Pregnancy Hypertension 18 (2019) 99–102

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

# Oxidative stress in early pregnancy and the risk of preeclampsia

Iman M. Ahmad[a,*], Matthew C. Zimmerman[b], Tiffany A. Moore[c]

[a] Department of Medical Imaging and Therapeutic Sciences, College of Allied Health Professions, University of Nebraska Medical Center (UNMC), Omaha, USA
[b] Department of Cellular and Integrative Physiology, UNMC, Omaha, USA
[c] College of Nursing, UNMC, Omaha, USA

ARTICLE INFO

*Keywords:*
Preeclampsia
Early pregnancy
Catalase
Oxidative stress
Superoxide
Superoxide dismutase
Glutathione

ABSTRACT

*Introduction:* Preeclampsia (PE), one of the most serious complications of pregnancy, is characterized by endothelial dysfunction and hypertension. The pathophysiology of the disease is still unknown; however, evidence suggests that placental and maternal oxidative stress promote the disease process. Several studies have assessed levels of oxidative stress during pregnancy, but after diagnosis of PE. However, few studies have examined oxidative stress before PE diagnosis. Thus, the present work was aimed to gain further insight into the role of oxidative stress prior to diagnosis of PE (*i.e.* 12–20 weeks of gestation) and to further understand and predict PE incidence.

*Methods:* Blood levels of superoxide ($O_2^{\cdot -}$) and erythrocyte antioxidants such as superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH) and oxidized glutathione (GSSG) levels were measured in 23 preeclamptic pregnant women and 91 women with normal pregnancies. We further used logistic regression of $O_2^{\cdot -}$ and each antioxidant level as the main predictor variable for PE risk.

*Results:* CAT activity, GSH, and Total glutathione (TGSH) were significantly lower with All PE pregnant groups, whereas $O_2^{\cdot -}$ levels were modestly, but significantly, higher in women with mild PE. Logistic regression analysis suggests increased CAT activity in pregnant women is associated with a decreased odds of being preeclamptic.

*Conclusion:* CAT is the only antioxidant as shown in our study to be related to the severity of the disease and may be a promising predictor for PE. Further studies are warranted to investigate the use of CAT as a novel therapeutic for PE.

## 1. Introduction

Preeclampsia (PE), a leading cause of preterm delivery and of maternal morbidity and mortality worldwide [1–3], is more than simply gestational hypertension during pregnancy [4]. It is characterized by new, sustained hypertension and proteinuria and other adverse conditions in the second half of pregnancy [1,5]. Despite significant progress in understanding the pathophysiology of PE, the cause of this disorder remains largely unknown. PE is proposed as a "2-stage model" [6] in which reduced placental perfusion leads to the maternal syndrome characterized by endothelial dysfunction and hypertension; however, the link between these stages is unclear. Oxidative stress, often referred to as an imbalance between reactive oxygen species (ROS) and antioxidants, increases during PE and results in increased production of lipid peroxides and ROS, such as superoxide ($O_2^{\cdot -}$) [7–9]. Oxidative stress is a known cause of endothelial dysfunction making it a potential contributor to PE [10,11]. Several studies have reported that markers of oxidative damage are elevated and antioxidant vitamin levels are lower in women with PE [12–16]. However, many of these previous studies measured antioxidant levels in mid and late pregnancy (*i.e.* after PE diagnosis). As such, it is unclear if changes in oxidative stress markers are causal to or an effect of PE. Thus, the purpose of this secondary analysis was to identify biomarkers in early pregnancy which may be associated with the eventual development of PE. These findings will enhance our understanding of the role of oxidative stress in early pregnancy with the incidence of PE. Our study objectives were to: 1) identify differences between maternal levels of ROS and antioxidants between 12 and 20 weeks gestation in women who develop PE and those who do not; and 2) identify predictive relationships of maternal $O_2^{\cdot -}$, and antioxidants measured between 12 and 20 weeks gestation with incidence of PE.

* Corresponding author.
*E-mail address:* iman.ahmad@unmc.edu (I.M. Ahmad).

https://doi.org/10.1016/j.preghy.2019.09.014
Received 5 March 2019; Received in revised form 13 September 2019; Accepted 22 September 2019
Available online 03 October 2019
2210-7789/ Published by Elsevier B.V. on behalf of International Society for the Study of Hypertension in Pregnancy.

**Table 1**
Clinical Characteristics of All PE and Normal Pregnancy Groups.

| Maternal characteristics | All PE, n = 25<br>Mean ± SD or n (%) | Normal pregnancy, n = 103<br>Mean ± SD or n (%) | P value |
|---|---|---|---|
| Age at delivery (years) | 30.6 ± 5.85 | 28.6 ± 4.94 | 0.083 |
| BMI | 31.80 ± 10.20 | 28.26 ± 8.14 | 0.065 |
| Gestational age at sampling (weeks) | 12–20 | 12–20 | |
| Baby birth weight (g) | 3162.80 ± 723.96 | 3317.53 ± 584.78 | 0.261 |
| Baby Gestational Age | 36.9 ± 2.43 | 38.8 ± 2.09 | < 0.001 |
| *Maternal Race* | | | |
| White | 23 (92) | 66 (64) | 0.007 (Fisher's exact) |
| Non-white | 2 (8) | 37 (36) | |
| Maternal Ethnicity (non Hispanic) | 24 (96) | 90 (87) | 0.227 |
| *Diabetes Mellitus (DM) Status* | | | |
| No | 12 (48) | 89 (86) | < 0.001 (chi square) |
| DMI | 4 (16) | 1 (1) | |
| DMII | 4 (16) | 2 (2) | |
| Gestational DM | 5 (20) | 11 (10) | |

Descriptive statistics includes testing differences between All PE and normal pregnancy groups using Chi-Square tests and *t*-tests.

## 2. Materials and methods

### 2.1. Sample collection

A prospective, longitudinal design was used to recruit 140 pregnant women between 12 and 20 weeks gestation from a maternal-fetal medicine practice group and a general obstetrics practice group associated with a Midwest tertiary perinatal center. The present study was reviewed and approved by the Institutional Review Board of University of Nebraska Medical Center (Protocol No. 154-14-EP and 794-15-EP), and written informed consent was obtained from each participant. Further details of the original study can be found in Moore et al. [17]. Demographic (age, body mass index (BMI), race, ethnicity, diabetes mellitis (DM)) and outcome (maternal PE, neonate's gestational age at birth, neonate's birth weight) data were collected from the electronic health records of the pregnant women after delivery. All pregnant women were followed until delivery and categorized as PE per documentation in the medical record. PE severity was diagnosed in 1 of 3 ways: (1) gestational hypertension if there was high blood pressure (BP) (systolic BP > 140 Hg and/or diastolic BP > 90 Hg); (2) mild PE if there was proteinuria and high BP (systolic BP > 140 Hg and/or diastolic BP > 90 Hg); (3) or severe PE was established by persistent high BP (systolic BP ≥ 160 Hg or diastolic BP ≥ 110 Hg) and proteinuria, and any of the following adverse conditions: creatinine > 1.0, liver enzymes 2× normal or more, platelets < 100, and symptoms such as headache, visual changes, shortness of breath, and chest pain.

### 2.2. Blood sampling

Blood samples were collected from all pregnant women into EDTA tubes at 12–20 weeks of gestation. Red blood cells (erythrocytes) were separated from plasma by centrifugation at 2500 × *g* at 4 °C for 5 min and the plasma and erythrocytes samples were then stored at −80 °C until analyzed.

### 2.3. $O_2^{\cdot -}$ measurements

$O_2^{\cdot -}$ was measured in whole blood using electron paramagnetic resonance (EPR) Spectroscopy [18]. Briefly, thirty minutes after blood collection, whole blood was incubated for 30 min at 37 °C with a superoxide-sensitive EPR spin probe, 1-hydroxy-3-methoxycarbonyl-2,2,5,5-tetramethylpyrrolidine (CMH), then frozen in liquid nitrogen. Oxidation of these spin probes results in the formation of stable nitroxide radicals that can be detected by EPR spectroscopy. The amplitude of the EPR spectrum is directly proportional to the concentration of $O_2^{\cdot -}$. All EPR measurements were performed with a Bruker eScan EPR spectrometer (Bruker BioSpin GmbH, Rheinstetten/Karlsruhe, Germany) and expressed as EPR arbitrary units (A.U.).

### 2.4. Antioxidants measurement

All antioxidants (*i.e.* superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH) and oxidized glutathione (GSSG)) were measured in red blood cell lysate using commercially available assays [(SOD Assay Kit-WST (DOJINDO, Inc, Rockville, MD, USA), OxiSelect Catalase Activity Assay Kit (Cell Biolabs, Inc., San Diego, CA, USA), GSSG/GSH Quantification kit (DOJINDO, Inc, Rockville, MD, USA)] and per the manufacture instructions.

### 2.5. Statistical analyses

SPSS version 25 (SPSS Inc, Chicago, IL) was used for statistical analysis. Descriptive statistics and parametric tests were used to describe and compare demographic and outcome variables between PE and normal pregnant groups. All biomarkers were log-transformed to account for skewed data and mean differences in each of the biomarkers between PE severity and normal pregnant groups were studied, using ANOVA and post hoc Bonferroni corrections. Spearman's correlations between oxidative stress biomarkers and PE severity were also studied. Logistic regression models for predicting the dichotomous outcome of PE/normal pregnancy was performed using log-transformed data.

## 3. Results

Description of the demographic and clinical characteristics of the study groups are shown in Table 1. All PE pregnant groups did not differ from those in the normal pregnancy group in age, BMI, gestational age at sampling, baby birth weight and maternal ethnicity. All PE pregnant groups delivered approximately two weeks earlier compared to normal pregnancy group ($p < 0.001$, Table 1). A greater proportion of the PE pregnant group were white compared to the normal pregnancy group ($p = 0.007$, Table 1). As expected, more women with PE had diabetes compared to women with normal pregnancies (Table 1).

Biochemical parameters for each pregnancy group are provided in Table 2. $O_2^{\cdot -}$ levels were modestly, but significantly, higher in women with mild PE compared with those with gestational hypertension and in the normal pregnancy group ($p < 0.05$). CAT activity was significantly lower in All PE pregnant groups compared with the normal pregnancy group and were also significantly lower in women with severe PE compared with the normal pregnancy group ($p < 0.01$). Levels of CAT activity seemed to be related to the severity of the disease. Total glutathione (TGSH) and GSH levels were significantly lower in All PE

**Table 2**
Descriptive statistics of biochemical parameters between PE vs normal pregnancy groups at 12–20 weeks of gestation.

| Biochemical parameters (unit) | Normal pregnancy, n = 91 | PE groups | | | |
|---|---|---|---|---|---|
| | | All PE, n = 23 | Gestational hypertension, n = 6 | Mild PE, n = 6 | Severe PE, n = 11 |
| Superoxide ($O_2^{\cdot -}$) (A.U.)[a] | 5.9 ± 0.2 | 5.9 ± 0.3 | 5.8 ± 0.2 | 6.1 ± 0.4[b] | 5.9 ± 0.2 |
| Catalase (CAT) (U/mL) | 10.7 ± 0.9 | 9.9 ± 0.9[c] | 10.2 ± 1.2 | 10.5 ± 0.7 | 9.5 ± 0.5[c] |
| Superoxide Dismutase (SOD) (U/mL) | 11.4 ± 0.9 | 11.1 ± 0.9 | 11.4 ± 0.7 | 11.4 ± 1.2 | 10.7 ± 0.7 |
| Total Glutathione (TGSH) (nmol/mL) | 7.5 ± 0.4 | 7.2 ± 0.3[c] | 7.1 ± 0.4 | 7.3 ± 0.2 | 7.2 ± 0.3 |
| Reduced Glutathione (GSH) (nmol/mL) | 7.4 ± 0.4 | 7.1 ± 0.3[c] | 7.1 ± 0.5 | 7.2 ± 0.2 | 7.2 ± 0.3 |
| Oxidized Glutathione (GSSG) (nmol/mL) | 3.6 ± 0.6 | 3.3 ± 0.8 | 3.2 ± 0.9 | 3.2 ± 1.2 | 3.4 ± 0.7 |

Values expressed as log means ± SD.
[a] Arbitrary Units.
[b] $p < 0.05$, vs normal and gestational hypertension.
[c] $p < 0.01$, vs normal pregnancy.

pregnant groups than in normal pregnancy group ($p < 0.01$). However, there was no significant differences between the study groups across the severity of the disease. SOD and GSSG concentrations showed no significant differences between PE severity groups or between the All PE pregnant groups and the normal pregnancy group ($p > 0.05$, Table 2).

As shown in Table 3, changes in the antioxidant levels of CAT, TGSH and GSH were negatively correlated with the severity of PE. Although there was a slight, but significant, increase in $O_2^{\cdot -}$ levels in mild PE versus normal pregnancy and gestational hypertensive women (Table 2), the odds ratio, as determined by the regression model analysis for $O_2^{\cdot -}$ was not significant ($p = 0.29$, Table 4). CAT was the only parameter significantly associated with a reduced risk of PE (Table 4). It is estimated that for one unit increase in the log of CAT, the odds of being preeclamptic decreases by 64% (calculated: (odds ratio (OR) − 1) * 100, $p < 0.05$, Table 4).

## 4. Discussion

This study demonstrates strong association between some oxidative stress parameters assessed at 12–20 weeks of gestation and PE. Higher levels of CAT was significantly associated with a reduced risk of PE. CAT is the only antioxidant known to be related to the severity of the disease. Our findings suggest that oxidative stress is a potential contributor to PE. High levels of ROS are detrimental to cells leading to oxidative damage to molecules such as lipids, proteins and DNA. However, the body is equipped with antioxidant systems to overcome the elevated levels of ROS. The non-enzymatic antioxidants includes GSH, ascorbic acid, tocopherol, carotene, uric acid, bilirubin and the enzymatic antioxidants include SOD, glutathione peroxidase, and CAT. Thus, the present work was aimed to gain further insight into the role of oxidative stress prior to diagnosis of PE (*i.e.* 12–20 weeks of gestation) and to further understand and predict PE incidence.

**Table 3**
*Correlations* between oxidative stress measures of superoxide ($O_2^{\cdot -}$), catalase (CAT), superoxide dismutase (SOD), total glutathione (TGSH), reduced glutathione (GSH), and oxidized glutathione (GSSG) levels and PE severity at 12–20 weeks gestation.

| Oxidative Stress Measure[a] | PE Severity |
|---|---|
| $O_2^{\cdot -}$ | (0.045, 0.637) |
| CAT | (−0.335, **0.000**) |
| SOD | (−0.164, 0.077) |
| TGSH | (−0.302, **0.001**) |
| GSH | (−0.299, **0.001**) |
| GSSG | (−0.101, 0.279) |

*Note:* Correlations were analyzed using Spearman's correlations ($r_s$, p-value). Statistically significant correlations ($p < 0.05$) are **bolded**.
[a] Log transformed.

**Table 4**
Logistic Regression Analysis of Biochemical Parameters for Predicting PE.

| Parameter[a] | OR | 95% CI | P value |
|---|---|---|---|
| $O_2^{\cdot -}$ | 12.06 | 0.12–1158.58 | 0.29 |
| CAT | 0.36 | 0.17–0.76 | 0.01 |
| SOD | 1.22 | 0.64–2.32 | 0.56 |
| GSH | 32.06 | 0.00–5.5E11 | 0.77 |

PE, preeclampsia; OR, odds ratio; CI, confidence interval.
[a] Log transformed.

Numerous studies have assessed levels of various antioxidants during pregnancy, but after PE diagnosis [19–27]. However, only a few studies have examined differences in their levels prior to diagnosis [28–31], which commonly occurs after the 20$^{th}$ week of gestation. Among previous studies that measured antioxidants prior to the diagnosis of PE, our study is the first known study to measure CAT activity and $O_2^{\cdot -}$ levels in early pregnancy (*i.e.* 12–20 weeks of gestation). Our results suggest that oxidative stress related to a decrease in CAT activity may be implicated in early-onset PE and may accelerate the progression of the disease.

In the present study, the observed increase in $O_2^{\cdot -}$ levels in mild PE to that of normal pregnancy group could be associated with the severity of PE. However, our results did not show significant association between $O_2^{\cdot -}$ and PE severity (Table 3). Although, SOD is the first barrier and antioxidant defense against $O_2^{\cdot -}$ [32], maternal erythrocyte SOD activity was not significantly altered between both groups. This result is in accordance with another study that showed no changes in SOD activity at 16–20 weeks of gestation [31]. A previous study reported lower levels of serum SOD in women with PE at 10–14 and 20–24 weeks of gestation [29]. The discrepancy between our data and previous study might be due to the source of sample collection. Maternal erythrocyte CAT activity was lower in PE pregnant group at gestation age < 20 weeks as compared to normal pregnancy group. The deficiency of CAT activity in women with severe PE before diagnosis may be of particular importance in understanding the pathophysiologic mechanism associated with PE, as the $O_2^{\cdot -}$ that is being generated continuously by numerous sources throughout the body is rapidly converted into $H_2O_2$, which if not detoxified can contribute to oxidative stress [33]. Unfortunately, we did not measure $H_2O_2$ levels in our study, however, we did measure CAT activity and GSH. Interestingly, there are fewer studies about erythrocyte CAT activities during pregnancy in women with PE after the diagnosis [34–38], whereas none of the studies assessed differences in CAT activity preceding PE diagnosis.

GSH is a major intracellular antioxidant. Erythrocytes contain high concentrations of GSH accounting for almost 98% of total blood content. In addition to their detoxifying function, GSH and other thiols maintain the redox balance of cells, thereby preventing oxidative damage [39]. In present study, there was a marked reduction in

antioxidant reduced GSH in PE pregnant group compared to normal pregnancy group. Our results are supported by previous studies [31,40]. However, CAT is the only antioxidant known to be significantly related to the severity of the disease. One unit increase in the log of CAT, the odds of being preeclamptic decreases by 64%, Table 4. Together, these findings suggest an increased oxidative stress which may play a role in the pathogenesis of PE. If this finding is corroborated in future studies, CAT may be a promising antioxidant to consider in PE prevention trials.

In summary, the present study demonstrates CAT activity is inversely associated with the severity of PE and suggests a correlation between oxidative stress with initiation and progression of PE. Further, well-designed and adequately powered studies are warranted to investigate the use of CAT as a novel therapy for the improved treatment of PE.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

The authors wish to thank the staff and patients at Nebraska Medicine and Olson Center, Jocelyn Jones, Colton T. Roessner, and Ellen Steffensmeier.

## Funding

This study was funded by NIH 1K01NR014474-01 and a University of Nebraska Medical Center's Edna Ittner Pediatric Support grant. EPR Spectroscopy data was collected in the University of Nebraska's EPR Spectroscopy Core, which was initially established with support from a Center of Biomedical Research Excellence grant from the National Institute of General Medical Sciences of the National Institutes of Health (P30GM103335) awarded to the University of Nebraska's Redox Biology Center.

## References

[1] L. Duley, The global impact of pre-eclampsia and eclampsia, Semin. Perinatol. 33 (3) (2009) 130–137.
[2] C.V. Ananth, A.M. Vintzileos, Maternal-fetal conditions necessitating a medical intervention resulting in preterm birth, Am. J. Obstet. Gynecol. 195 (6) (2006) 1557–1563.
[3] S. Lisonkova, Y. Sabr, C. Mayer, C. Young, A. Skoll, K.S. Joseph, Maternal morbidity associated with early-onset and late-onset preeclampsia, Obstet. Gynecol. 124 (4) (2014) 771–781.
[4] C.W. Redman, J.M. Roberts, Pre-eclampsia: more than pregnancy-induced hypertension, Lancet 341 (8858) (1993) 1447–1451.
[5] P. von Dadelszen, E.A. Steegers, J.J. Duvekot, R. Pijnenborg, Pre-eclampsia, Lancet 376 (9741) (2010) 631–644.
[6] C.A. Hubel, J.M. Roberts, Is oxidative stress the link in the two-stage model of pre-eclampsia? Lancet 354 (9181) (1999) 788–789.
[7] S. Gupta, N. Aziz, L. Sekhon, R. Agarwal, G. Mansour, J. Li, A. Agarwal, Lipid peroxidation and antioxidant status in preeclampsia: a systematic review, Obstet. Gynecol. Surv. 64 (11) (2009) 750–759.
[8] S. Chen, T.T. Hsieh, L.M. Lo, M.J. Li, Y.L. Yeh, T.H. Hung, The association between maternal oxidative stress at mid-gestation and subsequent pregnancy complications, Reprod. Sci. 19 (5) (2012) 505–512.
[9] R. Madazli, A. Benian, K. Gumustas, H. Uzun, V. Ocak, F. Aksu, Lipid peroxidation and antioxidants in preeclampsia, Eur. J. Obstet. Gynecol. Reprod. Biol. 85 (2) (1999) 205–208.
[10] H. Lum, K.A. Roebuck, Oxidant stress and endothelial cell dysfunction, Am. J. Physiol. Cell Physiol. 280 (4) (2001) C719–C741.
[11] C.A. Hubel, Oxidative stress in the pathogenesis of preeclampsia, Proc. Soc. Exp. Biol. Med. 222 (3) (1999) 222–235.
[12] R.S. Bowen, J. Moodley, M.F. Dutton, A.J. Theron, Oxidative stress in pre-eclampsia, Acta Obstet. Gynecol. Scand. 80 (8) (2001) 719–725.
[13] Z. Serdar, E. Gur, M. Colakoethullary, O. Develioethlu, E. Sarandol, Lipid and protein oxidation and antioxidant function in women with mild and severe pre-eclampsia, Arch. Gynecol. Obstet. 268 (1) (2003) 19–25.
[14] M.S. Mikhail, A. Anyaegbunam, D. Garfinkel, P.R. Palan, J. Basu, S.L. Romney, Preeclampsia and antioxidant nutrients: decreased plasma levels of reduced ascorbic acid, alpha-tocopherol, and beta-carotene in women with preeclampsia, Am. J. Obstet. Gynecol. 171 (1) (1994) 150–157.
[15] S.A. Ziari, V.L. Mireles, C.G. Cantu, M. Cervantes 3rd, A. Idrisa, D. Bobsom, A.T. Tsin, R.H. Glew, Serum vitamin A, vitamin E, and beta-carotene levels in preeclamptic women in northern Nigeria, Am. J. Perinatol. 13 (5) (1996) 287–291.
[16] C. Zhang, M.A. Williams, S.E. Sanchez, I.B. King, S. Ware-Jauregui, G. Larrabure, V. Bazul, W.M. Leisenring, Plasma concentrations of carotenoids, retinol, and tocopherols in preeclamptic and normotensive pregnant women, Am. J. Epidemiol. 153 (6) (2001) 572–580.
[17] T.A. Moore, I.M. Ahmad, K.K. Schmid, A.M. Berger, R.J. Ruiz, R.H. Pickler, M.C. Zimmerman, Oxidative stress levels throughout pregnancy, at birth, and in the neonate, Biol. Res. Nurs. 21 (5) (2019) 485–494.
[18] I.M. Ahmad, J.B. Temme, M.Y. Abdalla, M.C. Zimmerman, Redox status in workers occupationally exposed to long-term low levels of ionizing radiation: a pilot study, Redox Rep. 21 (3) (2016) 139–145.
[19] K.D. Dangat, S.S. Mehendale, H.R. Yadav, A.S. Kilari, A.V. Kulkarni, V.S. Taralekar, S.R. Joshi, Long-chain polyunsaturated fatty acid composition of breast milk in pre-eclamptic mothers, Neonatology 97 (3) (2010) 190–194.
[20] A.V. Kulkarni, S.S. Mehendale, H.R. Yadav, A.S. Kilari, V.S. Taralekar, S.R. Joshi, Circulating angiogenic factors and their association with birth outcomes in pre-eclampsia, Hypertens. Res. 33 (6) (2010) 561–567.
[21] S. Mehendale, A. Kilari, K. Dangat, V. Taralekar, S. Mahadik, S. Joshi, Fatty acids, antioxidants, and oxidative stress in pre-eclampsia, Int. J. Gynaecol. Obstet. 100 (3) (2008) 234–238.
[22] G. Loverro, P. Greco, F. Capuano, D. Carone, G. Cormio, L. Selvaggi, Lipoperoxidation and antioxidant enzymes activity in pregnancy complicated with hypertension, Eur. J. Obstet. Gynecol. Reprod. Biol. 70 (2) (1996) 123–127.
[23] H. Sunitha, S.V. Kashinakunti, K. Gurupadappa, D.S. Shankarprasad, G. Suryaprakash, J.B. Ingin, Lipid peroxidation and antioxidant status in pre-eclampsia, Al Ameen J. Med. Sci. 3 (1) (2010).
[24] R. Madazli, A. Benian, S. Aydin, H. Uzun, N. Tolun, The plasma and placental levels of malondialdehyde, glutathione and superoxide dismutase in pre-eclampsia, J. Obstet. Gynaecol. 22 (5) (2002) 477–480.
[25] M. Harma, M. Harma, O. Erel, Measurement of the total antioxidant response in preeclampsia with a novel automated method, Eur. J. Obstet. Gynecol. Reprod. Biol. 118 (1) (2005) 47–51.
[26] D. Mannaerts, E. Faes, P. Cos, J.J. Briede, W. Gyselaers, J. Cornette, Y. Gorbanev, A. Bogaerts, M. Spaanderman, E. Van Craenenbroeck, Y. Jacquemyn, Oxidative stress in healthy pregnancy and preeclampsia is linked to chronic inflammation, iron status and vascular function, PLoS One 13 (9) (2018) e0202919.
[27] E. Llurba, E. Gratacos, P. Martin-Gallan, L. Cabero, C. Dominguez, A comprehensive study of oxidative stress and antioxidant status in preeclampsia and normal pregnancy, Free Radic. Biol. Med. 37 (4) (2004) 557–570.
[28] M. Kramer, J.M. Cohen, R.W. Platt, O. Basso, R.W. Evans, S.R. Kahn, The association between maternal antioxidant levels in midpregnancy and preeclampsia, Am. J. Obstet. Gynecol. 213 (5) (2015) 695.e1–695.e13.
[29] H. Genc, H. Uzun, A. Benian, G. Simsek, R. Gelisgen, R. Madazli, O. Guralp, Evaluation of oxidative stress markers in first trimester for assessment of pre-eclampsia risk, Arch. Gynecol. Obstet. 284 (6) (2011) 1367–1373.
[30] C.B. Rudra, C. Qiu, R.M. David, J.A. Bralley, S.W. Walsh, M.A. Williams, A prospective study of early-pregnancy plasma malondialdehyde concentration and risk of preeclampsia, Clin. Biochem. 39 (7) (2006) 722–726.
[31] V. D'Souza, A. Rani, V. Patil, H. Pisal, K. Randhir, S. Mehendale, G. Wagh, S. Gupte, S. Joshi, Increased oxidative stress from early pregnancy in women who develop preeclampsia, Clin. Exp. Hypertens. 38 (2) (2016) 225–232.
[32] Oxidative Stress, Inflammation, and Health, CRC Press, Boca Raton, 2005.
[33] G. Ray, S.A. Husain, Oxidants, antioxidants and carcinogenesis, Indian J. Exp. Biol. 40 (11) (2002) 1213–1232.
[34] G. Kaur, S. Mishra, A. Sehgal, R. Prasad, Alterations in lipid peroxidation and antioxidant status in pregnancy with preeclampsia, Mol. Cell. Biochem. 313 (1–2) (2008) 37–44.
[35] G. Bayhan, Y. Atamer, A. Atamer, B. Yokus, Y. Baylan, Significance of changes in lipid peroxides and antioxidant enzyme activities in pregnant women with pre-eclampsia and eclampsia, Clin. Exp. Obstet. Gynecol. 27 (2) (2000) 142–146.
[36] U. Das, A.C. Kumar, Lipid peroxides, anti-oxidants and nitric oxide in patients with pre-eclampsia and essential hypertension, Med. Sci. Monit. 6 (5) (2000) CR901-907.
[37] Y. Atamer, Y. Kocyigit, B. Yokus, A. Atamer, A.C. Erden, Lipid peroxidation, antioxidant defense, status of trace metals and leptin levels in preeclampsia, Eur. J. Obstet. Gynecol. Reprod. Biol. 119 (1) (2005) 60–66.
[38] S.B. Patil, M.V. Kodliwadmath, M. Kodliwadmath, Lipid peroxidation and antioxidant activity in complicated pregnancies, Clin. Exp. Obstet. Gynecol. 36 (2) (2009) 110–112.
[39] M.T. Raijmakers, P.L. Zusterzeel, E.M. Roes, E.A. Steegers, T.P. Mulder, W.H. Peters, Oxidized and free whole blood thiols in preeclampsia, Obstet. Gynecol. 97 (2) (2001) 272–276.
[40] N.D. Vaziri, X.Q. Wang, F. Oveisi, B. Rad, Induction of oxidative stress by glutathione depletion causes severe hypertension in normal rats, Hypertension 36 (1) (2000) 142–146.