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# Lipid Peroxidation and Antioxidant Status in Preeclampsia

## A Systematic Review

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**Background:** Preeclampsia is characterized by increased lipid peroxidation and diminished antioxidant capacity; however, there is no consensus as to the extent of these conditions.

**Objective:** To assess the association of lipid peroxidation and antioxidant status with preeclampsia quantitatively using meta-analysis.

**Design:** Systematic review and meta-analysis.

**Search Strategy:** Studies were identified by performing an extensive search using BIOSIS (1986–2007), EMBASE (1986–2007), Medline (1986–2007), and the Cochrane database.

**Data Analysis:** Standardized mean differences (SMD) with 95% confidence intervals (CI) were used in the meta-analysis and sources of heterogeneity were examined.

**Main Results:** In the included studies, the overall SMD was a 1.21 nmol/mL increase in serum malondialdehyde in preeclampsia cases compared to controls (95% CI: 0.76, 1.66). Overall, total serum thiobarbituric acid-reactive substances SMD were 1.62 nmol/mL greater in cases than in controls (95% CI: 0.27, 2.96). The overall estimate SMD for serum vitamin E was 1.12 nmol/mL less in cases than controls (95% CI: –1.77, –0.48) and vitamin C SMD overall estimate was –0.53 (95% CI: –1.03, –0.02), significantly lower in cases compared with controls. The overall SMD for erythrocyte superoxide dismutase was –2.37 (95% CI: –4.76, 0.03), a marginally significant decrease in cases versus controls.

**Conclusions:** Established preeclampsia is associated with increased concentrations of oxidative stress markers including lipid peroxidation products, and a reduction in antioxidant concentrations.

**Target Audience:** Obstetricians & Gynecologists, Family Physicians

**Learning Objectives:** After completion of this educational activity, the participant should be better able to describe the pattern of oxidative stress markers associated with preeclampsia, and interpret the available literature as it relates to oxidative stress and preeclampsia.

There is a complex interaction between free radicals and antioxidants, which modulates the generation of oxidative stress. Oxidative stress occurs when generation of reactive oxygen species (ROS) increases and overwhelms the body's antioxidant defenses. Free radicals are molecules with one or more unpaired electrons in the outer orbit (1). These in-

clude hydroxyl radical, superoxide anion radical, and nitric oxide radical. On the other hand, ROS such as hydrogen peroxide and peroxynitrite do not have unpaired electrons.

Human cells have developed a wide range of antioxidant systems to limit production of ROS, inactivate them, and repair cell damage. ROS are a dual-edged

sword—they are key messengers in maintaining physiological functions in the female reproductive tract, however, excessive and unrelenting ROS generation causes various pathologies. Pregnancy is characterized by increased generation of ROS. The generation of ROS is enhanced by increased placental mitochondrial activity (2) and the greatly increased placental production of the radical superoxide (3,4). This increase in the generation of superoxide is also reported to be associated with decreased levels of superoxide dismutase (3), an antioxidant enzyme, in the placental trophoblast.

Preeclampsia is a complex multisystem disorder seen exclusively in the human species. Worldwide, it is a leading cause of maternal and fetal morbidity and mortality. Reduced perfusion as a result of abnormal placentation is thought to lead to ischemia reperfusion injury to the placenta. Placental oxidative stress, which results from the ischemia reperfusion injury, is increasingly reported to be involved in the etiopathogenesis of gestational hypertension/preeclampsia and associated with impaired glucose tolerance (5). Placental oxidative stress has been proposed as a promoter of lipid peroxidation, and endothelial cell dysfunction associated with preeclampsia (6–10). Lipid peroxidation has also been proposed to play an etiopathological role in various vascular complications of pregnancy, such as intrauterine growth restriction and gestational diabetes. However, this causal relationship between increased lipid peroxidation and preeclampsia is not universally supported. Some studies have reported that lipid peroxidation is not exacerbated in patients with preeclampsia (11–14).

Lipid peroxides are generated when free radicals interact with polyunsaturated fatty acids in the cell membrane and in plasma lipoproteins. This process can become self-perpetuating, leading to a cascade of lipid oxidation. The assessment of serum total thiobarbituric acid-reactive substances (TBARS) pro-

vides a measure of total serum lipid peroxidation, an indicator of whole-body free radical activity.

The increased lipid peroxidation leads to the consumption of antioxidants. This leads to reduction in levels of nonenzymatic antioxidants such as Vitamins A, C, and E, erythrocyte thiol, and glutathione as well as enzymatic antioxidants such as glutathione peroxidase and superoxide dismutase.

Research on oxidative stress in preeclampsia is mostly focused on studying the markers of oxidative stress locally in the placenta and systemically in the serum and plasma. A few studies have examined erythrocyte glutathione peroxidase levels. Most have been cross sectional or case-control studies comparing patients with preeclampsia to non-preeclamptic controls matched for age and gestational age.

There is a dearth of well-designed longitudinal studies investigating oxidative stress markers in preeclampsia. In this systematic review and meta-analysis, we aim to establish whether there is evidence to link lipid peroxidation and antioxidant status with preeclampsia.

## METHODS

### Identification of Studies

Studies were identified by performing an extensive search using BIOSIS, EMBASE, Medline, and the Cochrane database with the help of a professional librarian, as well as by hand-searching review articles and cross references (Fig. 1). The search stretched from

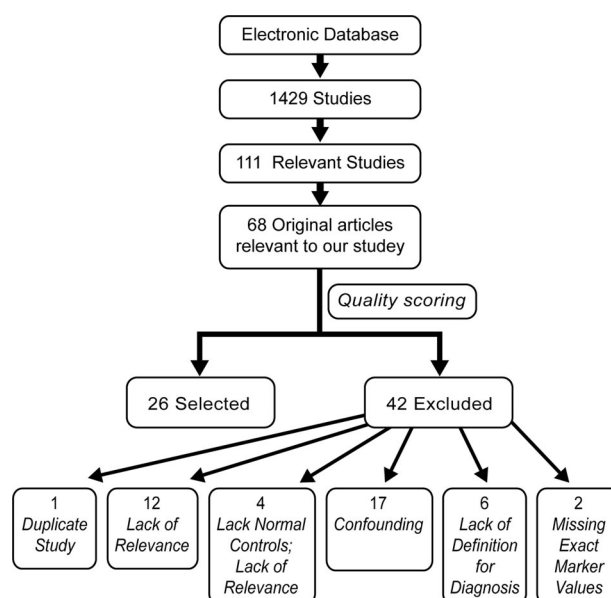


Fig. 1. Flow Diagram on selection of studies.

Unless otherwise noted below, each faculty's spouse/life partner (if any) has nothing to disclose.

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1986 to 2007. The key words used to search electronic databases included: "lipid peroxidation, ROS, preeclampsia, malondialdehyde (MDA), lipid peroxides, lipid hydroperoxides and antioxidants." No exclusions were made based on language. Articles were evaluated for relevance by examining titles and abstracts.

The diagnosis of preeclampsia was made by well-defined criteria, i.e., those of the World Health Organization (WHO) (15) or ACOG (16). These include a definition of preeclampsia as a blood pressure level of  $\geq 140/90$  mm Hg and, taken on 2 occasions 6 hours apart and 1+ proteinuria or greater.

### Criteria for Selecting the Studies

Studies that were found to examine relevant parameters in preeclampsia cases compared to controls were evaluated on quality based on a scoring system devised by the authors (available from the authors on request). The methods, results, tables, and figures for each study were extracted. Two reviewers, blinded to the concluding data, authors, journal, and publication date of the articles evaluated each study on its methodological merits. A score was assigned to each study based on 4 overarching categories of bias: selection or follow-up bias, confounding bias, information or detection bias, and other sources of bias such as misclassification (17). A higher score indicated less potential for bias. Studies that were deemed likely not to be biased despite deficiencies in reporting of methods, and those likely to be biased toward the null were included in the final meta-analysis (17).

### Data Extraction

The measures of interest for which data were extracted were all continuous and included MDA, lipid peroxides, lipid hydroperoxides, TBARS, isoprostanes, conjugated dienes, superoxide dismutase (SOD), catalase, glutathione transferase, glutathione peroxidase, and vitamins E and C in the appropriate fluids that included serum/plasma, erythrocytes, placenta, and urine. Population and study characteristics such as fasting or nonfasting samples (which may affect the MDA levels), selection of comparison group, and criteria for matching controls were extracted for potential further subgroup analyses.

### Data Analysis

The data were analyzed by meta-analysis based on standardized mean differences (SMD) between cases and controls. The SMD of individual studies was determined by the mean difference between cases and controls weighted by the sample sizes of the study. Overall SMD and its 95% confidence interval (95% CI) were estimated for a study. A random effects model was used as the studies were from different patient populations and we are interested in extrapolating conclusions to populations beyond those in the studies. To investigate potential sources of heterogeneity, the  $I^2$  statistic, which estimates the proportion of variability in the study due to heterogeneity rather than sampling error, was calculated. The  $I^2$  statistic was calculated in the same manner as in the RevMan User Guide (version 4.2) (available at: [www.cochrane.org](http://www.cochrane.org)). An  $I^2$  of  $<30\%$  indicates mild heterogeneity, whereas 30% to 50% and 50% to 100% reflect moderate heterogeneity and strong heterogeneity, respectively (18). For each of the meta-analyses, when heterogeneity was high, individual studies that made large contributions to the heterogeneity were identified, and subgroup analysis was performed after excluding the relevant studies or by controlling for certain confounders such as age and gestational age. A  $P < 0.05$  or SMD's within the 95% CI were considered significant in all statistical tests employed. The statistical software package R (available at: [www.R-project.org](http://www.R-project.org)) was used for all the analyses.

### RESULTS

A search of the electronic databases yielded 1429 studies (Fig. 1). Hand searches of the bibliography did not yield any additional articles. Of these 1429, a total of 111 relevant articles were identified by examining the abstracts and titles. About 68 original articles contained data relevant to the analysis. After quality scoring, 26 studies were selected (Table 1) and 42 were excluded. Data were extracted from the selected 26 studies and grouped according to the different sources (such as plasma, serum, placenta, or decidual tissue) from which measurements were taken (Table 2). Oxidative stress markers and antioxidants, which were examined in less than 3 studies, are not presented. Thus, the oxidative stress markers that were assessed in this meta-analysis included MDA, TBARS and the antioxidants SOD, and Vitamins E and C.

TABLE 1  
Included studies, outcomes measured, and study characteristics

| Study              | Study Characteristics  | Patient Characteristics  | Parameters Measured   | Conclusions   |
|--------------------|--|--|---|---|
| Aksoy et al 19     | Cross-sectional evaluation of cases and controls.  | Twenty-one patients with mild preeclampsia 19 normotensive pregnant women.   | AOP, MDA, Cp, Trf.  | Plasma AOP and MDA were significantly negatively correlated in all groups.  |
| Atamer et al 6     | Cross-sectional evaluation of preeclampsia cases and normotensive controls.                  | Thirty-two preeclamptic patients and 28 normotensive healthy pregnant women were compared.                                 | GSH, GSH-Px, SOD, MDA.  | Lipid peroxides were significantly increased in cases while antioxidants were significant decreased.  |
| Aydin et al 7      | Case-control study.  | 35 patients with preeclampsia and 34 healthy normotensive pregnant women.  | MDA, fibronectin, sE-selectin, NO, SOD and endothelin 1.                              | Increased plasma levels of MDA, fibronectin, sE selectin and endothelin 1. Decreased plasma levels of NO and SOD.   |
| Barden et al 20    | Cross-sectional evaluation of cases of preeclampsia and normotensive controls.               | A group of 20 preeclamptic cases in conjunction with 18 normotensive controls matched on maternal age and gestational age. | Plasma total and free 9-iso-prostane, urinary 8-iso-prostane.                         | A significantly greater amount of plasma free 8-iso-prostane was found in cases as compared to controls while plasma 8-isoprostane was not significantly different. Urinary 8-iso-prostane was significantly reduced in preeclamptic cases. |
| Barden et al 21    | Cross-sectional evaluation of cases of preeclampsia and normotensive controls.               | 21 preeclamptic cases were compared to 19 normotensive controls matched on maternal age and gestational age.               | F <sub>2</sub> -isoprostanes in urine, plasma, and plasma WBC incubates.              | F <sub>2</sub> -isoprostanes were significantly increased in preeclamptic women.  |
| Bayhan et al 22    | Prospective study.   | Study recruited 27 patients with preeclampsia, 18 with eclampsia, and 44 normotensive controls.                            | Serum lipid peroxides, erythrocyte GSH, erythrocyte SOD, erythrocyte catalase.        | Serum levels of lipid peroxides were significantly greater in cases than controls while antioxidant enzymes were significantly less.  |
| Bowen et al 12     | Cross-sectional evaluation of preeclampsia cases and normotensive controls.                  | Twenty-nine normotensive and 21 preeclamptic cases were examined.  | Plasma, cord and placental LPO, MDA, vitamin C, vitamin E.                            | Findings did not indicate a significant decrease in antioxidants or a significant increase in products of lipid peroxidation.   |
| Diedrich et al 13  | Cross-sectional evaluation of preeclampsia cases and normotensive pregnant controls.         | 36 women with uncomplicated pregnancies and 28 women with preeclampsia.  | Lipid hydroperoxides, TBARS, GSH-Px in plasma and erythrocytes, GSSG-R, GST, and SOD. | TBARS was not significantly increased in cases compared to control while GSH-Px activity was increased.   |
| El-Salahy et al 23 | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls.        | Twenty women with preeclampsia and 20 normotensive pregnancy controls were compared.                                       | VEGF, NO, MDA, vitamin E.   | MDA was significantly higher in cases while vitamin E was significantly decreased.  |
| Gratacós et al 10  | Nested cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls. | Thirty-four women with preeclampsia and 36 normotensive pregnancy controls were compared.                                  | Lipid peroxides in serum and placenta, TBARS, MDA, vitamin E in serum.                | The level of lipid peroxides was significantly higher in cases in comparison to controls. Along the same lines, vitamin E levels were significantly lower in cases compared to controls.  |

(continued)

TABLE 1  
Continued

| Study                   | Study Characteristics  | Patient Characteristics   | Parameters Measured   | Conclusions   |
|-------------------------|--|---|---|---|
| Gratacos et al 24       | Case-controlled study.   | 25 healthy pregnant women, 20 previously nonhypertensive women diagnosed with preeclampsia.   | Antibodies to oxidized LDL, malondialdehyde, vitamin E.   | Chronic hypertension is characterized by increased susceptibility to lipid peroxidation with a trend towards elevated levels of antibodies to oxidized LDL, malondialdehyde, vitamin E.                           |
| Kornacki et al 28       | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls.    | Thirty four patients with preeclampsia at third trimester of gestation and 21 women with uncomplicated pregnancy at third trimester of gestation.         | Serum concentration of lipid peroxides and malondialdehyde  | Lipid peroxide levels were significantly elevated in women with severe preeclampsia.  |
| Madazli et al 29        | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls.    | Twenty two preeclamptic patients were compared to 21 normotensive healthy pregnancy women.  | Vitamins E, and C, and MDA in plasma.   | MDA was significantly higher in the preeclamptic group while vitamins E and C were significantly higher in the control group.   |
| Morris et al 30         | Cross-sectional evaluation of preeclampsia cases and normotensive non-pregnant controls. | preeclampsia (n = 19), control pregnant women (n = 19) matched for gestation, age and parity and a group of non pregnant individuals of reproductive age. | 8 epi-prostaglandin F2alpha, lipid hydroperoxides, malondialdehyde and lipid soluble antioxidant vitamin E. | Circulating markers of oxidative stress are raised in normal pregnancy and pre-eclampsia.   |
| Mutlu-Türkoğlu et al 31 | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls.    | Seventeen subjects diagnosed with preeclampsia were compared to 10 normotensive pregnant women.   | TBARS, glutathione, GSH-Px, SOD, vitamin C.   | TBARS levels were found to be significantly higher in preeclamptic cases than controls while the level of antioxidant activities was significantly decreased.   |
| Panburana et al 32      | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls.    | The control group was composed of 60 normotensive singleton pregnancies. Thirty cases of mild preeclampsia were also recruited.                           | Vitamins A, C, E, MDA.  | Preeclamptic women were found to have significantly lower levels of vitamin C in comparison to controls. However, there was no significant difference in vitamins A and E levels after adjusting for cholesterol. |
| Paşaoğlu et al 33       | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls.    | Patients were excluded as controls if they have previous history of hypertension, renal disease, or other metabolic disease.                              | MDA in plasma and erythrocytes.   | Erythrocyte MDA was not significantly greater in cases than controls while plasma MDA was.  |
| Rajmaker et al 34       | Cross-sectional evaluation of pre-eclampsia cases and normotensive pregnancy controls.   | Forty women with preeclampsia were recruited for this study. Two groups of controls were recruited.   | TBARS.  | TBARS was not found to be significantly different between cases and controls matched on gestational age.  |

(continued)

TABLE 1  
Continued

| Study            | Study Characteristics   | Patient Characteristics  | Parameters Measured   | Conclusions  |
|------------------|---|--|---|--|
| Regan et al 11   | Prospective case-controlled study.  | Twenty-nine cases were analyzed with Twenty-nine controls who were matched to cases at the clinical center, and gestational age at urine collection. | 8,12 iso-iPF <sub>2</sub> -VI                                       | Urinary 8,12 iso-iPF <sub>2</sub> -VI did not vary significantly between cases and controls nor by gestational age.  |
| Serdar et al 35  | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls. | Thirty patients with mild preeclampsia were evaluated in comparison to 50 pregnancy normotensive controls.   | MDA in serum, placenta and decidua basalis, vitamin E and carotene. | Lipid peroxides in all tissues were found to be significantly higher in preeclampsia patients. Vitamin E and carotene levels were significantly lower in these patients as well. |
| Takacs et al 36  | Case-controlled study.  | Women with severe preeclampsia (preeclamptic plasma, N = 12) or plasma from normal pregnancies (normal plasma, N = 12).                              | Plasma MDA.   | Significantly elevated levels of lipid peroxides in women with preeclampsia.   |
| Uotila et al 37  | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls. | Twenty patients with mild preeclampsia were recruited to be evaluated in comparison to 20 healthy uncomplicated pregnancies.                         | Conjugated dienes, MDA, vitamin E, GSH-Px.                          | Conjugated dienes were found to be significantly higher in cases compared to controls.   |
| Var et al 38     | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls. | A total of 20 patients with preeclampsia were recruited in conjunction with 20 normotensive controls matched on gestational age.                     | MDA.  | MDA was significantly raised in preeclampsia patients in comparison to gestational age-matched controls.   |
| Wu et al 39      | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls. | Ten patients with preeclampsia were recruited for comparison with ten normotensive pregnant women.   | Serum MDA.  | Serum MDA was significantly higher in patients with preeclampsia in comparison to controls.  |
| Yanik et al 40   | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls. | Eighteen preeclamptic patients and 25 normotensive controls were recruited for this study.   | MDA, vitamin E.   | MDA was found to be significantly higher in cases while vitamin E was found to be significant lower.   |
| Yoneyama et al 8 | Cross-sectional evaluation of preeclampsia cases and normotensive pregnancy controls. | Twenty-six of preeclamptic women were recruited along with 26 normal controls.   | MDA and ADA.  | Levels of plasma MDA and ADA were both significantly raised in preeclampsia patients in comparison to controls.  |

MDA indicates malondialdehyde; LPO, lipid peroxides; TBARS, thiobarbituric acid reactive substances; Iso P, isoprostanes; SOD, superoxide dismutase; GSH-PX, glutathione peroxidase; GSSG, oxidized glutathione; GSSG-R, glutathione reductase; AOP, antioxidant potential; Cp, ceruloplasmin; NO, nitric oxide; GSSG-R, glutathione reductase; GST, glutathione S-transferase; VEGF, vascular endothelial growth factor; sE-selectin, Soluble-E-selectin.

TABLE 2  
Study characteristics: oxidative stress markers and their sources

| Study, Marker Source    | MDA |   | LP S | TBARS S | Iso-P U | SOD E | GSH-Px S | VE S | VC S | Fasting | Matched |    |
|-------------------------|-----|---|------|---------|---------|-------|----------|------|------|---------|---------|----|
|                         | S   | P |      |         |         |       |          |      |      |         | Age     | GA |
| Aksoy et al 19          | ✓   |   |      |         |         |       |          |      |      | X       |         | X  |
| Atamer et al 6          | ✓   | ✓ |      |         |         | ✓     |          |      |      | X       |         |    |
| Aydin et al 7           | ✓   |   |      |         |         |       |          |      |      | X       | X       | X  |
| Barden et al 20         |     |   |      |         | ✓       |       |          |      |      | X       | X       | X  |
| Barden et al 21         |     |   |      |         | ✓       |       |          |      |      |         | X       | X  |
| Bayhan et al 22         |     |   | ✓    |         |         | ✓     |          |      |      | X       |         |    |
| Bowen et al 12          | ✓   | ✓ | ✓    |         |         |       |          | ✓    | ✓    |         |         |    |
| Diedrich et al 13       |     |   |      | ✓       |         | ✓     | ✓        |      |      |         |         |    |
| El-Salahy et al 23      | ✓   |   |      |         |         |       |          | ✓    |      | X       | X       |    |
| Gratacos et al 10       | ✓   | ✓ |      | ✓       |         |       |          | ✓    | ✓    | X       |         |    |
| Gratacos et al 24       |     |   | ✓    |         |         |       |          | ✓    |      |         |         |    |
| Kornacki et al 28       | ✓   |   | ✓    |         |         |       |          |      |      |         |         |    |
| Madazli et al 29        | ✓   |   |      |         |         |       |          |      |      |         | X       | X  |
| Morris et al 30         | ✓   |   | ✓    |         | ✓       |       |          |      |      |         | X       | X  |
| Mutlu-Torkoglu et al 31 |     |   |      | ✓       |         |       | ✓        |      |      |         |         |    |
| Panburana et al 32      | ✓   |   |      |         |         |       |          | ✓    | ✓    |         | X       |    |
| Pasaoglu et al 33       | ✓   |   |      |         |         |       |          |      |      |         | X       | X  |
| Raijmakers et al 34     |     |   |      | ✓       | ✓       |       |          |      |      |         | X       | X  |
| Regan et al 11          |     |   |      |         |         |       |          |      |      |         |         |    |
| Serdar et al 35         | ✓   | ✓ |      |         |         |       |          | ✓    |      | X       |         | X  |
| Takacs et al 36         | ✓*  |   |      |         |         |       |          |      |      |         |         |    |
| Uotila et al 37         | ✓   |   |      |         |         |       | ✓        | ✓    |      |         |         |    |
| Var et al 38            | ✓   |   |      |         |         |       |          |      |      |         |         |    |
| Wu et al 39             | ✓   |   |      |         |         |       |          |      |      |         |         | X  |
| Yanik et al 40          | ✓   |   |      |         |         |       |          | ✓    |      |         |         |    |
| Yoneyama et al 8        | ✓   |   |      |         |         |       |          |      |      |         |         |    |
| Total                   | 18  | 4 | 5    | 4       | 4       | 3     | 3        | 12   | 3    | 10      | 10      | 10 |

\*Study was excluded because only severe cases of pre-eclampsia were included.

MDA indicates malondialdehyde; LP, lipid peroxides; TBARS, thiobarbituric acid reactive substances; Iso P, isoprostanes; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; VE, vitamin E; VC, vitamin C; S, serum; U, urine; P, plasma.

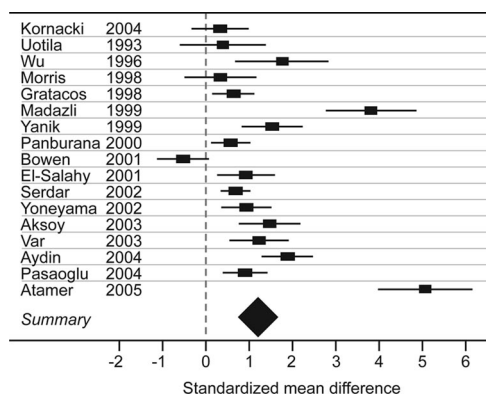


Fig. 2. Depiction of meta-analysis plot of SMD for MDA in cases versus controls (17 studies).

### Malondialdehyde

MDA was measured in serum or plasma in 17 studies (cases = 355, controls = 390). In 7 of these studies, samples were taken after fasting. Gestational age and maternal age were matched in 6 of these 14 studies. Of these 6 studies, only 1 required the sub-

jects to fast before serum samples were taken. The overall SMD in the 17 studies was an increase in MDA of 1.21 in cases compared to controls (95% CI: 0.76–1.66, Fig. 2). However, the  $I^2$  statistic that measures the degree of heterogeneity encountered in meta-analysis was found to be high at 88.9%. With the exclusion of 3 outlier studies (6,12,29), the SMD changed slightly with SMD = 0.94 (95% CI: 0.69–1.19) and the  $I^2$  statistic changed from 89% to 59%, which is a common degree of heterogeneity encountered in meta-analysis. This SMD became 1.31 (95% CI: 0.68–1.93) when examining only studies with gestational age matched cases and controls and 1.68 (95% CI: 0.81–2.55) when examining studies including only fasting subjects.

### Thiobarbituric Acid Reactive Substances

TBARS were examined in serum in 4 studies (cases = 119, controls = 106), (Fig. 3A). Overall, the SMD for TBARS was 1.62 nmol/mL greater in cases than in controls (95% CI: 0.27–2.96). The  $I^2$

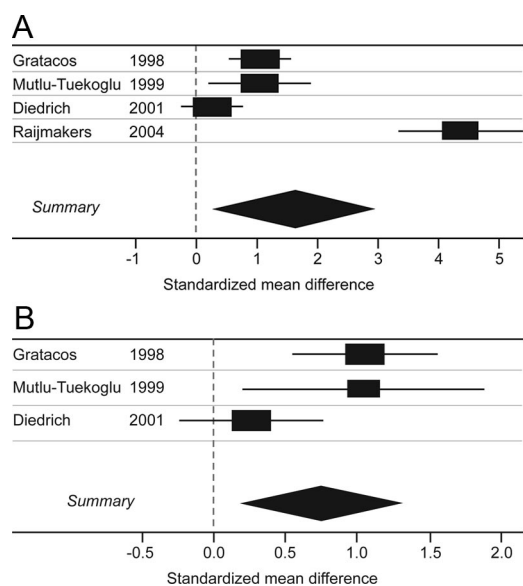


Fig. 3. A, Meta-analysis plot showing the overall SMD for TBARS in cases and controls (4 studies). B, Meta-analysis plot showing the overall SMD for TBARS in cases and controls after the exclusion of the outlier study. Reprinted with permission from *Acta Obstet Gynecol Scand* 2004;83:1173–1177.

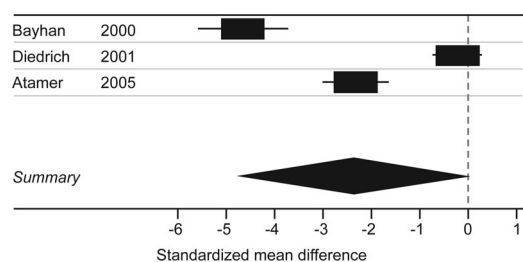


Fig. 4. Meta-analysis plot depicting the overall SMD for SOD in the 2 groups (3 studies).

statistic was found to be high at 94%. With the exclusion of the outlier study, i.e., Raijmackers et al (34) the SMD changed to 0.75 (95% CI: 0.18–1.32), and remained significant while the  $I^2$  changed from 94.0% to 63.7% (Fig. 3B). The significant TBAR difference remains even after subgroup analysis for heterogeneity adjustment according to the SMD values.

### Superoxide Dismutase

SOD was measured in erythrocytes in 3 studies (cases = 105, controls = 108) (Fig. 4). The overall estimate SMD estimate for SOD was  $-2.37$  (95% CI:  $-4.76$  to  $0.03$ ) with a trend toward being lower in cases than in controls. At 97%, the  $I^2$  was indicative of high heterogeneity.

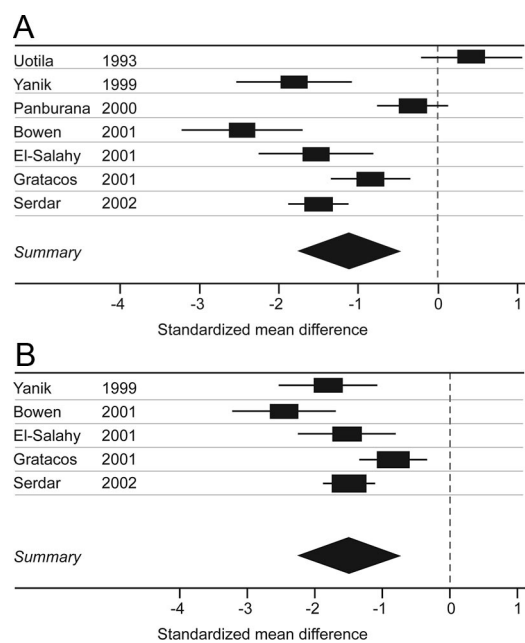


Fig. 5. A, Overall SMD for vitamin E in preeclampsia cases versus control (7 studies). B, Overall SMD for vitamin E in preeclampsia cases versus control (5 studies).

### Isoprostane Derivatives

Of the 26 studies, 3 assessed different isoprostane derivatives. Regan et al measured urinary 8,12-iso-iPF(2 $\alpha$ )-VI, in a case-control study of severe preeclampsia (11), Barden et al measured free and total plasma as well as urinary 8-iso-prostane (20). In another study in 2001, they measured total plasma total  $F_2$  isoprostanes (21). Because of these differences, the results could not be collated. In the 3 studies, these isoprostaglandin derivatives were found to be significantly raised in the respective compartment in cases compared to controls.

### Vitamin E

Seven studies were included in the meta-analysis (cases = 162, controls = 225). The concentration of vitamin E was significantly less in serum or plasma of cases compared to controls (Fig. 5A). The overall estimate of the difference based on SMD was 1.12 nmol/mL less in cases than controls (95% CI:  $-1.77$  to  $-0.48$ ). With the exclusion of Uotila (37) and Panburana (32), the SMD changed slightly to  $-1.57$  (95% CI:  $-2.05$  to  $-1.09$ ), while the  $I^2$  decreased from 89.6% to 70.9% (Fig. 5B).

### Vitamin C

Three studies were evaluated Vitamin C (cases = 71, controls = 126). The SMD for Vitamin C was

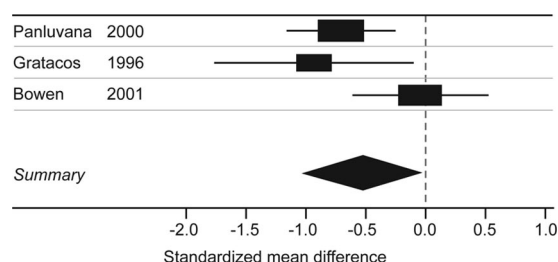


Fig. 6. Meta-analysis plot depicting the overall SMD for vitamin C in the 2 groups (3 studies).

-0.53 (95% CI: -1.03 to -0.02) with  $I^2 = 54.2\%$ . (Fig. 6).

## DISCUSSION

Our meta-analysis demonstrated a significant increase in serum MDA and TBARS levels in preeclamptic patients compared to those without preeclampsia. However, the conclusions about association, and the causality of that association in this meta-analysis, should be viewed with caution due to the limitations of studies in this review, differing study populations, different markers assessed, and various methodologies utilized to assess the markers (26,27). All the studies included were case-control studies and there can be an element of selection bias introduced because of confounding variables. It should also be noted that there may be element of publication bias as studies did not find an association between ROS markers and preeclampsia may not have been published.

There are various literature reports investigating the use of vitamin C and vitamin E supplementation to reduce oxidative stress, limit the injury of endothelial cells, and prevent or reduce disease severity of preeclampsia. Poston et al carried out a placebo-controlled trial in a diverse group of high-risk women, which demonstrated antioxidant supplementation was not associated with a reduction in the risk of preeclampsia; rather, it was associated with a significantly higher incidence of complications, including low birth weight, fetal academia, gestational hypertension, and the need for intravenous antihypertensive and magnesium sulfate therapies (41). There were no significant differences in the primary or secondary outcomes between the vitamin group and placebo group. No differences were reported in the risks of preeclampsia, infant mortality/morbidity, or delivery of a low birth weight infant. In another RCT by Rumbold et al, the supplementation also was associated with increased risk of hospitalization due to hypertension in women and the use of antihyper-

tensive therapy (42). However, some of these trials were powered to detect only a higher risk reduction for preeclampsia and, the possibility of a smaller benefit of antioxidant therapy cannot be ruled out. Until such evidence is available the routine use of antioxidant vitamins by nulliparous, low-risk pregnant women or high-risk pregnant women to prevent preeclampsia or to improve perinatal morbidity is not supported even if causal relationship between oxidative stress and preeclampsia is established.

## CONCLUSION

Overall, this meta-analysis emphasizes the biologic association of lipid peroxidation and preeclampsia. Deficiency of both enzymatic and nonenzymatic antioxidants is also observed in women with preeclampsia. However, future longitudinal studies estimating oxidative markers and antioxidants serially throughout pregnancy may be able to substantiate the association of elevated lipid peroxidation and diminished antioxidant levels with preeclampsia and the estimation of oxidative stress markers may be predictive of development of preeclampsia.

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