mg/dl were regarded as hypertriglyceridemia and low HDL respectively.

The proteinuria was measured by TC URS-10 strips (Urine Reagent Strips for urinalysis) from Teco Diagnostics. In order to test the fasting glucose, fasting insulin, lipid profile and antioxidant assays, 7 ml overnight fasting venous sample was collected. The fasting blood sugar was estimated using glucose oxidase and peroxidase methods by fully Automated Analyzer Hitachi 902. The fasting insulin was measured by specific chemiluminescence test [6]. Insulin resistance was calculated by Homeostasis Model Assessment (HOMA) formula and HOMA index was used to evaluate the insulin resistance (IR) [7]. A value of HOMA-IR above 2.5 was considered an indicator of insulin resistance. The total cholesterol, Triglycerides, HDL cholesterol and LDL cholesterol were analyzed using standard enzymatic methods on a fully Automated Analyzer Hitachi 902 [8]. Serum malondialdehyde, a product of lipid peroxidation, was measured by a thiobarbituric reaction described by Kei Sathoh [9]. The MDA equivalents of the sample were calculated using an extinction coefficient of $1.56 \times 10^5\,M^{-1}\,cm^{-1}$ The FRAP assay was done as per the method described by Benzie and Strain [10]. The cardiac output was calculated as the product of stroke volume and heart rate derived from transthoracic M-mode. The two-dimensional echocardiographic monitoring [AlokaSSD-5500, Japan] was performed by experienced operators and M-mode measurements were applied with the leading edge to leading edge principle as recommended by the American Society of Echocardiography [11]. The stroke volume was calculated as the difference between end-diastolic volume and end-systolic volume. The left ventricular end-diastolic and end-systolic volumes are calculated according to the Teichholz formula. The statistical analysis was carried out using SPSS 15.0 for Windows (SPSS™ Inc., Chicago, IL, USA). The demographic data and baseline characteristics were analysed using percentages for categorical data including mean and standard deviation for the continuous data. Parametric tests were used to compare the cases and controls (independent sample *t*-test) as the data were normally distributed. The Pearson's correlation coefficient was used to estimate the correlation between the variables and *p*-value $< 0.05$ was considered statistically significant.

## 3. Results

About fifty pregnant women with pre-eclampsia and hundred normotensive women matched for age and gestational age were included. The mean age was 27.3 years (SD = ± 3) years and 27.4 years (SD = ± 3.8) in normotensive pregnant women and preeclamptic women respectively (Table 1). The mean BMI in normotensive pregnant women was 21.3 kg/m$^2$ (SD = ± 2.8) and in preeclamptic women mean BMI was observed to be 23.8 kg/m$^2$ (SD = ± 3.1). The mean gestational age was 32 weeks 1 day (SD = ± 8.3) and 33 weeks 1 day (SD = ± 8.1) in normotensive pregnant women and in pre-eclamptic women respectively. The mean maternal weight gain was 10.6 kg (SD = 1.5) and 12.2 kg (SD = 1.8) in controls and cases respectively which was statistically significant (P value $< 0.05$).

Pre-eclampsia was not significantly associated with an increase in the parity. However, 34% pre-eclamptic women enrolled in the study reported a family history of hypertension which was significant. There existed a significant difference in the levels of fasting blood glucose, fasting Insulin, insulin resistance, total cholesterol, triglycerides, and LDL between the two groups ($p < 0.001$) as shown in Table 2. However, there was no significant increase in the HDL and malonaldehyde levels in pre-eclamptic women antenatally. The plasma FRAP assay indicating the antioxidant activity was significantly higher among pre-eclamptic women in comparison to controls ($p < 0.001$). The cardiac output and aortic wall distensibility were observed to be low in the pre-eclamptic women.

The serum malondialdehyde level was negatively correlated with total cholesterol level which was insignificant in the pre-eclamptic cases ($r = -0.028$, *p*-value- 0.849) as well as controls ($r = -0.038$, *p*-value-0.706) as shown in Fig. 1. The antioxidant activity was negatively

**Table 1**
Demographic profile of study participants (n = 150).

| Demographic factors | Control subjects (n = 100) | Pre-eclampsia subjects (n = 50) |
|---|---|---|
| Age (years) | 27.3 ± 3.0 | 27.4 ± 3.8 |
| Primi gravida (nulliparas) | 64 (64%) | 32(64%) |
| Gestational age at sampling (weeks) | 32.1 ± 8.3 | 33.1 ± 8.1 |
| *BMI at sampling (kg/m$^2$) | 21.3 ± 2.8 | 23.8 ± 3.1 |
| Family history of hypertension | 13% | 34% |

* BMI (body mass index).

**Table 2**
Metabolic factors, lipid profile, antioxidant assays, hemodynamic parameters of the study participants (n = 150).

| | Cases (n = 50) | Controls (n = 100) | *p-value* |
|---|---|---|---|
| FBS (mg/dl) | 90.6 ± 6.5 | 81.4 ± 6.6 | < 0.001 |
| Fasting insulin | 19.3 ± 7.7 | 10.1 ± 4.0 | < 0.001 |
| Insulin resistance (HOMA > 2.5) | 4.3 ± 1.7 | 2.0 ± 0.8 | < 0.001 |
| Total cholesterol (mg/dl) | 265.5 ± 57.7 | 217.2 ± 43.7 | < 0.001 |
| Triglycerides (mg/dl) | 266.5 ± 82.4 | 168.8 ± 61.5 | < 0.001 |
| HDL(mg/dl) | 53.6 ± 11.8 | 54.7 ± 10.2 | 0.546 |
| LDL(mg/dl) | 161.1 ± 32.5 | 135.2 ± 33.8 | < 0.001 |
| MDA (nmol/l) | 0.36 ± 0.1 | 0.27 ± 0.1 | 0.250 |
| FRAP ((nmol/l) | 2.63 ± 1.0 | 1.29 ± 0.5 | < 0.001 |
| Cardiac output | 4440.7 ± 803.2 | 5698.3 ± 1009.4 | < 0.001 |
| Aortic wall distensibiity [*cm2/dyn/103*] | 3.6 ± 0.7 | 4.1 ± 1.2 | 0.007 |

FBS (Fasting Blood Sugar), HOMA (Homeostasis Model Assessment), HDL (High Density Lipids), LDL (Low Density Lipids), FRAP (ferric reducing ability of plasma), MDA (Malondialdehyde).

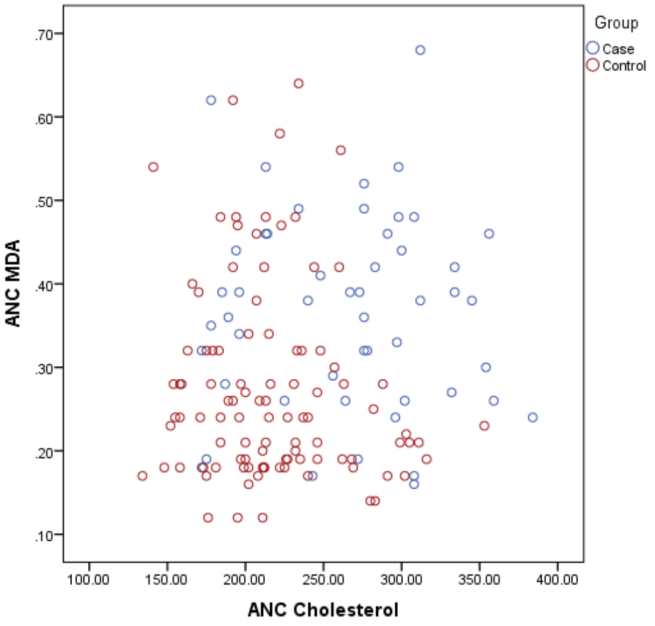


**Fig. 1.** The serum malondialdehyde level was negatively correlated with total cholesterol level which was insignificant in the pre-eclamptic cases ($r = -0.028$, $p$-value- 0.849) as well as controls ($r = -0.038$, $p$-value-0.706).

correlated with total cholesterol level in cases ($r = -0.214$, $p$-value 0.136) which was demonstrated in Fig. 2. Meanwhile, there existed a positive correlation between antioxidant activity (FRAP assay) and total cholesterol levels in controls which was insignificant ($r = 0.191$, $p$-value-0.06).

## 4. Discussion

The elevated cholesterol level in pregnancy leads to augmented lipid peroxidation and formation of free radicals. There was a significant elevation in total cholesterol levels as well as serum malonaldehyde levels in pre-eclamptic women compared to controls even though the malonaldehyde level was negatively correlated with high cholesterol levels. The antioxidant levels were observed to be raised in the plasma of pre-eclamptic women in spite of having a higher cholesterol. The stiffness of the aorta is an independent indicator of cardiovascular mortality, irrespective of previous cardiovascular events, ageing and diabetes mellitus. Aortic stiffness is routinely measured by non-invasive pulse wave velocity method (PWV). We employed M-mode and two-

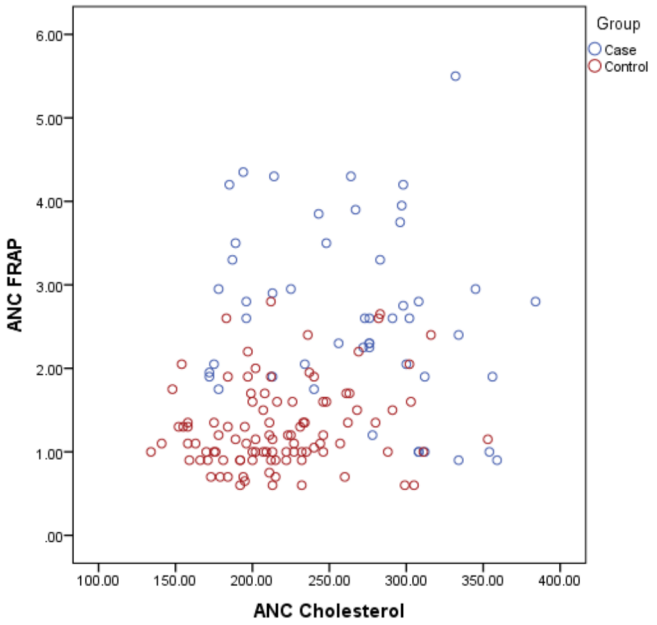


**Fig. 2.** The antioxidant activity was negatively correlated with total cholesterol level in cases ($r = -0.214$, $p$-value 0.136) which was demonstrated in Fig. 2. Meanwhile, there existed a positive correlation between antioxidant activity (FRAP assay) and total cholesterol levels in controls which was insignificant ($r = 0.191$, $p$-value-0.06).

dimensional echocardiography which provides high-resolution images to assess the aortic stiffness. Pre-eclamptic women having metabolic risk factors were observed to be associated with increased stiffness of aorta.

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Several studies have demonstrated that metabolic syndrome components intensify the arterial stiffness in all age groups [12,13]. Dane et al studied insulin resistance in the pre-eclamptic and normotensive group and found that pre-eclamptic women were associated with significantly high insulin resistance [14]. Women demonstrated an increased risk of pre-eclampsia in the presence of hypertriglyceridemia which is one of the main components of metabolic syndrome [15–18]. A Study by Hubel et al showed that antepartum 50% raise in malondialdehyde concentration in women with pre-eclampsia [15]. A significant increase in malondialdehyde levels was reported among pre-eclamptic women in previous studies from Mangalore, India also [19,20]. The study by Visser et al reported a lower cardiac stroke volume index and a higher systemic vascular resistance index in untreated pre-eclamptic patients [18]. Meanwhile, the study by Easterling et al observed a significant increase in cardiac output in pre-eclamptic women compared to normotensive women [19]. Women with early-onset pre-eclampsia present with a higher incidence of carotid wall thickness and greater risk of subclinical atherosclerosis in later life [20]. A raised serum uric acid level is attributed to the high antioxidant capacity of serum. Pre-eclampsia results in an increase in total antioxidant capacity measured by TRAP (Total Radical Trapping Antioxidant Potential) method and FRAP assay [21]. However, the influence of uric acid levels in the measurement of total antioxidant capacity remains uncertain and require further research. Harsem et al also reported a raise in both malondialdehyde and FRAP levels in pre-eclampsia [22].

The disparity in the serum malonaldehyde elevation in pre-eclamptic women in comparison to previous studies was mainly attributed to the

interassay and intraassay variations in laboratory techniques. There occurs an elevation in circulating concentrations of LDL and VLDL (very low-density lipoproteins) with advancing gestational age which is often replicated as a marked increase in triglycerides and cholesterol [23]. Unlike our study, most of the studies reporting high levels of cholesterol and serum malondialdehyde enrolled women at 39–40 weeks and followed up for initial 48 h of delivery [15]. We enrolled pregnant women between 28 and 34 weeks of gestation in this study. Our study was limited to a small geographic area and to ascertain the role of raised lipoproteins in pre-eclampsia, uniform methodologies involving a larger number of patients at varying gestational ages are essential [24]. However, pre-eclampsia patients constitute a high-risk group for future metabolic syndrome and should be followed up longterm for the development of cardiovascular diseases.

## 5. Conclusion

The present study indicates that abnormal lipid metabolism and high lipid peroxide concentrations observed in pre-eclampsia may contribute to oxidative stress and vascular dysfunction. Metabolic syndrome components play an important role in hypertensive incidents that occur during pregnancy.

## Recommendations

Controlling deranged lipid parameters before pregnancy for individuals at high risk of pre-eclampsia may be considered. Since there is a robust association of pre-eclampsia with future cardiovascular risks, lifestyle modifications may be advised to women developing high blood pressure during pregnancy.

## Conflicts of interest

The authors state that they have no conflict of interest.

## Contributions

PV Bhat: Proposal development, manuscript writing, final editing.
VV: data collection, manuscript writing.
AN: Data collection, manuscript writing.
AK: Data analysis.

## Compliance with ethical standards

### *Ethical approval*

All the procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed written consent was obtained from all the enrolled women.

## References

[1] K.S. Reddy, D. Prabhakaran, V. Chaturvedi, P. Jeemon, K.R. Thankappan, L. Ramakrishnan, et al., Methods for establishing a surveillance system for cardiovascular diseases in Indian industrial populations, Bull. World Health Organ. 84 (2006) 461–469 Doi:/S0042-96862006000600015.

[2] J.A. Lykke, J. Langhoff-Roos, B.M. Sibai, E.F. Funai, E.W. Triche, M.J. Paidas, Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother, Hypertens Dallas Tex 2009 (53) (1979) 944–951, https://doi.org/10.1161/HYPERTENSIONAHA.109.130765.

[3] N. Sattar, I.A. Greer, Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 325 (2002) 157–160.

[4] K.G. Alberti, P.Z. Zimmet, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation, Diabet. Med. 15 (1998) 539–553, https://doi.org/10.1002/(SICI)1096 9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S.

[5] J.L. Bartha, F. González-Bugatto, R. Fernández-Macías, N.L. González-González, R. Comino-Delgado, B. Hervías-Vivancos, Metabolic syndrome in normal and complicated pregnancies, Eur. J. Obstet. Gynecol. Reprod. Biol. 137 (2008) 178–184, https://doi.org/10.1016/j.ejogrb.2007.06.011.

[6] A. Pfützner, T. Kunt, M. Langenfeld, M. Löbig, M. Knesovic, T. Forst, Clinical and laboratory evaluation of specific chemiluminescence assays for intact and total proinsulin, Clin. Chem. Lab. Med. 41 (2003) 1234–1238, https://doi.org/10.1515/CCLM.2003.189.

[7] D.R. Matthews, J.P. Hosker, A.S. Rudenski, B.A. Naylor, D.F. Treacher, R.C. Turner, Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man, Diabetologia 28 (1985) 412–419.

[8] R.W. Evans, T.J. Orchard, Oxidized lipids in insulin-dependent diabetes mellitus: a sex-diabetes interaction? Metabolism 43 (1994) 1196–1200.

[9] K. Satoh, Serum lipid peroxide in cerebrovascular disorders determined by a new colorimetric method, Clin. Chim. Acta Int. J. Clin. Chem. 90 (1978) 37–43.

[10] I.F. Benzie, J.J. Strain, The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": the FRAP assay, Anal. Biochem. 239 (1996) 70–76, https://doi.org/10.1006/abio.1996.0292.

[11] D.J. Sahn, A. DeMaria, J. Kisslo, A. Weyman, Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements, Circulation 58 (1978) 1072–1083.

[12] Y. Güray, M. Refiker, B. Demirkan, U. Güray, A. Boyaci, S. Korkmaz, Aortic strain and distensibility in patients with metabolic syndrome, Turk. Kardiyol. Dernegi Arsivi Turk. Kardiyol. Derneginin Yayin Organidir 38 (2010) 14–19.

[13] C. Kaihura, M.D. Savvidou, J.M. Anderson, C.M. McEniery, K.H. Nicolaides, Maternal arterial stiffness in pregnancies affected by preeclampsia, Am. J. Physiol. Heart Circ. Physiol. 297 (2009) H759–H764, https://doi.org/10.1152/ajpheart.01106.2008.

[14] B. Dane, C. Dane, M. Kiray, M. Koldas, A. Cetin, A new metabolic scoring system for analyzing the risk of hypertensive disorders of pregnancy, Arch. Gynecol. Obstet. 280 (2009) 921–924, https://doi.org/10.1007/s00404-009-1029-9.

[15] C.A. Hubel, M.K. McLaughlin, R.W. Evans, B.A. Hauth, C.J. Sims, J.M. Roberts, Fasting serum triglycerides, free fatty acids, and malondialdehyde are increased in preeclampsia, are positively correlated, and decrease within 48 hours post partum, Am. J. Obstet. Gynecol. 174 (1996) 975–982.

[16] U. Adiga, V. D'souza, A. Kamath, N. Mangalore, Antioxidant activity and lipid peroxidation in preeclampsia, J. Chin. Med. Assoc. 70 (2007) 435–438, https://doi.org/10.1016/S1726-4901(08)70034-0.

[17] S.B. Patil, M.V. Kodliwadmath, S.M. Kodliwadmath, Correlation between lipid peroxidation and non-enzymatic antioxidants in pregnancy induced hypertension, Indian J. Clin. Biochem. 23 (2008) 45–48, https://doi.org/10.1007/s12291-008-0011-9.

[18] W. Visser, H.C. Wallenburg, Central hemodynamic observations in untreated pre-eclamptic patients, Hypertens. Dallas Tex 1991 (17) (1979) 1072–1077.

[19] T.R. Easterling, T.J. Benedetti, B.C. Schmucker, S.P. Millard, Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study, Obstet. Gynecol. 76 (1990) 1061–1069.

[20] M. Christensen, C.S. Kronborg, R.K. Carlsen, N. Eldrup, U.B. Knudsen, Early gestational age at preeclampsia onset is associated with subclinical atherosclerosis 12 years after delivery, Acta Obstet. Gynecol. Scand. 96 (2017) 1084–1092, https://doi.org/10.1111/aogs.13173.

[21] S. Kharb, Total free radical trapping antioxidant potential in pre-eclampsia, Int. J. Gynaecol. Obstet. 69 (2000) 23–26.

[22] N.K. Harsem, K. Braekke, A.C. Staff, Augmented oxidative stress as well as antioxidant capacity in maternal circulation in preeclampsia, Eur. J. Obstet. Gynecol. Reprod. Biol. 128 (2006) 209–215, https://doi.org/10.1016/j.ejogrb.2005.11.014.

[23] J.M. Potter, P.J. Nestel, The hyperlipidemia of pregnancy in normal and complicated pregnancies, Am. J. Obstet. Gynecol. 133 (1979) 165–170.

[24] A.E. Fanshawe, M. Ibrahim, The current status of lipoprotein (a) in pregnancy: a literature review, J. Cardiol. 61 (2013) 99–106, https://doi.org/10.1016/j.jjcc.2012.09.009.