Oxidative Stress and Antioxidants in Preeclampsia

Jeng-Hsiu Hung*

Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, and National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

Oxidative Stress is Closely Related to Clinical Severity of Preeclampsia

Oxidative stress in aerobic life can be defined as the imbalance between the generation of reactive oxygen species (ROS) and the rate of their consumption by antioxidants. In normal pregnancies, there is an increase in free radical production and lipoperoxidation towards the end of pregnancy when compared with non-pregnant women.[1] In a parallel fashion, total antioxidant capacity (uric acid, vitamins C and E, etc.) gradually increases during pregnancy, leading to an oxidative balance maintained throughout pregnancy.[1]

In preeclamptic women, lipoperoxidation products, especially malondialdehyde (MDA), increase,[2] while enzymatic antioxidants superoxide dismutase (SOD), glutathione peroxidase (GPx), and non-enzymatic antioxidants (vitamins C and E) decrease. During preeclampsia, levels of available nitric oxide (NO) in plasma and placenta decrease, while an increase in nitric oxide synthase (NOS) activity occurs.[3] The superoxide anion is known to inactivate NO in a chemical reaction forming the potent free radical peroxynitrite anion ($ONOO^-$). The reaction of NO with superoxide is 3 times faster than the rate of reaction of O_2 with SOD. When NO out-competes SOD for O_2, production of $ONOO^-$ is favored. Peroxynitrite excess is responsible for the inflammation and nitration of tyrosine residues in proteins (nitrotyrosine) and the increase of prostaglandin synthesis as a product of the oxidation of arachidonic acid in lipidic membranes, with a subsequent blockage of vascular relaxation and increased smooth muscle contracture, leading to the hypertensive phenomena.[1]

Endothelial Cell Damage in Preeclampsia

In recent years, there has been increasing evidence that free radicals may play a key role in and oxidative stress may cause endothelial cell dysfunction in preeclampsia.[4] It was hypothesized that intermittent placental perfusion, secondary to deficient trophoblast invasion of the endometrial arteries, leads to an ischemia–reperfusion-type insult and results in the generation of free radicals.[4] Free radicals attack free fatty acids in cell membranes, and lipid hydroperoxides are formed. Consequently, lipid peroxides may cause endothelial dysfunction and an increase in sensitivity to vasopressors in preeclampsia.[4] Free radical production occurs continuously in all cells during normal aerobic metabolism as part of normal cellular function. However, cells have multiple protective mechanisms against oxidative stress. There is an equilibrium between prooxidant and antioxidant systems in intact cells.[4] Imbalance favors prooxidants, which may lead to cell and tissue damage in preeclampsia.[4]

Enzyme Activity of Basal Plasma Membranes of Syncytiotrophoblast from Normotensive and Preeclamptic Pregnant Women

The Ca-ATPase activity of the plasma membranes of several tissues in preeclamptic pregnant women is significantly reduced when compared with the corresponding values in normotensive pregnant women. These results give strong support to the hypothesis that lowered Ca-ATPase activity described in the plasma membranes of preeclamptic women is the consequence of increased levels of lipid peroxidation.[5] This condition

*Correspondence to: Dr Jeng-Hsiu Hung, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: jhhung@vghtpe.gov.tw • Received: July 2, 2007 • Accepted: August 6, 2007

has been considered to be the consequence of extensive placental lipid peroxidation and failure of the antioxidant protective mechanisms. Lipid produces inhibition of membrane-bound enzymes that are strongly dependent on the level of membrane lipid peroxidation.[5] Ca-ATPase is 1 of these enzymes. If the plasma membrane of the syncytiotrophoblast is also sensitive to the level of intracellular calcium, the diminution of Ca-ATPase activity as a consequence of a rise in lipid peroxidation of the plasma membrane would lead to an increase in the level of intracellular calcium, which would potentiate the level of lipid peroxidation of the plasma membrane and so forth. In addition, lipid peroxidation products, such as MDA, might raise the viscosity of the blood that is circulating through the placenta and contribute to increased blood pressure.[5]

Endothelium-derived NO Released in Arteries of Normal Pregnancies

The accumulation of oxidized low-density lipoprotein (LDL) in vascular walls during atherogenesis impairs vascular endothelial function. Normally, the vascular endothelium prevents inappropriate adhesion of leukocytes and platelets and vasospasm, in part through the constitutive release of endothelium-derived NO.[6] However, oxidized LDL impairs the release of NO from normal arteries. This finding has been attributed to the interruption of G protein-dependent stimulation of NO release as well as to direct inactivation of NO by lipid peroxidation products of oxidized LDL. Thus, in the presence of oxidized LDL, the physiologic action of NO is impaired, which might contribute to the platelet adhesion and vasospasm that are involved in the pathogenesis of acute coronary syndromes[6] and in preeclampsia.[7]

Oxidative Stress Also Affects the Newborn

Recently, it has been suggested that oxidative stress might play a pivotal role in developmental processes that later predispose to obesity, insulin resistance, and glucose dysregulation.[8] A variety of events that are associated with poor fetal growth or preterm birth are also associated with oxidative stress.[6] These events include maternal undernutrition and overnutrition, infection, inflammation, and smoking, as well as conditions such as gestational diabetes and gestational hypertension.[8] The oxidative stress theory suggests that these stresses in the fetus lead to increased lipid peroxidation, but more importantly, to modifications in gene expression that lead to adverse perinatal programming. The susceptibility of an individual fetus will depend on the time during gestation when metabolic programming occurs and on the genetic susceptibility of the fetus. Adiposity rebound, or an increase in weight after initial slow growth and slow early postnatal growth, has been implicated as a risk factor for diabetes and as another explanation for the increased metabolic risk for those with low birth weight.[8] The age at adiposity rebound may be associated with the risk of type 2 diabetes mellitus. The increase in the prevalence of obesity may be related not only to environmental circumstances but also to epigenetic mechanisms that might have triggered the phenomenon. The adverse intrauterine environment could have a lasting effect on the fetus through altered DNA methylation rates.

Increased Biological Oxidation and Reduced Anti-oxidant Enzyme Activity in Preeclamptic Placentae

Preeclampsia is a pregnancy-specific, multisystem disorder that can have considerable adverse effects on both mother and fetus. More recently, antioxidants have been proposed as a potential preventive strategy on the basis of data suggesting that endothelial dysfunction is fundamental to the development of preeclampsia and that increased oxidative stress, particularly in the placenta, may contribute to endothelial dysfunction.[9] Support for this concept comes from observations that markers of oxidative stress are increased and endogenous antioxidant capacity is reduced in women with preeclampsia.[9] Although the magnitude of the oxidative stress and of the reduction in antioxidant activity in women with preeclampsia is the subject of considerable controversy, there has been interest in the use of supplementation with vitamin C and vitamin E to reduce oxidative stress, limit the injury to endothelial cells, and prevent or reduce the severity of preeclampsia.[10]

Limitation of the Use of Antioxidants in the Prevention of Preeclampsia

Until recently, the data supporting the efficacy of supplementation with vitamin C and vitamin E for the prevention of preeclampsia have been limited. Published trials have focused on the use of antioxidants in

pregnant women at high risk for developing preeclampsia. In 1 randomized study involving 283 women at high risk for preeclampsia on the basis of abnormal uterine-artery Doppler waveforms or a history of the disease, those receiving antioxidant therapy had a lower rate of preeclampsia than did controls (8% *vs.* 17%), and significant improvement in markers of endothelial and placental function (ratio of plasminogen activator inhibitors type 1 to type 2).[10]

The Maternal–Fetal Medicine Units Network of the National Institute of Child Health and Human Development is currently conducting in the United States a multicenter trial of supplementation with vitamin C and vitamin E for the prevention of preeclampsia, with an anticipated sample of 10,000 low-risk women.[10] The data safety monitoring committee has decided to continue this trial without modification after reviewing the results provided by Poston et al.[11] There are also ongoing international trials of antioxidant therapy to prevent preeclampsia, some involving women in developing nations, where the intake of antioxidants may be less and the benefit of supplementation may be greater than in developed nations.[10] Until more data become available, given the scant evidence of benefit and the potential for harm, supplemental antioxidant therapy for the prevention of preeclampsia should not be prescribed as part of routine practice.

Acknowledgments

This work was supported by research grants NSC94–2314-B-075-014 from the National Science Council and V96C1-159 from Taipei Veterans General Hospital, Taiwan, R.O.C. The assistance of Yi-Chen Lin in the preparation of this manuscript is gratefully acknowledged.

References

1. Chamy VM, Lepe J, Catalan A, Retamal D, Escobar JA, Madrid EM. Oxidative stress is closely related to clinical severity of pre-eclampsia. *Biol Res* 2006;39:229–36.
2. Adiga U, D'souza V, Kamath A, Mangalore N. Antioxidant activity and lipid peroxidation in preeclampsia. *J Chin Med Assoc* 2007;70:435–8.
3. Lowe DT. Nitric oxide dysfunction in the pathophysiology of preeclampsia. *Nitric Oxide* 2000;4:441–58.
4. Tastekin A, Ors R, Demircan B, Saricam Z, Ingec M, Akcay F. Oxidative stress in infants born to preeclamptic mothers. *Pediatr Int* 2005;47:658–62.
5. Borrego E, Proverbio T, Marin R, Proverbio F. Lipid peroxidation and Ca-ATPase activity of basal plasma membranes of syncytiotrophoblast from normotensive pregnant women. *Gynecol Obstet Invest* 2006;61:128–32.
6. Diaz MN, Frei B, Vita JA, Keaney JF Jr. Antioxidants and atherosclerotic heart disease. *N Engl J Med* 1997;337:408–16.
7. Slaghekke F, Dekker G, Jeffries B. Endogenous inhibitors of nitric oxide and preeclampsia: a review. *J Matern Fetal Neonatal Med* 2006;19:447–52.
8. Ingelfinger JR. Prematurity and the legacy of intrauterine stress. *N Engl J Med* 2007;356:2093–5.
9. Vanderlelie J, Venardos K, Clifton VL, Gude NM, Clarke FM, Perkins AV. Increased biological oxidation and reduced antioxidant enzyme activity in pre-eclamptic placentae. *Placenta* 2005;26:53–8.
10. Jeyabalan A, Caritis SN. Antioxidants and the prevention of preeclampsia—unresolved issues. *N Engl J Med* 2006;354:1841–3.
11. Poston L, Briley AL, Seed PT, Kelly FJ, Shennan AH. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomized placebo-controlled trial. *Lancet* 2006;367:1145–54.