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The Role of Placental Oxidative Stress and Lipid Peroxidation in Preeclampsia

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Preeclampsia is a complex multisystem disorder exclusively seen in human species that is characterized by hypertension and proteinuria. This disorder has the highest maternal and fetal morbidity and mortality of all pregnancy-related complications. Growing evidence suggests that placental oxidative stress is involved in the etiopathogenesis of preeclampsia. Reduced perfusion as a result of abnormal placentation leads to ischemia reperfusion injury to the placenta. Placental oxidative stress, which results from the ischemia reperfusion injury, is being increasingly reported to be involved in the etiopathogenesis of preeclampsia. It has been proposed as a promoter of lipid peroxidation and the endothelial cell dysfunction that is commonly seen in this condition. Although preeclampsia is characterized by increased lipid peroxidation and diminished antioxidant capacity, there is no consensus regarding causality of lipid peroxidation in preeclampsia. In this article, we address the question of the biologic association of lipid peroxidation and preeclampsia. Lipid peroxidation and leukocyte activation may play a pivotal role in endothelial cell dysfunction. We also review the different factors that have been proposed to cause endothelial cell dysfunction in preeclampsia, trials investigating the role of antioxidant supplementation in preeclampsia, and the lack of consensus among the trials. Additional longitudinal studies are necessary to determine if the various oxidative stress biomarkers estimated early in pregnancy can be narrowed to a single marker for predicting preeclampsia.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader should be able to recall that placental oxidative stress is involved in the etiopathogenesis of preeclampsia, state that placental oxidative stress results from ischemic reperfusion injury, and explain that ischemic reperfusion injury is a promoter of lipid peroxidation and endothelial cell dysfunction seen in preeclampsia.

Preeclampsia is a complex multisystem disorder that occurs during pregnancy. It is associated with hypertension and proteinuria and has the highest

maternal and fetal morbidity and mortality of all pregnancy complications. It is exclusively seen in humans (1). In the United States, preeclampsia affects 5% to 8% of all pregnancies (2).

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Preeclampsia is characterized as a state of oxidative stress resulting from increased generation of free radicals and decreased levels of antioxidants, which scavenge free radicals. Some research now suggests that placental oxidative stress may be involved in the etiopathogenesis of preeclampsia. Oxidative stress occurs when generation of reactive oxygen species (ROS) increases and overwhelms the body's antiox-

idant defenses. Reactive oxygen species are molecules that contain one or more unpaired electrons in their outer orbit such as the hydroxyl radical, superoxide anion radical, and nitric oxide radical. Reactive oxygen species such as hydrogen peroxide and peroxynitrite do not have unpaired electrons. Regardless, they attack the phospholipids of cell membranes and react with polyunsaturated fatty acids to form lipid peroxides resulting in cellular injury. Reactive oxygen species have been proposed as a promoter of lipid peroxidation and the endothelial cell dysfunction that is commonly associated with preeclampsia. Reduced uteroplacental perfusion as a result of aberrant placentation leads to ischemia reperfusion injury to the placenta (3). Placental contribution of increased free radical-induced lipid peroxidation may therefore act as a catalyst for increased oxidative stress.

The human placenta is classified as hemochorial, and the establishment of the maternal placental circulation is influenced by the trophoblastic invasion. Extravillous trophoblastic invasion transforms the low-caliber, high-resistance spiral arteries into high-caliber, low-resistance, and high-capacity uteroplacental arteries. At 10 to 12 weeks gestation, changes in the placenta result in an oxidative burst. Abnormal placentation has been implicated in the pathogenesis of preeclampsia and miscarriage.

Preeclampsia has been proposed as a two-stage disorder. In the first stage, the placenta produces a cytotoxic factor. In the second stage, the maternal response to the placental factor occurs such as the formation of ROS. Mitochondrial activity increases, which results in increased generation of ROS (4). Increased mitochondrial activity has been demonstrated by the increasing accumulation of 4-hydroxynenal-modified proteins in the placental mitochondria, which may be the main site of lipid peroxidation.

PLACENTAL OXIDATIVE STRESS

Abnormal placentation leads to placental ischemia (5). The ischemia reperfusion injury to the placenta leads to generation of placental oxidative stress. Oxidative stress may play a role in the pathophysiology of abortions, preeclampsia, and in pregnancies complicated by intrauterine growth retardation (IUGR) (6–8). Generation of free radicals increases during pregnancy, and placental mitochondria are the major sources of ROS production. Lipid peroxides are formed and bind to the lipoproteins and are then transported to distant sites in the body. This transportation causes dissemination of the lipid peroxides,

thereby resulting in damage at distant sites. Increased lipid peroxidation has been reported in preeclampsia, IUGR, and deliveries complicated by acidemia (9–11). Nicotinamide adenine dinucleotide phosphate (NAD[P]H) oxidase is an important enzyme that generates superoxide radicals localized in the placenta syncytial microvillous membrane (12,13). NAD(P)H oxidase may play a role in placental lipid peroxidation by generating increased amounts of the superoxide radical.

A significant increase in lipid peroxidation levels and a trend toward increased protein carbonyl concentrations in the placenta of women with preeclampsia has been demonstrated (14–16). In addition, some upregulated scavenging capabilities of the placenta have also been demonstrated in some preeclamptic patients. Significantly reduced mean placental levels of glutathione and superoxide dismutase were reported in women with preeclampsia (17). Reduction in the glutathione and superoxide dismutase levels correlate with the incremental increases in the diastolic blood pressure.

LIPID PEROXIDATION: ROLE IN PREECLAMPSIA

Pregnancy is characterized by increased generation of prooxidants from the placenta. Poor antioxidant reserves can also tilt the balance in favor of prooxidation. Lipid peroxidation results in primary lipid peroxidation products such as lipid hydroperoxides and secondary products such as malondialdehyde (MDA) and lipid peroxides. Lipid hydroperoxides are formed and bind to lipoproteins. They are then carried to distant sites where the hydroperoxides can cause ongoing lipid peroxidation and result in systemic oxidative stress. Increased superoxide ion generation in the placenta has been detected with the direct electron paramagnetic spin resonance technique, which is the most direct method of measuring the free radicals (18). Increased generation of ROS leads to increased lipid peroxidation. Increased placental production of lipid peroxides and thromboxane was demonstrated from both the trophoblast and the villous core components of placentas in patients with preeclampsia (19).

Normal pregnancy is associated with physiological hyperlipidemia (20). Physiological alterations are manifested by increased levels of triglycerides and cholesterol in pregnancy, which decrease rapidly after delivery. Preeclampsia is characterized by further elevation of serum triglycerides and serum free fatty acids (21). Hypertriglyceridemia has been proposed to be a

potential risk factor for preeclampsia. A large cohort nested-control study found that hypertriglyceridemia, if demonstrated before 20 weeks gestation, may serve as a marker for early onset of preeclampsia (22).

The placenta may be the site of generation of the lipid peroxides (14). Increased generation of lipid

peroxides has been reported in the placenta of preeclamptic women (23–25). There is a lack of consensus on whether there is an association between lipid peroxidation and preeclampsia, although many studies suggest that the factors are associated (16,26) (Table 1). An increase in diastolic pressure correlates

TABLE 1
Studies demonstrating a significant association between preeclampsia and circulating levels of various biomarkers of oxidative stress

Study	Study Population	Oxidative Stress Biomarkers	Results
Atamer et al, 2005 ¹⁶	Nonpregnant women (n = 25) Normotensive pregnant women (n = 28) Preeclampsia (n = 32)	Serum MDA Placental MDA Erythrocyte SOD Erythrocyte catalase Placental GSH-Px Placental GSH	Significant increase in serum and placental MDA levels in preeclamptic patients Decreased placental glutathione peroxidase and glutathione levels
Aydin et al, 2004 ²⁶	Normotensive (n = 34) Preeclampsia (n = 35)	Plasma MDA SOD sE-selectin Fibronectin Endothelin-1 NO	Plasma levels of MDA, sE-selectin, fibronectin, and ET-1 significantly increase with increments in diastolic blood pressure (P < .001) Plasma SOD and NO levels were significantly lower and decreased with increments in diastolic blood pressure
Yoneyama et al, 2002 ⁴¹	Normotensive (n = 26) Preeclampsia (n = 26)	Plasma MDA Adenosine deaminase	Significantly higher levels of MDA and deaminase in preeclampsia (P < .05)
Gratacos et al, 1998 ³²	Healthy pregnant women (n = 36) Pregnant women with hypertension (n = 92)	Serum lipid peroxides Vitamin E	Serum LPO elevated and vitamin E levels significantly decreased in patients with preeclampsia and severe gestational hypertension
Orhan et al, 2003 ⁴²	Normotensive controls (n = 16) Preeclampsia (n = 9) Gestational diabetes mellitus (n = 3)	Maternal plasma and erythrocyte TBARS Glutathione transferase Glutathione peroxidase catalase activity	Erythrocyte Se-GPX activity significantly higher in hypertensive preeclamptic pregnancy and insulin-dependent diabetic pregnancy patients Concurrent increase in plasma levels of TBARS
Hubel et al, 1996 ²¹	Preeclampsia (n = 8) Normotensive controls (n = 9)	Antepartum and postpartum Serum triglyceride Free fatty acids Malondialdehydes	Antepartum serum triglycerides and fatty acid concentrations, elevated twofold in nulliparous women with preeclampsia Antepartum concentrations of MDA were 50% higher in women with preeclampsia and decreased postpartum
Moretti et al, 2004 ⁴⁰	Primiparas with preeclampsia (n = 26) Normotensive, primiparas (n = 38)	Breath markers Breath methylated alkane counter, C4–C20 alkanes Nonmethylated alkanes	Breath test demonstrated significantly elevated oxidative stress in women with preeclampsia
Takacs et al, 2001 ⁴³	Preeclampsia (n = 12) Normal pregnancy (n = 12)	Plasma MDA NFκB activation ICAM-1 expression in human umbilical endothelial cells	A 4.5-fold higher concentration of MDA in preeclampsia patients

SOD indicates superoxide dismutase; MDA, malondialdehyde; NO, nitric oxide; FFA, free fatty acids; ICAM-1, intercellular adhesion molecule-1; NFκB, nuclear factor kappa B; ET-1, endothelin -1; TBARS, thiobarbituric acid reactive substances; LPO, lipid peroxides; Se-GPX, selenium-glutathione peroxidase; sE-selectin, soluble E-selectin.

significantly with an increase in lipid peroxide levels, indicating that the severity of hypertension is correlated with the extent of lipid peroxidation (26,27).

Compared with normotensive pregnant women, women with preeclampsia have significantly higher mean plasma levels of MDA and significantly lower superoxide dismutase levels (26). The decrease in nitric oxide (NO) and superoxide dismutase (SOD) levels followed by a concomitant increase in levels of MDA, fibronectin, endothelin-1 (ET-1), and soluble-E selectin (sE-selectin) correlate with an increase in diastolic blood pressure (26). In their comprehensive study, Lurba et al reported a lack of a generalized state of oxidative stress in women with preeclampsia (Table 2). They speculated that the free radical-induced formation of lipid peroxide is neutralized by the increase in the concentrations of scavenging antioxidants. Their results suggest oxidative stress biomarkers are mildly elevated in preeclampsia and that increased lipid peroxidation and protein oxidation may be limited to the placental compartment (28).

Diedrich et al included patients with hemolysis, elevated liver enzymes, and low platelet counts (HELLP syndrome) in their study. These patients had significantly higher levels of thiobarbituric acid reactive substances (TBARS) than the control subjects ($P < .001$) and patients with preeclampsia ($P < .01$) (29). Bowen et al found significantly higher levels of cord blood MDA in patients with eclampsia (30). The studies by Diedrich et al and Bowen et al suggest that oxidative stress increases with the severity of HELPP syndrome and eclampsia. In less severe forms of the disease, the antioxidants and the placenta may be able to scavenge prooxidants. This may explain why lipid peroxides were not elevated in some of the studies.

In a longitudinal study, MDA levels in maternal erythrocytes were significantly elevated in women who developed preeclampsia. The risk of developing preeclampsia was 24-fold higher when MDA levels were above the cutoff value of 35.98 nmol malondialdehyde/g (31). This cutoff value had a high sensitivity, specificity, and negative predictive value.

TABLE 2

Studies showing lack of a significant association between preeclampsia and lipid peroxidation

Study	Study Population	Oxidative Stress Biomarkers	Results
Regan et al, 2000 ³³	Severe preeclampsia (n = 29) Normotensive controls (n = 29)	Urinary 8, 12-iso-iPF2 α -VI	Urinary levels did not differ significantly between cases and controls
Bowen et al, 2001 ³⁰	Preeclampsia (n = 21) Eclampsia (n = 6) Nonpregnant matched controls (n = 21)	Maternal and cord blood concentrations Uric acid LPO MDA Ascorbic acid vitamin E	No significant difference in maternal blood levels of LPO, MDA, ascorbic acid, and vitamin E between women with preeclampsia and the matched normotensive controls Cord plasma concentrations were significantly higher in eclampsia compared with preeclampsia and normal controls
Diedrich et al, 2001 ²⁹	Women with uncomplicated pregnancy (n = 36) Women with preeclampsia and HELLP syndrome (n = 28) Women with HELLP (n = 10)	Lipid hydroperoxides TBARS Radical scavenging enzymes in plasma and erythrocytes	Lipid hydroperoxides were not detectable in women with preeclampsia Elevated TBARS and GPX levels in HELLP syndrome
Lurba et al, 2004 ²⁸	Normotensive pregnant women (n = 30) Preeclamptic women (n = 53)	Plasma and erythrocyte MDA concentration	No intracellular or extracellular increases in secondary end products of lipid peroxidation, or MDA and LPO

Iso-iPF2 α -VI indicates isoprostaglandin F $_2\alpha$; HELLP syndrome, hemolysis, elevated liver enzymes and low platelets; TBARS, thiobarbituric acid reactive substances; MDA, malondialdehyde; LPO, lipid peroxides; GPX, glutathione peroxidase.

Gratacos et al found elevated levels of lipid peroxides measured with the thiobarbituric acid method and high-pressure liquid chromatography. However, the lipid peroxide to vitamin E ratio was decreased as a result of a decrease in the vitamin E levels (32).

Some studies found no evidence to suggest a causal relationship between lipid peroxidation products, LPO, and MDA and preeclampsia (30) (Table 2). Furthermore, no evidence of increased production of lipid peroxidation products was reported in a study conducted in African women. However, Bowen et al demonstrated that the cord plasma MDA and vitamin E levels were higher in patients with eclampsia than in patients with preeclampsia and in normotensive pregnant patients. Regan et al pointed out that the interpretation of conventional methods of lipid peroxidation may be limited by factors such as nonspecificity of the route of peroxide formation, imprecise analytical methodology and *ex vivo* lipid peroxidation (33). Major urinary isoprostanes such as 8, 12-iso-IPF2 α did not differ significantly between the patients with preeclampsia and the normotensive pregnant control subjects (33,34). The lack of unanimity regarding the role of lipid peroxidation may be the result of the lack of comparative methods used to measure the oxidative stress markers, inadequate assays used, evanescence of the product, and lack of sensitivity and specificity of different oxidative stress biomarkers.

Hyperhomocystinemia has been proposed to play a role in the etiopathogenesis of preeclampsia, exerting its effects through oxidative stress and endothelial dysfunction. Using metaanalytic techniques, Mignini et al reported elevated markers of oxidative stress in patients with preeclampsia and hyperhomocystinemia. A significant association was reported between oxidative stress biomarkers and preeclampsia (standardized mean difference 1.85; 95% confidence interval [CI], 0.31–3.39) (35). Malondialdehyde levels were measured in two of the four studies included in this metaanalysis (36,37).

Altered eicosanoid synthesis has also been implicated in the pathophysiology of preeclampsia. Eicosanoids have vasoactive properties and enhance lipid peroxidation and decrease prostacyclin synthesis. Increased production of 15-hydroxyeicosateranoic acid was demonstrated *in vitro* by cytotrophoblast from the placenta (38). The generation of the eicosanoid, 15-hydroxyeicosateranoic acid by the placenta was higher in women with preeclampsia than in normotensive control subjects. In preeclampsia, there is increased synthesis of thromboxane and reduced synthesis of prostacyclin. Walsh et al hypothesized that lipid peroxides may stim-

ulate the cyclooxygenase enzyme to produce more thromboxane, resulting in a hypercoagulable state (39).

Compared with normotensive pregnant patients, patients with preeclampsia have higher levels of oxidative stress during breath alkane testing. This test is reported to be a highly sensitive and specific marker of lipid peroxidation (40). C4 to C20 alkanes are generated as a result of the lipid peroxidation of polyunsaturated fatty acids in the membranes.

ANTIOXIDANT LEVELS IN PREECLAMPSIA

Antioxidants can be enzymatic or nonenzymatic. The enzymatic antioxidants are superoxide dismutase, thioredoxin, thioredoxin reductase, and glutathione peroxidase. The nonenzymatic antioxidants can be lipid-soluble such as vitamin E or water-soluble such as vitamin C. Serum levels of vitamin E and beta carotene were significantly lower in women with mild and severe preeclampsia (44,45). Studies have also shown that women with preeclampsia have significantly reduced serum coenzyme Q10 and α -tocopherol levels (46). Significantly lower levels of ascorbic acid were reported in the plasma of women with mild to severe preeclampsia (47). Similarly, serum α -tocopherol levels were significantly reduced in pregnancies complicated by severe preeclampsia, and the total antioxidant capacity was significantly reduced in pregnant women with mild and severe preeclampsia (47). The balance between lipid peroxides and antioxidant vitamin E is tipped in favor of lipid peroxides in patients with mild and severe preeclampsia.

In one study, the total antioxidant responses (TAR) and oxidative stress index (OSI) were analyzed in women with preeclampsia. The TAR was determined by the redox status of the plasma and measured using the automated colorimetric method, and the OSI was calculated from the percent ratio of the total plasma peroxide levels (48). Both TAR and OSI were found to be significantly higher in women with preeclampsia. A twofold increase in the ratio between lipid peroxidation and antioxidant capacity was reported in the antepartum period in women with preeclampsia (49).

In a controlled clinical trial, significantly lower levels of vitamin C, E, and total thiol were seen in women with preeclampsia (50). In patients with preeclampsia, antioxidants scavenge the increased free radicals, resulting in lowered antioxidant levels. Water-soluble antioxidants may function as a first line of antioxidants to scavenge excess ROS in plasma, whereas lipid soluble antioxidants such as α -tocopherol and β -carotene help scavenge ROS affecting the membrane lipids (23). Glutathione and its related enzymes are antioxidants that

help detoxify the increased generation of free radicals. Significantly reduced whole blood glutathione levels have been reported in women with preeclampsia and HELPP syndrome (17,51).

LEUKOCYTE ACTIVATION AND ITS ROLE IN PREECLAMPSIA

Pregnancy has been characterized as an inflammatory state, and these changes are exacerbated in preeclampsia (11,52,53). Activated leukocytes, both monocytes and granulocytes, generate excess ROS resulting in oxidative stress (54). Compared with matched normotensive pregnant women, women with preeclampsia have higher levels of calprotectin, a protein involved in various physiological inflammatory processes, which is indicative of leukocyte activation (52). Increased TNF- α secretion by leukocytes was detected in blood from patients with preeclampsia, providing further evidence of leukocyte activation (55).

Elevated levels of adhesion molecules were found in neonates born to mothers with preeclampsia, indicating the presence of activated neutrophils (56). The expression of surface adhesion molecules on cord blood neutrophils was significantly higher in infants born to women with preeclampsia than in infants born to the control subjects. Preeclampsia is thus characterized by leukocyte activation, which results in increased generation of ROS and expression of adhesion molecules. The activation of the leukocytes may result from the increased levels of cytokines such as TNF- α , as demonstrated in preeclampsia.

ENDOTHELIAL CELL DYSFUNCTION AND PREECLAMPSIA

Preeclampsia is a multisystem disorder, and endothelial dysfunction is one of the main pathogenic features of preeclampsia (Table 3). The markers of endothelial dysfunction such as tissue plasminogen activator, von Willebrand factor, sE-selectin, and fibronectin are elevated in patients with preeclampsia (26,57–60). Although the exact mechanisms of vascular endothelial damage in preeclampsia are unclear, increased lipid peroxidation may lead to endothelial cell dysfunction (61). Different mediators have been proposed to cause endothelial dysfunction (Table 3). TNF- α , tissue factor (TF) of placental origin, endothelial nitric oxide synthase (eNOS), and excessive activity of the enzyme poly (ADP-ribose) polymerase may contribute to endothelial dysfunction.

Compared with normotensive pregnant women, women with preeclampsia have reduced expression of endothelial mRNA and protein for eNOS. Reduced expression of constitutive NOS in the vascular system leads to reduced production of NO. NOS inhibition lead to increased endothelial permeability and an abnormal response of the endothelial cells to the stress challenge of preeclampsia (62).

Aberrant placental vasculature development and abnormal placental blood flow are characterized by increased impedance in Doppler velocimetry. Doppler velocimetry of uterine arteries at 18 to 22 weeks gestation has been used as a screening test for preeclampsia (63). Studies have investigated the cor-

TABLE 3
Endothelial dysfunction and preeclampsia

Authors	Markers of Endothelial Dysfunction	Mechanism of Endothelial Cell Activation
Di Paolo et al, 2003 ⁶⁵	Placental expression of endothelin-1(ET-1), nitric oxide synthase (NOS), and tissue factor	NO/ET-1 balance implicated in preeclampsia Strong increase in TF factor expression in the endothelial cells of basal decidua, which was correlated with marked increase in impedance of umbilical artery and uterine arteries
Hung et al, 2004 ⁷⁰	TNF- α , mRNA, E-Selectin	Activation of endothelial cells through TNF- α -mediated upregulated expression of platelet-derived growth factor, cell adhesion molecules, endothelin-1, and plasminogen activator inhibitor-1
Wang et al, 2004 ⁶²	Relative mRNA and protein expression for endothelial NOS	Significantly decreased in endothelial cells from patients with preeclampsia compared with cells from normal pregnancy
Beckmann et al, 2004 ⁵⁵	TNF- α concentrations in blood culture	Significantly higher concentrations in patients with preeclampsia compared with normotensive pregnant women

NO indicates nitric oxide; TF, tissue factor; mRNA, messenger ribonucleic acid.

relation between Doppler flow abnormalities and endothelial dysfunction associated with preeclampsia and IUGR (64,65). These abnormalities were significantly correlated with expression of TF in the placenta of women with severe preeclampsia (65). The expression of TF was found to be markedly increased in the endothelial cells within the basal deciduus. Doppler impedance modifications were significantly correlated to the endothelial cell activation.

Endothelial dysfunction may also result from increased shedding of syncytiotrophoblast membrane microvesicular (STBM) particles into the maternal circulation (66–68). *In vitro* studies in which STBM particles were perfused into subcutaneous arteries resulted in endothelial cell dysfunction (66). The exact mechanism by which the STBM particles affect endothelial dysfunction is unclear. Protease inhibitors reversed the effects of STBM particles on the morphology of endothelial cells, indicating that matrix metalloproteinases may have a role in endothelial dysfunction (67). In patients with preeclampsia, placental lesions are similar to those seen in atherosclerosis, indicating that endothelial dysfunction in preeclampsia and atherosclerosis may have common pathophysiological mechanisms (69).

TNF- α , a circulating cytokine, has also been implicated as causing endothelial dysfunction in preeclampsia (70). Blood cultured from patients with preeclampsia showed higher TNF- α release from the leukocytes in patients with preeclampsia compared with normotensive pregnant women (55). Significantly higher tissue levels of TNF- α were demonstrated in the placenta from women with preeclampsia (71). An *in vitro* study demonstrated significantly increased expression of TNF- α from placental tissue exposed to hypoxia/reoxygenation, which suggests that the placenta is the source of TNF- α in preeclamptic patients (70). Higher levels of TNF- α lead to increased generation of E-selectin, a marker of endothelial activation from the human umbilical endothelial cells *in vitro*.

VITAMIN C AND VITAMIN E SUPPLEMENTATION DURING PREGNANCY

Significantly decreased levels of vitamins C and E were reported in patients with preeclampsia (23). Oxidative stress occurs when there is an imbalance between prooxidants and antioxidants, which favors oxidation. Deficient levels of vitamins E and C can lead to oxidative stress. Vitamin E is a lipid peroxidation chain breaking antioxidant that inhibits NAD(P)H oxidase in the placental tissues (72). Vi-

tamin C helps convert oxidized vitamin E into a biologically useful form (73). Vitamins C and E have mutually beneficial effects. Supplementation with vitamins C and E has been initiated in various ongoing trials for the prevention of preeclampsia (74).

Lowered dietary intake of vitamins C and E is associated with a higher incidence of preterm labor (75). Oxidative stress leads to focal collagen damage in the fetal membranes and results in preterm labor (76). The effects of antioxidant supplementation have been investigated in preterm labor and preeclampsia (77,78). In one study, a mixture of up to six supplements that included vitamin C, Halibut liver oil (vitamins A and D), and vitamin B1 was investigated in 1530 primigravida women (79). Supplementation initiated before 24 weeks of gestation resulted in a lower incidence of hypertension and albuminuria. In a systematic review aimed at assessing the benefits of vitamin supplementation in improving various pregnancy outcomes, women who were taking any type of vitamin(s) were less likely to develop preeclampsia than control subjects (relative risk, 0.68; 95% CI, 0.54–0.85) (80). The meta-analysis included four trials comprising 5580 women (77,79,81,82). The risk of preeclampsia significantly decreased after supplementation with vitamins C and E and after multivitamin supplementation.

STUDIES ON DIETARY INTAKE OF ANTIOXIDANTS AND PREECLAMPSIA

The importance of nutrient balance in pregnant women is increasingly being recognized. Both dietary intake of antioxidants and the status of oxidative stress in the mother may influence IUGR (11). Dietary intake of vitamins C and E is important, because these are not synthesized endogenously. There is a frequent occurrence of IUGR in patients with preeclampsia, and both may have similar etiopathogenesis involving aberrant placentation, vascular dysfunction, and oxidative stress. A recent report indicated maternal plasma levels of vitamins C and E to be significantly associated with birth weight and length of live-born infants (83). The highest birth weights and heights were seen in the newborns whose mothers had the highest levels of plasma vitamins C and E. In a large prospective cohort study, women who consumed less than 85 mg of vitamin C per day had a threefold higher risk of developing gestational diabetes and a twofold risk of preeclampsia (62,84). On the other hand, no relationship was seen between dietary intake of vitamin C and preeclampsia risk, although low vitamin E intake significantly increased the risk of hypertensive com-

plications (85). High intake of vitamins C and E, which is common in the Mediterranean diet, has also been shown to be related to a lowered incidence of preeclampsia (28).

INTERVENTIONS TO OVERCOME OXIDATIVE STRESS IN PREECLAMPSIA

Randomized, controlled trials investigating calcium supplementation or low-dose aspirin therapy did not reduce the incidence or severity of preeclampsia. Thus, no interventions are currently available for the prevention of preeclampsia (86). Randomized, controlled trials investigating the benefits of antioxidant supplementation in patients with preeclampsia do not show beneficial results in patients with established preeclampsia (87,88). Results of two trials suggest that early (16–20 weeks gestation) antioxidant supplementation is helpful (87). Chapell et al found that the incidence of preeclampsia fell by more than 50% when antioxidant supplementation with vitamin C and vitamin E was initiated at 16 to 22 weeks of pregnancy in patients at high risk for preeclampsia (77).

In another prospective, randomized, controlled study, lycopene was found to reduce preeclampsia and IUGR in primigravida women, and an overall reduction of 51% was seen in the incidence of preeclampsia (89). The results of the trials by Chappell et al and Sharma et al are interesting, because both reported a 50% reduction in the incidence of preeclampsia in the supplementation group. However, these results have to be viewed with caution in light of results of a trial by Beazley et al. These investigators failed to show any difference in the rates of preeclampsia between the supplemented group (18.8%) and the placebo group (17.3%) in women at high risk for preeclampsia (90).

The results of these trials with small patient numbers need to be duplicated and confirmed by large multicenter trials. The results of ongoing trials with sufficient patient numbers and power to demonstrate statistically significant results such as the Diabetes and Preeclampsia Trial (DAPIT) will be helpful. This is a multicentered, randomized, double-blind, placebo-controlled trial in which antioxidant supplementation will be initiated at 8 to 22 weeks of pregnancy in patients with type 1 diabetes, and the beneficial effects of supplementation in preventing preeclampsia will be investigated (74).

CONCLUSIONS

Based on the literature, placental oxidative stress and lipid peroxidation play an important role in the pathophysiology of preeclampsia. Although many of the studies have shown a qualitative association between lipid peroxidation and preeclampsia, the results are contradictory. Variations in the results of different studies can be attributed to differences in the quality of the studies, different criteria for defining preeclampsia, different biomarkers assessed for oxidative stress, and variations in disease severity. Results of the two meta-analyses discussed in this article demonstrate a significant association between lipid peroxidation and preeclampsia and the beneficial effects of vitamin supplementation in reducing the risk of preeclampsia. Biomarkers can be used to measure the efficiency of the antioxidants. Longitudinal studies are needed to detect an oxidative stress biomarker or a combination of these biomarkers with high sensitivity and specificity for early prediction of preeclampsia. Reference values are necessary to predict preeclampsia early in pregnancy before the onset of clinical signs and symptoms. This will help identify women at high risk who need closer monitoring during pregnancy. The results of the ongoing trials using vitamins C and E supplementation may be able to further help delineate the role of oxidative stress in the etiopathogenesis of preeclampsia. Large, randomized, and controlled trials with antioxidant supplementation are necessary to further reinforce the effectiveness of these strategies in overcoming oxidative stress and preventing preeclampsia.

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