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Review Article

Comprehensive analysis of oxidative stress markers and antioxidants status in preeclampsia

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ABSTRACT

Preeclampsia is a hypertensive disorder in pregnant women, which can be the leading cause of maternal and neonatal death or premature birth. Although the cause of preeclampsia is still not clear, local or systemic oxidative stress may explain the pathological features associated with this complication. However, it is not clear whether oxidative stress is the cause or the result of preeclampsia. For this purpose, the present meta-analysis was intended to evaluate the oxidant and antioxidant status in women with preeclampsia.

Relevant studies were identified after a preliminary investigation of research articles published up to September 2017.

In the overall analysis, including 2953 cases and 3621 controls, a statistically significant reduction in total antioxidant capacity, nitric oxide, superoxide dismutase, glutathione, vitamin E and C was observed in preeclampsia women. On the other hand, a statistically significant increase in malondialdehyde, protein carbonyl, total peroxide, glutathione peroxidase, catalase and uric acid were observed in preeclampsia women. The increased products of oxidative stress, which were found in the present meta-analysis might be an underlying mechanism for endothelial dysfunction in preeclampsia.

This meta-analysis provides a scientific support that primary reduction of antioxidant capacity and increased levels of oxidative stress products may induce a condition in which the pathways responsible for blood pressure homeostasis are disrupted. In conclusion, it is hypothesized when oxidative stress is established, a protective response is induced by increasing some antioxidants. Further studies are warranted to investigate the role of dietary supplementation and genetic variation in women with different ethnicity.

Introduction

Preeclampsia is the most serious and life-threatening pregnancy complication for both mother and embryos. Various factors have been proposed as risk factors associated with preeclampsia including age, obesity, chronic hypertension, renal disease and diabetes mellitus [1]. Despite the involvement of multiple risk factors in preeclampsia, its specific etiology is still unknown. Some evidence suggests that placental and systemic oxidative stress play a crucial role in the development of preeclampsia [2,3]. The potential causes of oxidative stress may be ascribed to a series of physiological changes, mineral deficiencies and increased oxygen consumption during pregnancy. Reduced perfusion and ischemic reperfusion in placenta result in placental hypoxia and, as a consequence, leading to raised synthesis of the free radical including superoxide anion in placenta [4]. In normal conditions, production of free radicals in endothelial cells is relatively low. They are neutralized by active defense systems, including chemical scavengers or antioxidant molecules such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Some changes in the levels of various enzymatic and non-enzymatic antioxidants during pregnancy could affect pregnancy outcome through alterations in maternal and fetal metabolism. Free radicals produced in preeclampsia are suspected of increasing the utilization of antioxidants. It is unclear whether endothelial dysfunction due to excess oxidative stress and antioxidant insufficiency are implicated in development of preeclampsia or improper function as caused by established preeclampsia may lead

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to oxidative stress. There is evidence that oxidative stress occurs prior to the onset of preeclampsia and the placenta is referred as central organ responsible for free radical generation in women with preeclampsia [5].

An excessive increase in biomarkers of oxidative stress and lipid peroxidation has been reported in women with preeclampsia [6]. Increased lipid peroxidation is considered to be a causative pathogenesis factor for preeclampsia [7]. To support this concept, increased plasma lipid peroxidation products known as malondialdehyde (MDA) have been reported in preeclamptic women compared with healthy pregnant women [8]. In fact the increased production of lipid peroxides in preeclamptic women may cause vascular endothelial cell dysfunction. However, despite these reports, a few studies failed to approve the association between lipid peroxidation level and endothelial dysfunction in early or late preeclampsia [9].

The association of maternal oxidative stress with subsequent development of pregnancy complications has been investigated in some studies. Although scientific evidence indicated that free radicals and oxidative stress might play a significant role in preeclampsia, not all studies have produced consistent results about antioxidant balance in preeclampsia. While some studies reported a decreased level of enzymatic and non-enzymatic antioxidant in placenta, erythrocytes or plasma [8], other studies reported an increased level or even no difference in values of antioxidants in preeclamptic women [10,11]. Mikhail and Jendryczko reported reduced levels of vitamin C and vitamin E in preeclampsia [12,13]. However, most of the studies reported that vitamin C and vitamin E supplementation did not only associated with reduced risk for preeclampsia but also is associated with increased rate of low weight birth nascent [14]. A more recent study, Williamson et al. proposed the inefficiency of antioxidant therapy in the treatment of preeclampsia [15].

Nevertheless, these studies were not comprehensive because of small sample size or few markers of oxidative stress. Some authors suggest that antioxidant supplementation reduces the risk of preeclampsia, but others did not find such effect. This meta-analysis performed to characterize the oxidative status and profiles of antioxidant response in preeclamptic women by exploring of oxidative stress markers including MDA, protein carbonyl, total peroxide and also enzymatic and non-enzymatic antioxidants including SOD, GPx, CAT, glutathione (GSH), vitamin E and C.

Materials

Search procedures

Systematic literature search from PubMed, ScienceDirect, Springer and Google scholar Databases was performed to identify all the relevant English-language articles during the 27-years period from 1990 through September 25, 2017. The following keywords were used: (preeclampsia OR pregnancy hypertension) AND (antioxidant OR oxidation OR oxidative stress OR antioxidant enzyme OR total antioxidant capacity OR superoxide dismutase OR glutathione peroxidase OR catalase OR glutathione reductase OR vitamin C OR vitamin E OR uric acid OR nitric oxide OR peroxide OR malondialdehyde OR protein carbonyl).

Data extraction and quality assessment

All data from eligible studies have been extracted independently by two authors in accordance with inclusion criteria. Any discrepancies were resolved by discussion between the two authors. All full text articles without overlap with other studies were carefully selected for meta-analysis. Furthermore, additional relevant studies were identified by searching the references cited in the original studies or review papers on this topic. The data extraction for meta-analysis was limited to English-language research articles. 176 articles were initially identified using our search terms that have been revised in order to decide if they fulfilled the purpose of the study. After initial reviewing of the titles and abstracts, only 87 articles represented the activities or levels of different antioxidants and oxidative stress biomarkers in women with preeclampsia, which full text was further evaluated to find if they fulfilled the inclusion criteria. The levels of antioxidants and oxidative stress biomarkers in peripheral blood of preeclampsia women and healthy, normal pregnancy was extracted as Mean ± SD. Data of only two groups of preeclampsia women and healthy, normal pregnancy was used if there were more than two groups in one study. However, we did not perform any population-based studies and subgroup analysis.

The following information was extracted from each study: the name of first author, year of publication, type of study, the number of cases and controls, data for mean serum or plasma level of various antioxidants, oxidative stress biomarkers and standard deviation (SD) in preeclamptic women and healthy normal pregnants.

Inclusion criteria

Studies with following criteria were included in our analysis: 1) original case–control studies; 2) studies on human pregnant with the gestational age of 28–40 weeks; 3) studies measuring at least one biomarkers of oxidative stress and antioxidants in the serum or plasma of preeclamptic and healthy pregnant women; 4) studies provided subject numbers, means and standard deviations for calculation of effect size; 5) inclusion of a preeclampsia women as diagnosed by systolic and diastolic blood pressure or screened with urine analysis; or 6) studies in English language.

Exclusion criteria

Studies with following criteria were excluded from our analysis: 1) studies published as reviews, conference abstracts, case reports and editorial letters; 2) animal studies; 3) studies that compare the biomarkers of oxidative stress with antioxidants among preeclamptic women and non-pregnant control; or 4) studies were only shown the levels of biomarkers by figures without detailed data.

Statistical analysis

Meta-analysis were conducted to summarize the differences levels of various antioxidants and oxidative stress biomarkers between 2953 preeclamptic women and 3621 healthy normal pregnant women.

Hedge's g and 95% confidence interval (CI) were calculated as a summary statistic in meta-analysis for the difference in the levels of each parameter between preeclamptic women and healthy normal pregnant women. Comprehensive Meta-Analysis package, version 2 was used for all analyses.

Results

Out of a total of 176 documents identified in the primary screening, 111 eligible studies remained to be included in the meta-analysis, whereas 65 irrelevant articles for the objective of this meta-analysis were excluded after screening titles and abstracts. Full-text evaluation was conducted for these remaining articles, and 24 articles were excluded because they didn't fulfill the inclusion criteria or represented the data as figures. Finally 87 articles were selected to construct a database for the analysis.

The main statistical measure we chose to describe the effect of oxidative stress in preeclampsia was Hedge's g, hereafter called simply "effect size". Hedge's g describes the difference between normal pregnant women and preeclamptic women in terms of the concentration of oxidant or antioxidant as a proportion of the pooled standard deviation of the two groups.

Thirteen studies including 425 preeclampsia women and 511 normal pregnant women have been conducted describing total antioxidant capacity (TAC) of serum in both groups. Overall, significant decrease in TAC level was found in preeclampsia women compared to normal pregnant women, effect size −0.493 (95% CI −0.876 to −0.110, p = 0.012, Fig. 1); although there was significant heterogeneity through the dataset (I-squared = 86.866%, p < 0.001).

Forty-five studies reporting MDA levels were included in this meta-analysis including 1433 women with preeclampsia and 1578 normal pregnant; MDA levels were significantly elevated in preeclampsia compared to normal pregnancy, effect size 2.006 (95% CI: 1.624 to 2.378, p < 0.001). Substantial inter-study heterogeneity was observed in this meta-analysis (I-squared = 94.717%, p < 0.001, Fig. 2).

For evidence of oxidative protein damage, protein carbonylation in plasma of preeclamptic women was investigated in seven studies including 229 preeclamptic women and 226 healthy pregnant women; there was a significant positive association of protein carbonyl with preeclampsia across six studies, effect size 1.225 (95% CI: 0.571 to 1.878, p < 0.0001, Fig. 3). Substantial inter-study heterogeneity was observed for oxidative protein damage in this meta-analysis (I-squared = 96.072%, p < 0.001).

Total peroxide was determined in 5 studies, including 399 preeclamptic women and 529 healthy pregnant women. Three studies showed significantly higher total peroxide levels in preeclamptic women compared with normal pregnant women, and the other two were showing an insignificant difference between two groups of normal pregnancy and preeclampsia. Overall, meta-analysis results show that preeclamptic women had higher total peroxide levels than normal pregnant women (effect size 0.700; 95% CI: 0.055 to 1.345; p = 0.033, Fig. 4).

Serum NO levels have been described in seventeen studies, including 557 preeclamptic women and 606 normal pregnant women, collectively finding a significant reduction in preeclamptic women (effect size −1.316; 95% CI: −2.425 to −0.208, p = 0.020, Fig. 5); although there was significant heterogeneity through the dataset (I-squared = 98.022%, p < 0.001).

SOD in serum/plasma from 739 preeclamptic women and 906 normal pregnant women has been described by twenty six studies, and cumulatively there was a significant association between SOD and preeclampsia, effect size −1.271 (95% CI: −1.774 to −0.768, p < 0.001, Fig. 6). Substantial inter-study heterogeneity was observed in this meta-analysis (I-squared = 95.014%, p < 0.001).

Thirteen studies described glutathione peroxidase activity from 127 preeclamptic women and 121 normal pregnant women, and the data in aggregate suggested increased glutathione peroxidase activity in serum of preeclamptic women (effect size 0.782, 95% CI: 0.021 to 1.354, p = 0.007, Fig. 7); although there was significant heterogeneity through the dataset (I-squared = 93.069%, p < 0.001).

Glutathione reductase from 102 preeclamptic women and 89 normal pregnant women has been described by four studies, and cumulatively there was no significant association with preeclampsia (effect size −0.566, 95% CI: −1.369 to −0.236, p = 0.167, Fig. 8); although there was significant heterogeneity through the dataset (I-squared = 85.474%, p < 0.001).

Eleven studies including 296 preeclampsia women and 323 normal pregnant women have been conducted describing catalase activity. There was a significant negative association of catalase activity with preeclampsia across three studies but positive association with remaining eight studies. The date in aggregate showed decreased catalase activity in preeclamptic women (effect size −0.975, 95% CI: −0.030 to −1.920, p = 0.043, Fig. 9); however, there was significant heterogeneity through the dataset (I^2 = 96.030%, P < 0.001).

Eleven studies including 532 preeclamptic women and 581 normal pregnant women have been conducted describing the GSH level. The present meta-analysis was indicative of significant depletion of GSH levels in the preeclamptic women across nine studies; however, increased levels of GSH was found only in one study; cumulatively GSH level was significantly reduced in preeclamptic women (effect size −1.332, 95%CI: −2.011 to −0.654, P < 0.001, Fig. 10). Substantial inter-study heterogeneity was observed in this meta-analysis (I-squared = 96.065%, p < 0.001).

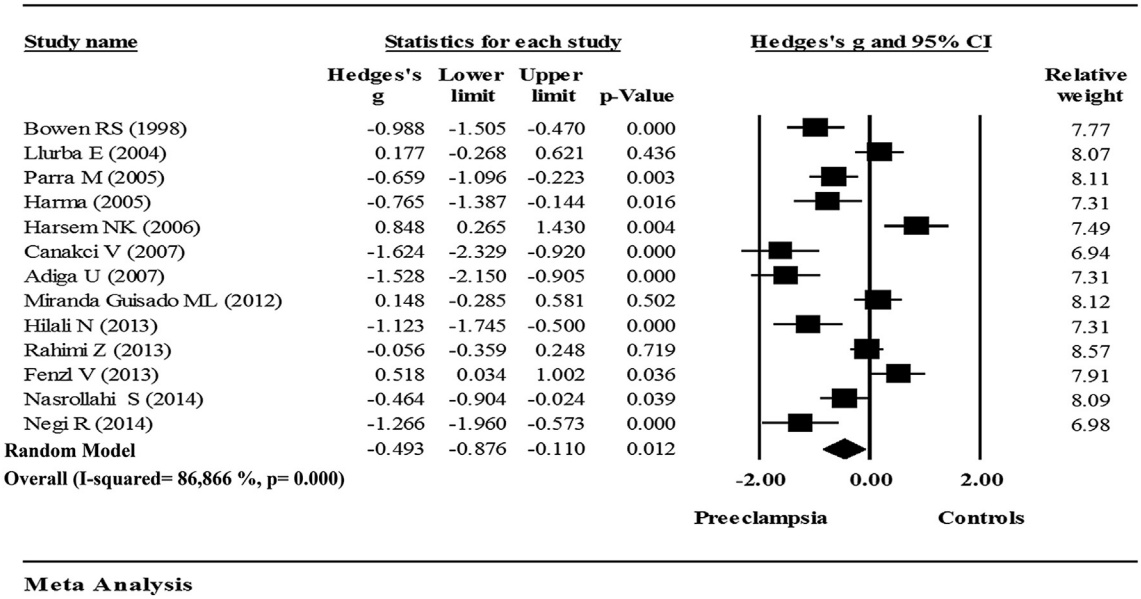

Fig. 1. Forest plots showing total antioxidant level (in plasma/serum) from women with preeclampsia compared to normal pregnant. Total antioxidant level are significantly decreased in preeclampsia women, effect size −0.493 (95% CI −0.876 to −0.110, p = 0.012; random effects model, p = 0.012).

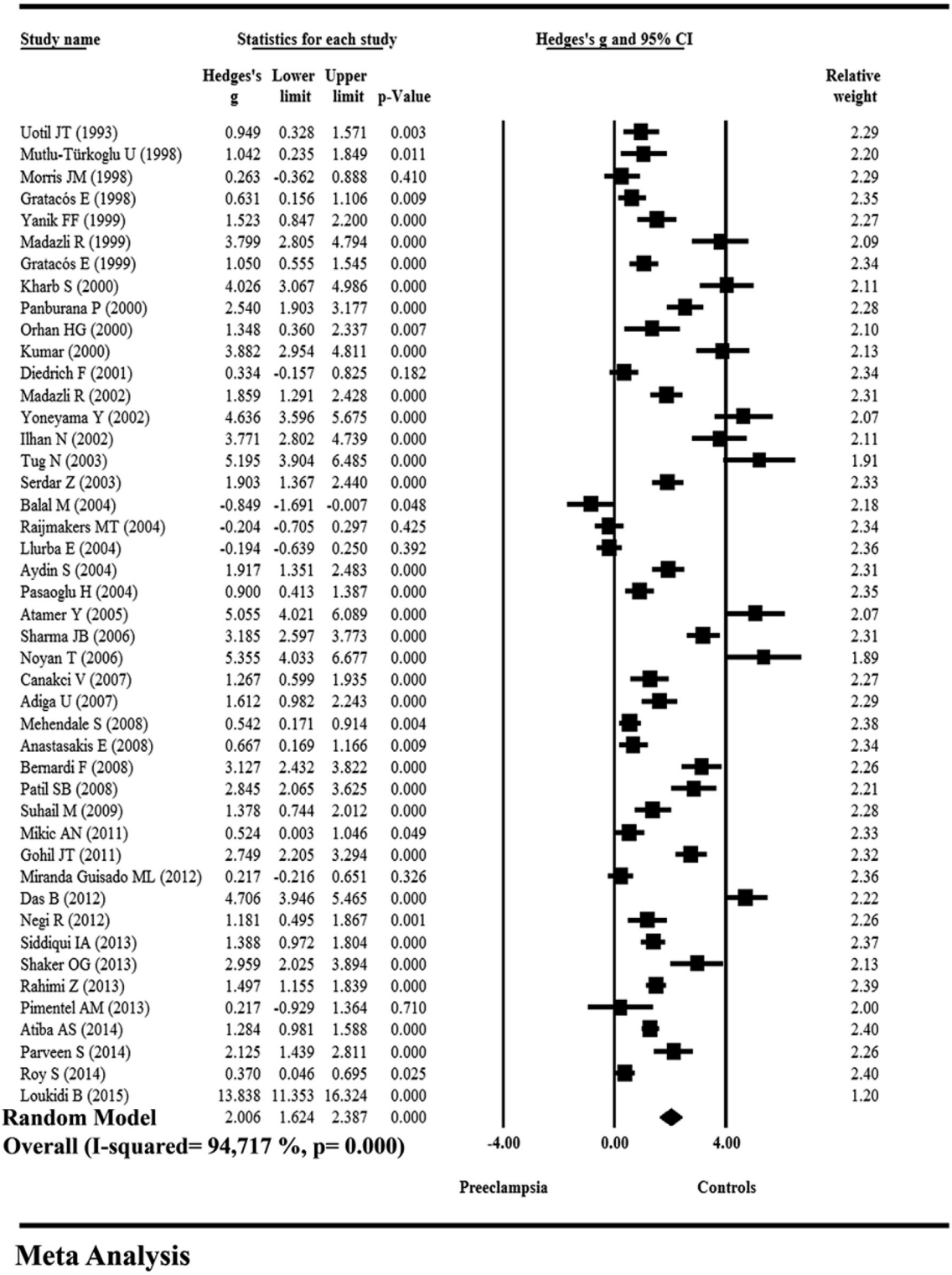

Fig. 2. Forest plots showing MDA level (in plasma/serum) from women with preeclampsia compared to normal pregnant. MDA level are significantly increased in preeclampsia women, effect size 2.006 (95% CI: 1.624 to 2.378, $p < 0.001$; random effects model, $p < 0.001$).

Uric acid concentration has been described in eighteen studies, including 508 preeclamptic women and 602 normal pregnant women, collectively uric acid level was significantly elevated in preeclamptic women compared to normal pregnant women (effect size 2.309, 95% CI: 1.457 to 2.620, $p < 0.0001$, Fig. 11). Substantial inter-study heterogeneity was observed in this meta-analysis (I-squared = 93.112%, $p < 0.001$).

Vitamin E and vitamin C concentrations were investigated in several studies. Although, there have been conflicting reports in vitamin E and vitamin C concentrations in preeclampsia, several

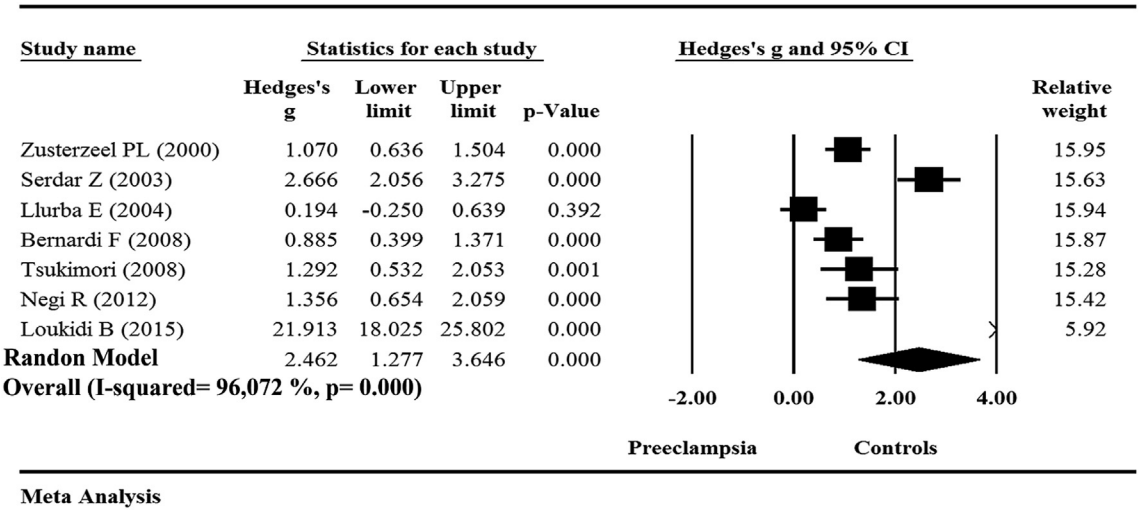

Fig. 3. Forest plots showing carbonyl level (in plasma/serum) from women with preeclampsia compared to normal pregnant. Carbonyl level are significantly increased in preeclampsia women, effect size 1.225 (95% CI: 0.571 to 1.878, p < 0.0001; random effects model, p < 0.001).

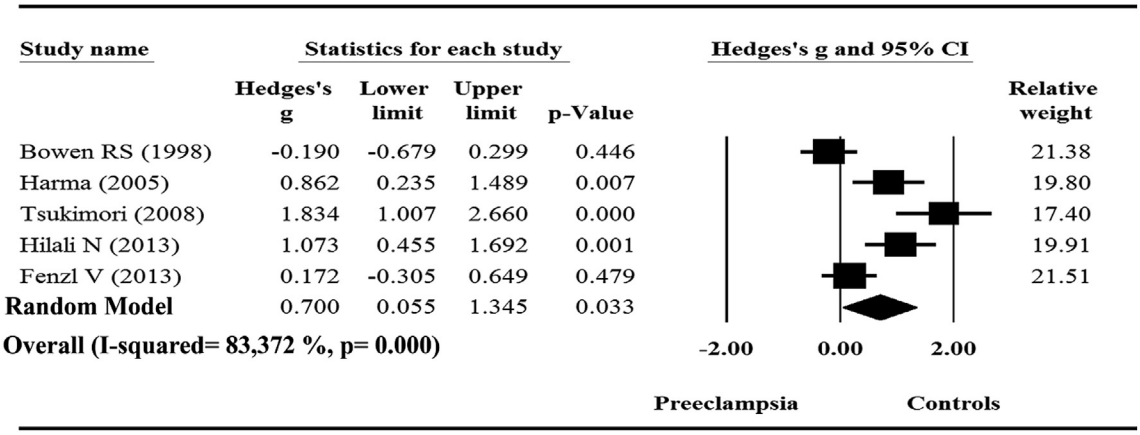

Fig. 4. Forest plots showing total peroxide level (in plasma/serum) from women with preeclampsia compared to normal pregnant. Total peroxide level are significantly increased in preeclampsia women, effect size 0.700; 95% CI: 0.055 to 1.345; p = 0.033; random effects model, p = 0.033).

studies reported reduced vitamin E and vitamin C concentrations in preeclamptic women [16–18]. Overall, the present meta-analysis showed a significant decrease in vitamin E level in 612 preeclampsia women compared to 721 normal pregnancies, effect size −0.939 (95% CI: −1.454 to −0.425, p < 0.0001, Fig. 12); however, there was significant heterogeneity through the dataset (I^2 = 92.995%, P < 0.001).

Also, the present meta-analysis showed a significant decrease in vitamin C level in 803 preeclamptic women compared to 972 normal pregnant women, effect size −0.889 (95% CI: −1.348 to −0.431, p < 0.0001, Fig. 13); however, there was significant heterogeneity through the dataset (I^2 = 95.461%, P < 0.001).

In order to assess publication bias, funnel plots were constructed. Symmetric funnel plots were observed for all parameters and, no significant publication bias was found in the current meta-analysis using a Egger's test.

Discussion

It is proposed that oxidative stress, defined as oxidant-antioxidant imbalance, is implicated in the pathophysiology of preeclampsia. Various studies have focused on the role of oxidative stress in preeclamptic women, in whom placental tissue demonstrated to produce high levels of superoxide as compared to normal pregnant women [19,20]. Normally, oxidative stress occurs in normal healthy pregnant women compared with non-pregnant women, but reactive free radicals is further raised in preeclampsia. Reactive oxygen species, including superoxide anion and hydrogen peroxide have shown to cause smooth muscles contraction directly. These reactive species can also inactivate nitric oxide, an endothelium derived relaxing factor, thereby affecting vascular tone. It is not well clear whether oxidative stress and antioxidant insufficiency are the direct cause of preeclampsia or secondary consequence of preeclampsia. Determination of the level of various antioxidants or the oxidative stress end products offers guidelines for the diagnosis and management of preeclampsia. Regardless of the reason, existence of oxidative stress and insufficiency in antioxidant defense systems might be a factor leading to an increased lipid peroxidation in preeclampsia. Lipid peroxidation which might indirectly provide information about cellular damage suggested to be an important factor in the pathogenesis of preeclampsia, as an increased level of MDA was observed in our meta-analysis.

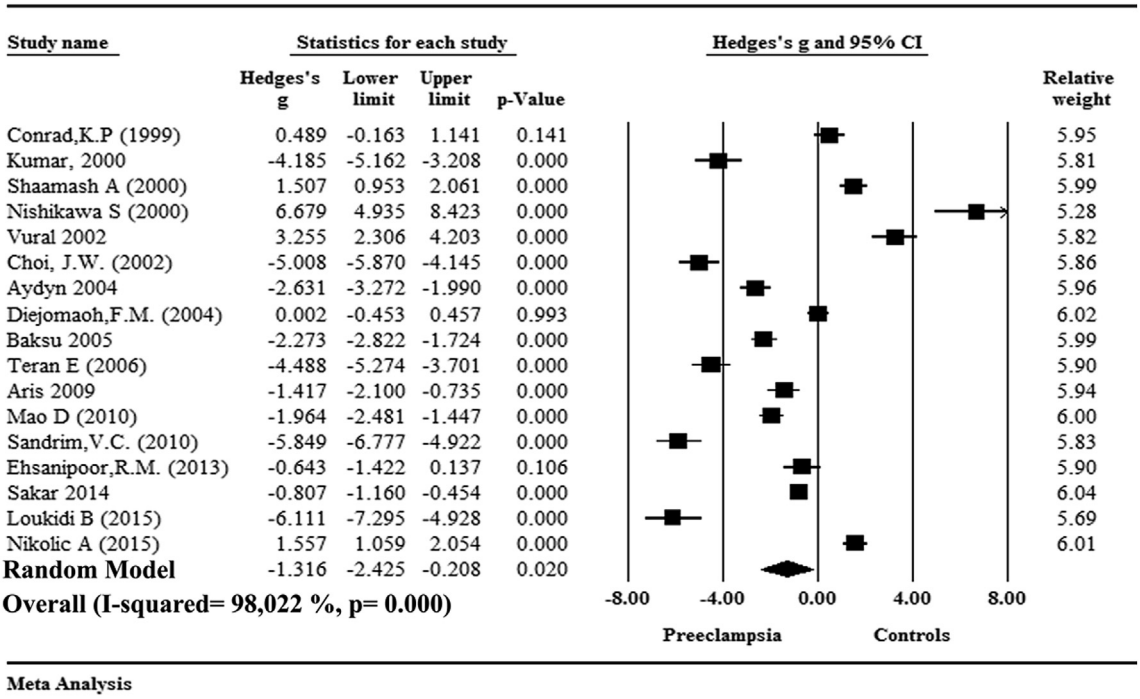

Fig. 5. Forest plots showing nitric oxide level (in plasma/serum) from women with preeclampsia compared to normal pregnant. Nitric oxide level are significantly decreased in preeclampsia women, effect size −1.316; 95% CI: −2.425 to −0.208, p = 0.020; random effects model, p = 0.020).

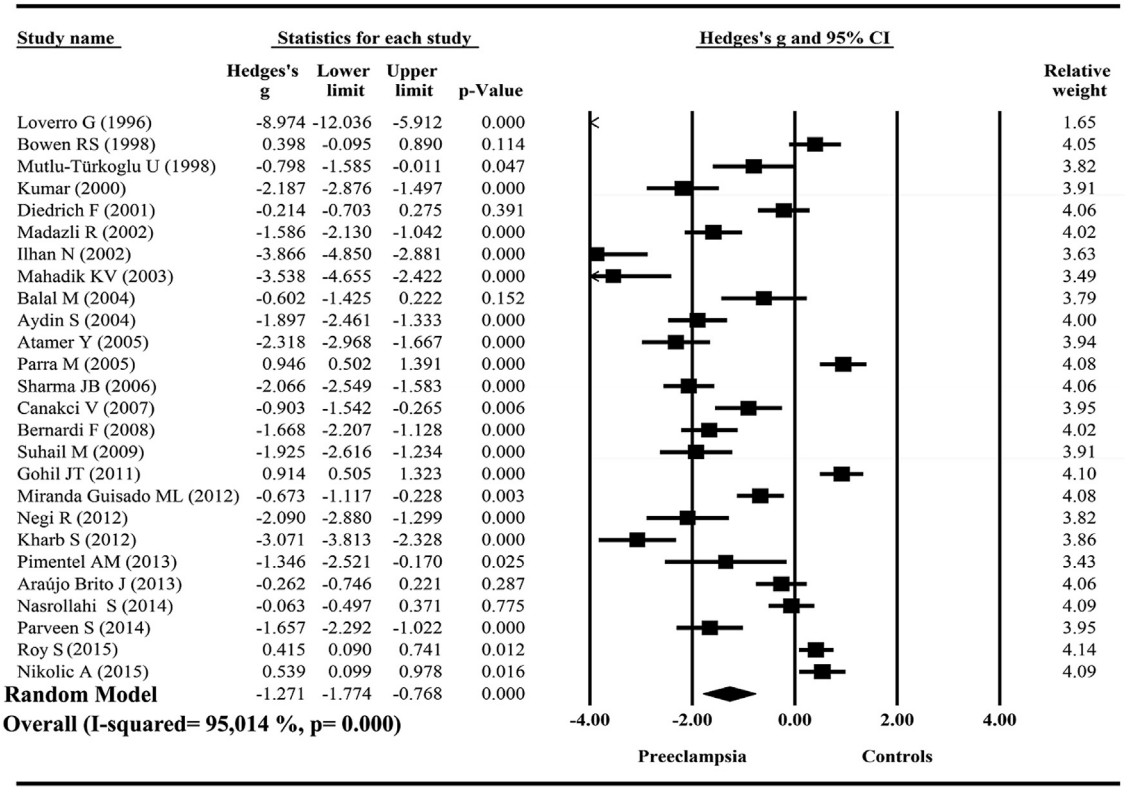

Fig. 6. Forest plots showing superoxide dismutase activity (in plasma/serum) from women with preeclampsia compared to normal pregnant. Superoxide dismutase activity are significantly decreased in preeclampsia women, effect size −1.271 (95% CI: −1.774 to −0.768, p < 0.001; random effects model, p < 0.001).

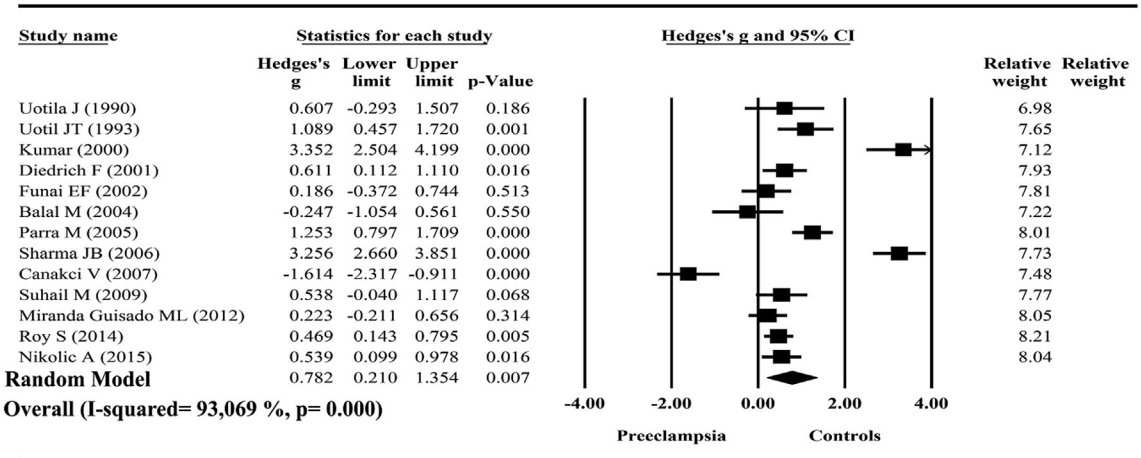

Fig. 7. Forest plots showing glutathione peroxidase activity (in plasma/serum) from women with preeclampsia compared to normal pregnant. Glutathione peroxidase activity are significantly increased in preeclampsia women, effect size 0.782, 95% CI: 0.021 to 1.354, p = 0.007; random effects model, p = 0.007).

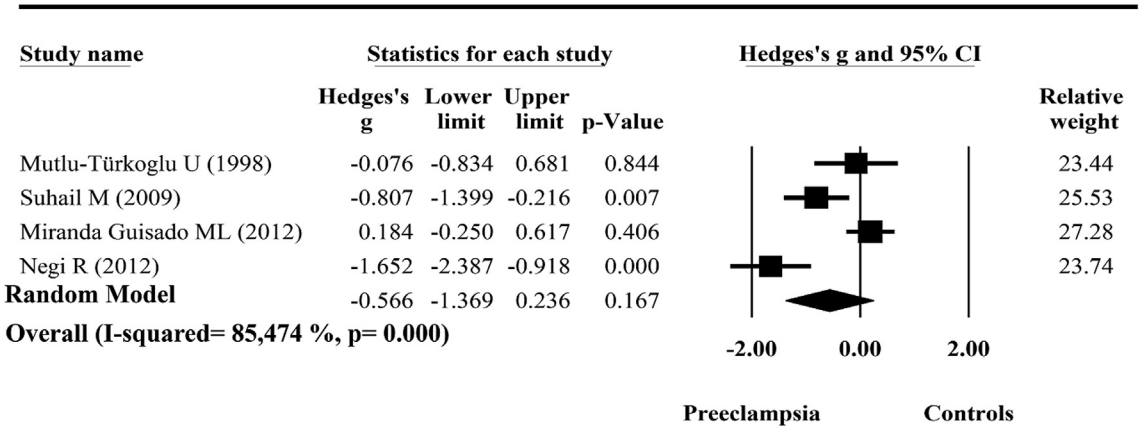

Fig. 8. Forest plots showing glutathione reductase activity (in plasma/serum) from women with preeclampsia compared to normal pregnant. Glutathione reductase activity are not significantly changed in preeclampsia women, effect size −0.566, 95% CI: −1.369 to −0.236, p = 0.167; random effects model, p = 0.167).

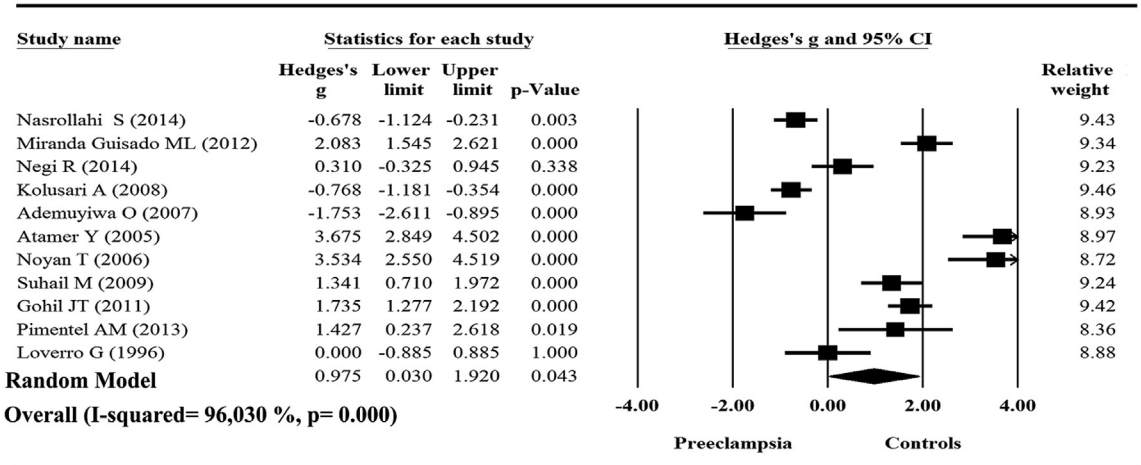

Fig. 9. Forest plots showing catalase activity (in plasma/serum) from women with preeclampsia compared to normal pregnant. Catalase activity are significantly increased in preeclampsia women, effect size −0.975, 95% CI: −0.030 to −1.920, p = 0.043; random effects model, p = 0.043).

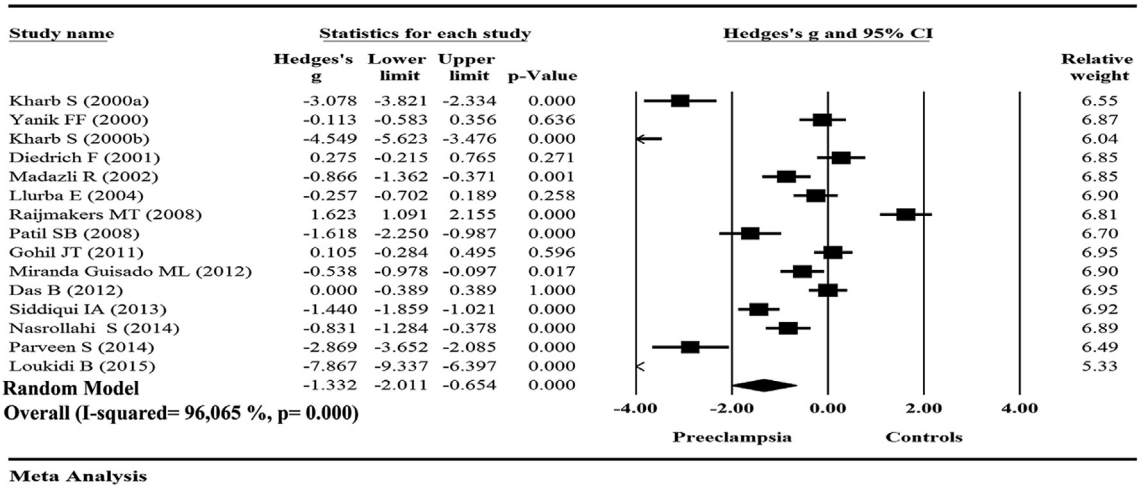

Fig. 10. Forest plots showing GSH level (in plasma/serum) from women with preeclampsia compared to normal pregnant. GSH level are significantly decreased in preeclampsia women, effect size −1.332, 95%CI: −2.011 to −0.654, P < 0.001; random effects model, p < 0.001).

However, increased lipid peroxidation products were reported in both normal pregnancy and preeclampsia as compared with non-pregnant women [21,22]. The association between MDA level and blood pressure was analyzed in pregnant women. Positive correlation was reported between MDA level and blood pressure [23], so MDA level might be a causative factor for pathogenesis of pre-eclampsia. Based on previous reports, MDA is always more elevated in the blood of pregnant women who suffer from preeclampsia. Furthermore, high statistic difference in MDA level was reported in pregnant women with sever and mild pregnancy-induced hypertension [24]. Thus along with other factors, it is a good biomarker for investigating the status of oxidative stress. Recently, the correlation of TBARS, as a lipid peroxidation marker, with ultrasound and cardiotocography parameters were analyzed in pregnancy induced

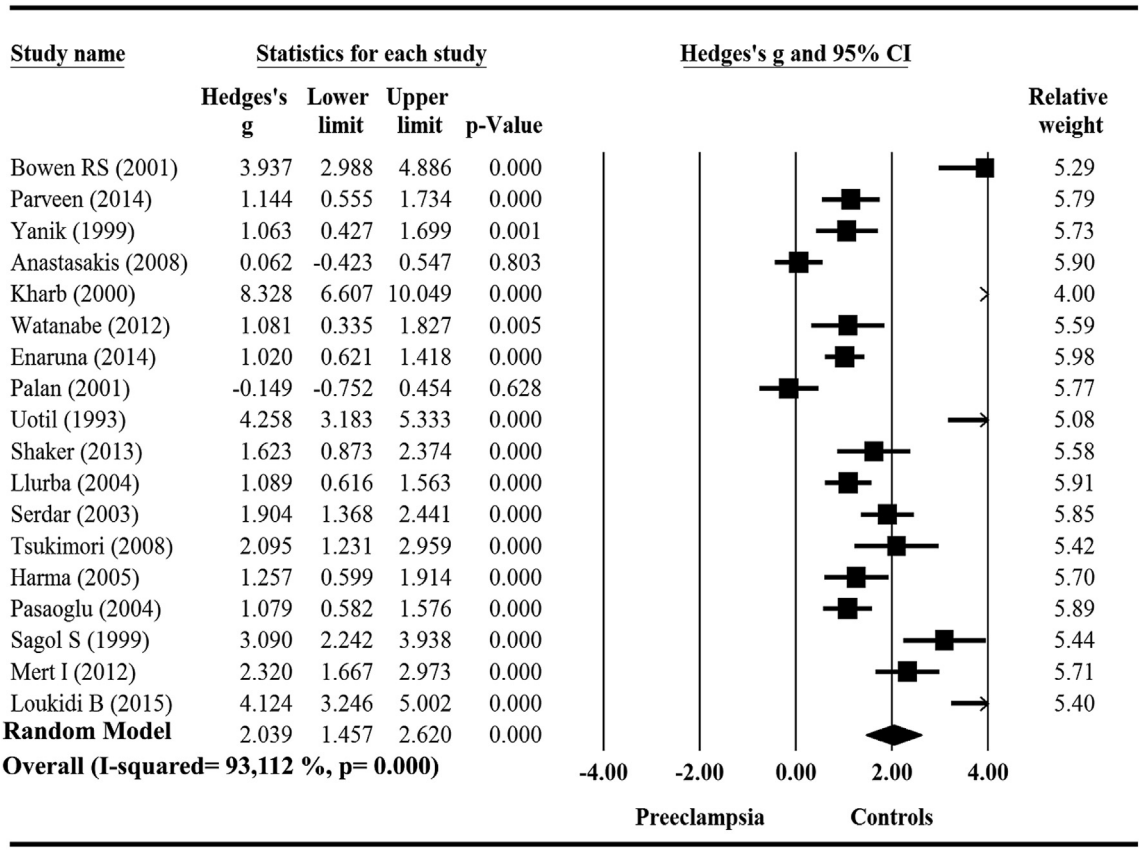

Fig. 11. Forest plots showing uric acid level (in plasma/serum) from women with preeclampsia compared to normal pregnant. Uric acid level are significantly increased in preeclampsia women, effect size 2.309, 95% CI: 1.457 to 2.620, p < 0.0001; random effects model, p = 0.043).

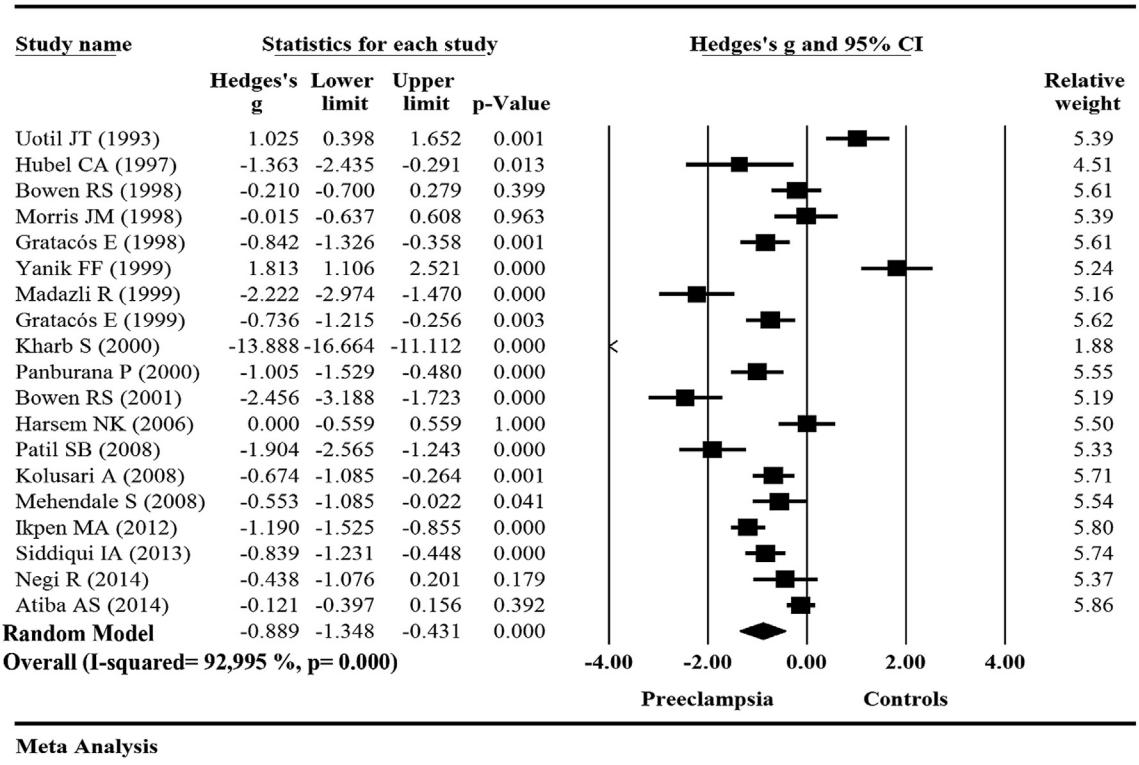

Fig. 12. Forest plots showing vitamin E level (in plasma/serum) from women with preeclampsia compared to normal pregnant. Vitamin E level are significantly decreased in preeclampsia women, effect size −0.939 (95% CI: −1.454 to −0.425, p < 0.0001; random effects model, p < 0.001).

hypertension. It is supposed that TBARS could be used for assessment of hypertensive pregnant women and decisions on pregnancy termination period [25].

It has been proposed that depletion of antioxidants upon free radical generation and elevation of circulating lipid peroxides may contribute to vascular endothelial cell damage, thereby compromising cellular functions in preeclampsia [26]. On the other hand, improvement of defense mechanisms against free radicals was also reported in progress of pregnancy [27]. As such, reinforcement of antioxidant capacity is the body attempt to overcome oxidative stress during pregnancy. In view of these facts, the present study was planned to investigate the level of various antioxidants in preeclamptic women by measuring the plasma antioxidants. Hence, the level of various antioxidants was investigated in this meta-analysis.

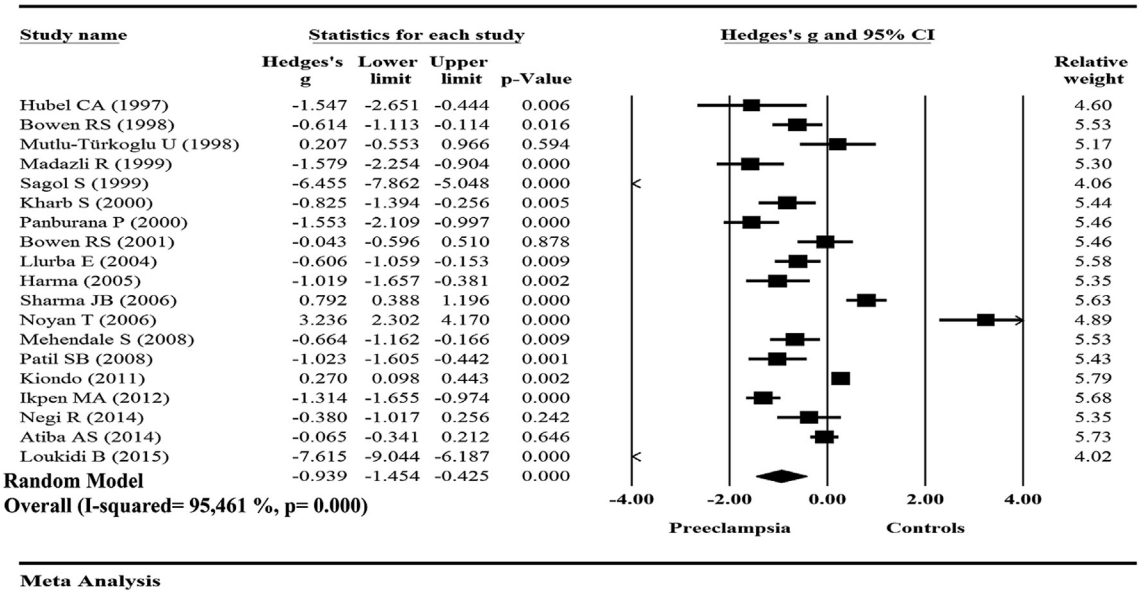

Fig. 13. Forest plots showing vitamin C level (in plasma/serum) from women with preeclampsia compared to normal pregnant. Vitamin C level are significantly decreased in preeclampsia women, effect size −0.889 (95% CI: −1.348 to −0.431, p < 0.0001; random effects model, p < 0.001).

Several studies have found significantly higher total antioxidant capacity in preeclamptic women, whereas other studies [28] have found significantly lower total antioxidant capacities. In present meta-analysis, significant reduction in total antioxidant capacities were found, despite significant elevation in total peroxide and oxidative stress end products. Plasma total antioxidant status proposed by Rice-Evan as an accurate index of oxidative stress and measure of the total plasma defense capacity against ROS [29]. Based on our meta-analysis, total defense capacity of plasma is not reinforced enough to combat oxidative stress in preeclampsia.

Various studies have suggested that oxidative stress is the reason of many vascular complications. Angiogenesis is mediated by proangiogenic factors including vascular endothelial growth factor (VEGF), placental growth factor (PlGF), transforming growth factor β, heme oxygenase-1 (HO-1), and angiopoietin-1 (ANG-1) [30]. Increased expression of these factors in the placental tissue was found in response to hypoxia and oxidative stress. Altered placental vascular development due to relative fetal hypoxia has shown to be associated with fetal growth restriction. Oxidative stress and increased placental angiogenesis are believed to be arised in pathological conditions like chorangiosis [31]. However, in normal pregnancy, increased production of ROS is balanced by the increase in synthesis of various antioxidants to protect placental tissues against toxic reactive products. There are several ways in which antioxidants could reduce the risk and severity of preeclampsia. Some antioxidants are able to protect maternal and fetal cells against oxidative damages directly by quenching or neutralizing free radicals. Superoxide anion and H_2O_2 are the most potent and versatile free radicals produced in various pathways. Superoxide dismutase counteracts free radical disturbances by dismutatation of O_2^- radicals, and thereby protect cell membranes against free radical mediated lipid peroxidation [32]. Several studies were found significantly higher SOD activity in preeclamptic women [33,34], whereas other studies were found significantly lower SOD activity [35–37]. Overall, meta-analysis of SOD activity was indicative of lower SOD activity in preeclamptic women. It was previously found that the increase in diastolic blood pressure of preeclamptic women is negatively correlated with the plasma and placental levels of SOD [38]. The increased concentrations of superoxide, due to superoxide dismutase deficiency, in presence of iron would result in lipid peroxidation [39]. The other deleterious aspect of superoxide anion accumulation is its interaction with nitric oxide, a potent vasodilator substance. When superoxide anion does not detoxified by SOD, it also react with NO to form peroxynitrite. Peroxynitrite is a powerful oxidizing agent capable of initiating lipid peroxidation [40]. This reasonable consequence observed in our meta-analysis; superoxide anion would not be inactivated effectively because of deficiency in SOD activity, which leads to a decrease in NO concentrations. There are conflicting results as to the role of NO in preeclampsia. Several studies were found significantly increased levels [34,41,42], decreased levels [43,44] or even no change at all [45,46]. Overall, meta-analysis result shows that preeclamptic women have lower level of NO than normal pregnant women. Decreased levels of NO lead to vasoconstriction and increased blood pressure in preeclamptic women. The lower concentration of this vasodilator substance along with other factors could be contributing to the higher pressure implicated in preeclampsia.

Our meta-analysis demonstrated a significant increase in GPx activity in preeclamptic women compared to normal pregnant women. However, a few studies were found significantly lower GPx activity in preeclamptic women. Chamy et al. measured GPx activity in blood samples and found that decreased GPx activity was associated with increased risk and severity of preeclampsia [47].

Moreover, GPx is also able to reduce free radical attack and damage to the endothelium through their ability to decompose hydrogen peroxide and organic hydroperoxides such as lipid and phospholipid hydroperoxides using GSH. H_2O_2 in its higher levels is also decomposed by catalase, so deleterious effects of reactive oxidants would be reduced by catalase. Both glutathione peroxidase and catalase are distributed in red blood cells and plasma. Higher significant activity of glutathione peroxidase and catalase reflect the persistence of oxidative stress. The observation of increased catalase and GPx activities in preeclamptic women, suggests that these enzymes are responsible for H_2O_2 decomposition proportional to H_2O_2 levels. On the other hand, catalase and GPx activity increased in preeclamptic women to combat oxidative stress. Increased glutathione peroxidase activity in preeclampsia may probably serve as a compensatory mechanism to prevent further damage by reactive radicals or other toxins. However, the significant effect size of 0.782 for GPx in the plasma preeclamptic women may reflect a possible protective response against increased oxidative stress. Furthermore, increase in glutathione peroxidase activity accompany with an increase in MDA level has interpreted by researchers as a compensatory mechanism of the enzyme to defend against the increased peroxide concentration [48]. Lipid peroxides are also produced in placenta but uncontrolled production of lipid peroxides can result in oxidative stress which finally leads to disruption of cell integrity. Our meta-analysis demonstrated a significant increase in serum MDA level in preeclamptic women compared to normal pregnant women.

Glutathione and glutathione-related enzymes, as one of the major defense systems and free-radical scavenger, may play an important role in controlling oxidative stress. SOD, GPx and catalase detoxifies free radicals whereas GSH is a general scavenger. In contrast to glutathione peroxidase, GSH in blood was significantly reduced among preeclamptic women compared with normal pregnant women. This finding is rational because increased activity of GPx results in consumption of GSH. This situation is suggestive of the fact that protection against reactive oxidants by GSH in preeclamptic women is hampered. GSH can also inhibit lipid peroxidation via membrane-bound GPx. Reduced level of GSH in preeclamptic women could be associated with increased local or systemic oxidative stress on this group. Together with the increase in the activity of GPx and catalase, decreased concentrations of GSH may indicative of much higher level of the circulating hydrogen peroxide in preeclampsia. It is proposed that increased resistance to peroxide occurs through upregulation of GPx and catalase [49]. Based on our meta-analysis, it is hypothesized that inhibition of SOD occurred by hydrogen peroxide. This condition results in accumulation of superoxide radical, which finally leads to the lipid peroxidation as evidenced by increased level of MDA. In other hand, activity of the hydrogen peroxide consuming enzyme including catalase and GPx increases in order to purge the H_2O_2 substrate. This situation could account for the results of this meta-analysis.

Protein carbonyl, other marker of oxidative stress, was showed significantly higher levels in preeclamptic women than in normal pregnancy. Protein carbonyl levels may serve as a useful and sensitive biomarker for oxidative stress-induced protein damage. Plasma protein carbonyl level is increased as a result of protein damage due to increased ROS production. Protein carbonyl may be generated by different ways such as oxidative cleavage of proteins, direct oxidation of amino acid residues or reaction with MDA. Significant association of local oxidative stress with increased formation of protein carbonyls were reported by Zusterzeel et al. [50]. Based on pooled effect size, we found that the circulating markers of oxidative stress including total peroxide, MDA and protein carbonyl, are significantly increased in plasma of preeclamptic women.

A significant positive correlation between elevated levels of plasma hydrogen peroxide and protein carbonyl with serum uric acid levels were reported in preeclamptic women [51]. Increased

production of uric acid has been attributed to increased purine metabolism in ischemic tissue such as placenta. Therefore, serum uric acid may be used as another indicator of the oxidative stress in preeclampsia. This study also provided conclusive evidence of an involvement of uric acid in the maternal circulation of preeclamptic women.

Also antioxidant vitamins, especially vitamin E and C, plays an effective role in preventing free radical damage. Vitamin C has been proposed as a first-line defense in the aqueous phase protecting lipoproteins from peroxidation by a wide spectrum of free radicals. However, vitamin C in high amounts may serve as pro-oxidant and lipid peroxidation products may be increased in this situation. In the present meta-analysis vitamin E level, which is the most important chain breaking antioxidant, was significantly reduced in preeclamptic women as compared to normal pregnant women. Lower level of vitamin C was also found in preeclamptic women compared to normal pregnant women. In previous meta-analysis by Cohen JM et al. (2015), non-enzymatic antioxidants including vitamins A, C, and E were showed to have negative association with overall analysis between preeclamptic women and control group. Furthermore, significant heterogeneity was reported without any explanation through all meta-analysis [52]. This report is consistent with our meta-analysis performed on different antioxidants. We supposed, the genetic differences in studied populations, methodological difference, the quality of the studies, small sample size and different inclusion criteria may be the major source of heterogeneity.

Conclusion

Based on the level of oxidative end products and antioxidant levels it is hypothesized that oxidative stress might be a potential risk factor for initiation of preeclampsia because of primary inability of antioxidant capacity to neutralize free radicals and increased levels of oxidative stress products. However, when oxidative stress established, protective response is induced by increasing some antioxidants, as observed for catalase and glutathione peroxidase in the present meta-analysis. Increased products of oxidative stress were found in our study might be an underlying mechanism for endothelial dysfunction in preeclamptic women. The data available from this study, however, support the hypothesis that the concentrations of oxidants are raised in preeclampsia compared with that of a normal pregnancy. Further studies are warranted to investigate the role of dietary supplements in preventing preeclampsia and evaluation of genetic variation of antioxidant enzymes contributing to this morbid condition in women with different ethnics.

Conflict of interest

The author declares that they have no conflict of interest.

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