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Antioxidant Therapy to Prevent Preeclampsia

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Preeclampsia is a 2-stage disorder. Stage 1 is decreased placental perfusion and generates stage 2 of the disorder, the maternal syndrome characteristic of preeclampsia. How the 2 stages are linked has been a topic of intense investigation for many years. One candidate phenomenon, which includes many other suggested linkages, is oxidative stress. This hypothesis predicts that the administration of antioxidants would decrease oxidative stress and modify stage 2. Experience with the treatment of preeclampsia including a small trial of antioxidants in women with manifest preeclampsia makes it clear that the use of any therapy once preeclampsia is evident will not be successful. Trials evaluating prophylactic aspirin and supplemental calcium from early pregnancy suggest that therapy before evident preeclampsia may be successful in selected populations. Guided by these concepts and by experience with antioxidant therapy in other settings, 1 small study (<80 women in the treatment arm) was very encouraging with an almost two-thirds reduction of the frequency of preeclampsia in high-risk women. Antioxidants currently are being evaluated in several larger trials in the United States, Canada, Mexico, England, and in several developing nations. These studies should definitively establish the efficacy and safety of this therapy for the mother and fetus.

KEYWORDS preeclampsia, oxidative stress, antioxidant, ascorbate, vitamin C, vitamin E

Preeclampsia remains a major cause of infant and maternal mortality and morbidity. In developing countries, preeclampsia causes an estimated 50,000 maternal deaths per year.[1] These deaths are largely prevented in developed countries by standard management of preeclampsia, delivery of women with evidence of disease to prevent progression. However, this approach, although successful in reducing maternal mortality, can result in premature delivery with an attendant increase in infant morbidity and mortality. In the United States, indicated deliveries for preeclampsia are responsible for 15% of premature births.[2] It also does not prevent substantial maternal morbidity. Thus, the ideal management of preeclampsia is prevention. Numerous strategies attempting to accomplish this have been attempted with minimal success.[3] However, information gained from recent trials to prevent preeclampsia by using aspirin or calcium and emerging concepts of pathology and pathophysiology have suggested a new approach to prevention. Antioxidant therapy is now being tested in several large trials.

In this article we present the rationale for antioxidant therapy as it is directed by current concepts of pathology and pathophysiology. Specifically, we address the evidence for oxidative stress in preeclampsia and its proposed origins in the disorder. The choice of antioxidants for prophylaxis and special considerations in pregnancy also are considered.

Pathology and Pathophysiology

Preeclampsia can be considered a 2-stage disorder (Fig 1). The initiation of preeclampsia appears to be related to decreased placental perfusion (stage 1). This decreased perfusion results in the maternal syndrome of preeclampsia (stage 2). The linkage of the 2 stages is a prime target for preventive therapy.

Preeclampsia is a pregnancy-specific disorder and the necessary component of pregnancy is the placenta. Preeclampsia is terminated by delivery but more specifically by delivery of the placenta. This point was strikingly shown by a case of the disorder occurring during the course of an abdominal ectopic pregnancy.[4] In this case, the placenta had implanted on the lateral pelvic wall in close proximity to major vessels and for

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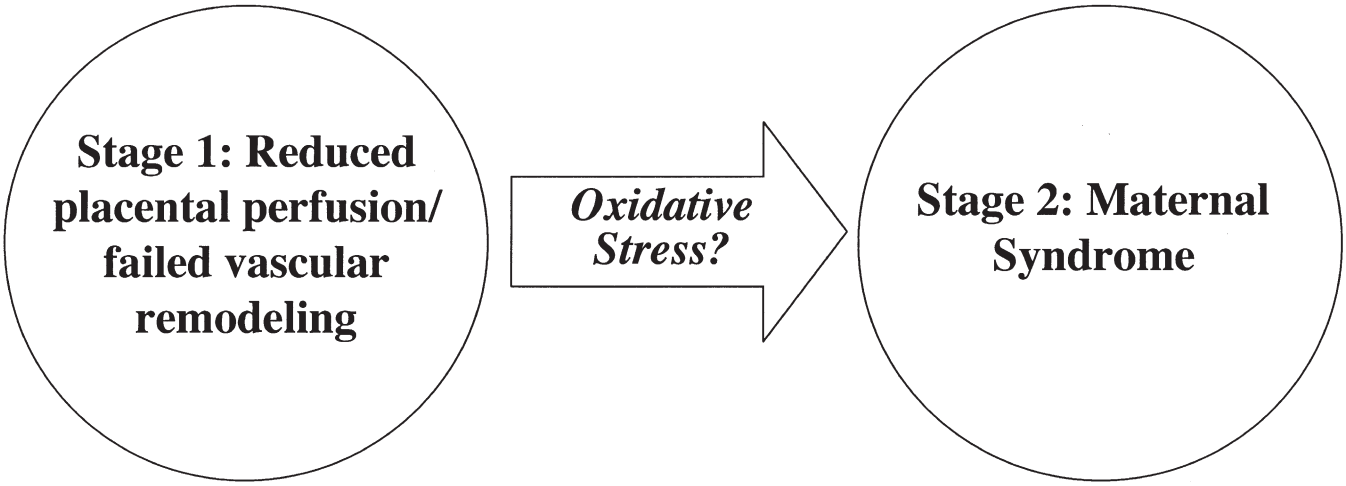

Figure 1 Preeclampsia as a 2-stage disorder. Preeclampsia can be considered a 2-stage disorder. Stage 1 is the abnormal perfusion of the placenta that is frequently secondary to failed remodeling of the maternal vessels that supply the intervillus space. It is posited that material(s) produced by the placenta enter the systemic circulation to generate stage 2, the maternal syndrome that characterizes preeclampsia. This model proposes that this linkage is oxidative stress generated in the intervillus space that is transferred to the systemic circulation by, for example, activated neutrophils or monocytes, cytokines, or fragments of placental villae containing oxidatively modified lipids.

this reason when the infant was delivered the placenta was left in place to reabsorb spontaneously. This took several months and signs and/or symptoms of preeclampsia did not disappear until this reabsorbtion had occurred. The feature of the placenta that is thought to result in preeclampsia is decreased perfusion of the organ. This concept, originally posited many years ago,[5] is supported by the observation that medical disorders associated with microvascular disease such as hypertension and diabetes increase the risk for preeclampsia.[6] Furthermore, complicated pregnancies characterized by very large placentas such as hydatidiform moles and multiple gestations also increase the risk for preeclampsia.[6] The placenta in these settings is proposed to be so large that it cannot be perfused adequately, resulting in relatively decreased placental perfusion. The most compelling evidence, however, for the role of decreased perfusion in preeclampsia is the failure to remodel maternal myometrial and decidual vessels supplying the placental site (see article, "Abnormal Placentation and the Syndrome of Preeclampsia", by McMaster et al in this issue). In normal pregnancy, the luminal diameter of these vessels increases 4-fold and the vascular smooth muscle of the media and the inner elastic lamina are lost.[7] This increases blood flow to the placenta through flaccid vessels with minimal possibility for humoral or neural modification. This change does not occur in preeclampsia.[8] The result is a substantial decrease in placental perfusion.

Stage 2

The maternal syndrome of preeclampsia is far more than the hypertension and renal dysfunction used to diagnose the disorder.[9] A major pathophysiologic feature is decreased blood flow to virtually all maternal organs.[6] This is proposed to be secondary to vasoconstriction, activation of the coagulation cascade with microthrombi, and decreased vascular volume from the loss of fluid from the intravascular space. The vasoconstriction is caused by increased sensitivity to all pressor agents rather the production of unique pressors or increased concentrations of usual endogenous pressors.[10] Increased sensitivity to pressors is an early change of preeclampsia shown months before clinically evident disease.[11] Similarly, activation of coagulation, in particular of platelets, and decreased plasma volume are evident in groups of women destined to develop preeclampsia long before manifest disease.[12] This constellation of changes that antedate hypertension and proteinuria led to the hypothesis that a proximate pathophysiologic event in preeclampsia was endothelial dysfunction.[13] This hypothesis, advanced more than 10 years ago, has gained substantial experimental support.[14] It recently has been extended to propose that endothelial activation be considered part of a generalized increase in inflammatory activation.[15] Normal pregnancy is associated with a striking increase in inflammatory response that is increased further in preeclampsia.

Linkage of Stage 1 and Stage 2

A question of major importance to the prevention of preeclampsia is what is the linkage between the 2 stages of preeclampsia? How does decreased placental perfusion result in a systemic maternal disease? An obvious hypothesis is the production of toxins by the placenta that enter the maternal circulation and alter endothelial function leading to the subsequent maternal syndrome.[13] Investigators studying preeclampsia have sought this "substance X" for years, with minimal success.[16] Recently, attention has been directed to villous fragments resulting from placental apoptosis that enter the maternal circulation,[17] placental cytokines[18] and the growth factor inhibitor, soluble fms-like tyrosine kinase 1.[19] An appealing hypothesis with the potential to unify many of

these current concepts is the generation of mediators of oxidative stress in the intervillus space with transfer to the maternal systemic circulation.[6] Oxidative stress is increased with inflammation, can stimulate apoptosis and cytokine production, and is produced, as is soluble fms-like tyrosine kinase 1, in response to hypoxia.[20] Furthermore, products of oxidative stress damage proteins, DNA, and lipids, and activate and injure vascular endothelium.[20] A potentially particularly relevant enzyme inactivated by oxidative stress is dimethylarginine dimethylaminohydrolase, an enzyme that degrades the endogenous nitric oxide antagonist, asymmetric dimethyl arginine. Dimethylarginine dimethylaminohydrolase, present in the placenta, has been shown to be exquisitely sensitive to conditions associated with oxidative stress, including hyperhomocysteinemia,[21] hypercholesterolemia,[22] and diabetes mellitus.[23] Asymmetric dimethyl arginine, which competitively inhibits nitric oxide synthesis to decrease nitric oxide production, is decreased during normal pregnancy and increased with preeclampsia.[24]

Oxidative Stress

Oxidative stress is the presence of reactive oxygen species or free radicals in excess of buffering antioxidants.[25] An obvious but unusual source of free radicals is exposure to increased environmental oxygen. More commonly, excess free radicals are produced at ambient oxygen concentrations. Free radicals are produced by mitochondria but usually are sequestered. When produced in excess or with mitochondrial injury, reactive oxygen species exit mitochondria. A common phenomenon leading to excess mitochondrial free radical production and mitochondrial injury is hypoxia followed by reoxygenation. During hypoxia there is increased degradation of adenosine triphosphate to adenine monophosphate, which in the absence of oxygen cannot be recycled to adenosine triphosphate. Excess adenine monophosphate is degraded to adenosine, hypoxanthine, and finally is metabolized by the bifunctional enzyme xanthine oxidase/dehydrogenase (XO/XOD). In XOD, the enzyme products are uric acid and reduced nicotinamide adenine dinucleotide.[26] However, with hypoxia, XO predominates. Uric acid is again an enzyme product but with XO activity the free radical superoxide also is formed. The generation of free radicals is exacerbated further with reperfusion. The depletion of endogenous antioxidants by superoxide results in subsequent massive generation of free radicals with reoxygenation. Reactive oxygen species also are produced in settings of inflammation.[27] These molecules activate neutrophils and monocytes, preparing them to release free radicals as a normal mechanism to inactivate foreign microbes. This release also can occur abnormally when these cells contact inappropriately activated endothelial cells. The transition metals, copper and iron, catalyze many reactions in which free radicals are generated or by which free radicals modify proteins or lipids.[28,29] Copper and iron usually are inactivated by binding proteins, however, when there is excess free iron or copper, free radical production and free radical damage are increased. Alternatively, a decrease of available antioxidants can increase free radicals and reactive oxygen species even in the absence of excess generation. Antioxidant activity can be either enzymatic or chemical. Chemical antioxidants are depleted as they are oxidized and must be reduced, synthesized, or ingested to reverse oxidative stress. Antioxidants also must be in the relevant compartment to be active. There are lipid-soluble (vitamin E [tocopherols]) and water-soluble (eg, glutathione, vitamin C [ascorbate], uric acid) antioxidants. In humans, the linch-pin antioxidant is ascorbate. Ascorbate reduces and recycles oxidized tocopherol at the lipid aqueous interface.[30] Vitamin E and other antioxidants are not consumed until ascorbate is substantially oxidized. Ascorbic acid is not produced in humans and must be supplied by diet, raising the potential for the dietary origin of oxidative stress.

Not surprisingly, oxidative stress has been implicated in several human diseases, and its role in atherosclerosis has been explored extensively. The oxidation hypothesis of atherosclerosis posits that the predisposing dyslipidemia of atherosclerosis results in the generation of small dense low-density lipoproteins (LDLs), an LDL moiety with increased potential to enter and remain sequestered in the subendothelial space.[31] In this setting, these particles, which are inherently more easily oxidized than other LDL particles, are not protected by endogenous plasma antioxidants and are oxidized to oxidized LDL. Oxidized LDL particles have the capacity to injure tissues including endothelium and lead to the increased expression of endothelial selectins that attract monocytes. Monocytes phagocytize LDL with the subsequent formation of foam cells and the fatty streak. The phenomenon of hypoxia reperfusion accounts for much of the damage with myocardial infarction and stroke and is relevant to necrotizing enterocolitis in newborns. In addition, oxidative stress is implicated in aging and carcinogenesis.

Oxidative Stress in Preeclampsia

The concept that oxidative stress might be present in preeclampsia and contribute to its pathophysiology dates back many years. Over 40 years ago experimental eclampsia was induced in pregnant rats using an anti–vitamin E diet[32] and lipid peroxides, lipid products of oxidative stress, reportedly were increased in the blood of women with preeclampsia more than 20 years ago.[33] The idea received increasing attention in the late 1980s,[34] and since that time much supporting data has been accumulated (Table 1).[25] Nonetheless, the role of oxidative stress in preeclampsia is not without controversy.[35]

To establish the role of oxidative stress in preeclampsia several questions must be answered. First and most obvious is how reliable is the evidence for oxidative stress in preeclampsia? The earliest and predominant evidence for oxidative stress in preeclampsia was excess concentrations of products of lipid oxidation in biological materials from women with preeclampsia. These lipid products can be measured in several ways but a very common approach is the measure-

Table 1 Evidence of Oxidative Stress in Preeclampsia

Circulating markers
Nonlipid
Antibodies to LDL[61]
Ascorbate oxidizing activity[62]
Increased nitrosothiols[63]
Lipid markers
Lipid oxidation products[64]
Antibodies to oxidized LDL[61]
Antioxidants
Decreased vitamin C levels[48]
Decreased carotenoids levels[65]
Decreased glutathione levels[66]
In maternal tissues
Increased nitrotyrosine residues in blood vessels[41]
Activated neutrophils and monocytes[67]
In decidua
Atherosis with lipid-laden macrophages[68]
Increased lipid peroxide levels[69]
Increased isoprostanes (8 iso prostaglandin F2α)[70]
Protein carbonyls[39]
In placenta
Nonlipid markers
Increased xanthine oxidase levels in invading trophoblast cells[47]
Increased nitrotyrosine residues in fetal blood vessels[71]
Protein carbonyls[39]
Antioxidants
Decreased superoxide dismutase levels[47, 72]
Decreased glutathione peroxidase levels[73]
Lipid markers
Increased malondialdehyde levels[74]
Increased lipid peroxides levels[61]

ment of lipid peroxides. The problem with these measurements is that lipid peroxides can be generated ex vivo and thus may be an artifact. An alternative measurement less subject to artifact is the measurement of oxidative products formed from arachidonate, the isoprostanes. These molecules are purported to be formed nonenzymatically by oxidative modification of arachidonate. Because they measure the oxidation of only one fatty acid they are not as sensitive as general measures of lipid peroxidation. They are, however, especially interesting because some isoprostanes are biologically active and thus serve not only as markers of oxidative stress but also may be relevant pathophysiologically. There are a myriad of isoprostanes, many of which have been described as increased in preeclampsia. A frequently measured isoprostane in preeclampsia is 8-iso-prostaglandin F2α, a product that has been shown to have biological activities in vitro relevant to preeclampsia. These activities include decreasing trophoblast invasion[36] and increasing the expression of endothelin receptors on endothelial cells.[37] Despite the concept that isoprostanes are not formed enzymatically, cautions have been expressed that 8-iso-prostaglandin F 2α can be formed from cyclooxygenase, raising concerns about their specificity as a marker of oxidative stress.[35]

There are, however, several other lines of evidence supporting oxidative stress in preeclampsia. Protein carbonyls are protein oxidation products that are not synthesized enzymatically or spontaneously in vitro.[38] Protein carbonyls are increased in the placenta of women with preeclampsia associated with the hemolysis-elevated liver enzymes-low platelet syndrome.[39] Nitric oxide reacts with the free radical, superoxide, to generate the free radical peroxynitrite. Peroxynitrite subsequently can interact with tyrosine residues in proteins to form nitrotyrosine. Nitrotyrosine is increased in the placenta,[40] and, more importantly, in the maternal vasculature[41] of women with preeclampsia. Furthermore, activated neutrophils and monocytes have increased capacity to release free radicals and there is evidence of activation of these blood products in preeclampsia.[42-44]

What is the origin of oxidative stress in preeclampsia? Is there a source for increased free radical generation and/or is antioxidant availability decreased? It has been known for decades that free iron levels are increased in women with preeclampsia, reflecting, perhaps, low-grade hemolysis. Additionally, another transition metal, copper, exists in a redox active form even when bound to albumin in women with preeclampsia.[29] As pointed out, these metals can catalyze free radical generation. The increase of activated neutrophils and monocytes is an additional source of oxidative stress.

Another interesting possibility is the generation of free radicals in the intervillus space by a hypoxia-reperfusion mechanism. The uterus in humans is not a privileged organ and uterine perfusion is decreased, for example, with exercise and meals. Furthermore, a hazard of upright posture is a striking variation in uterine perfusion with different postures in late pregnancy. Standing, sitting, and lying supine all decrease uterine perfusion. All of these physiologic processes and postures influence uterine and hence placental blood flow only transiently, with a subsequent return of normal perfusion. Additionally, a normal part of uterine physiology during labor is a temporary occlusion of arteries traversing the myometrium with uterine contractions. This temporarily decreases placental blood flow. All of these perturbations seem to have the potential to induce the hypoxia reperfusion scenario in the intervillus space. This does not seem to be the case in normal pregnancy, although there is evidence of a slight increase of markers of oxidative stress in normal pregnancy.[45] There are likely protective mechanisms to prevent the generation of free radicals in this setting. The placenta, for example, has a much lower content of XOD/XO than other tissues.[46] Is it possible that with the decreased placental perfusion characteristic of preeclampsia that the same perturbations that are tolerated in normal pregnancy may result in hypoxia reperfusion in the intervillus space of preeclamptic women? This hypothesis is supported by a striking increase in the holoenzyme and the oxidase form of XO/XOD, xanthine oxidase, which is known to be up-regulated with hypoxia reperfusion, in the invasive cytotrophoblast from preeclamptic pregnancies.[47]

An alternative source of oxidative stress is decreased antioxidants. Decreased antioxidants are present in women with preeclampsia (Table 1) but could be evidence of either an antioxidant deficiency or excess free radical generation with

consumption of antioxidants. There is evidence that ascorbate levels are decreased in early pregnancy before clinically evident disease in women who later develop preeclampsia.[48] Even in this setting, however, decreased ascorbate levels may indicate consumption with depletion rather than a primary deficit. Asymmetric dimethyl arginine levels also are increased in early gestation in women who later develop preeclampsia.[49] This endogenous inhibitor of nitric oxide is increased in settings of oxidative stress consistent with down-regulation of dimethylarginine dimethylaminohydrolase supporting excess oxidative stress even before manifest preeclampsia. There currently is little dietary data to support a deficient intake of ascorbate in women who subsequently develop preeclampsia. In one study,[50] based on dietary recall, women with preeclampsia reported a lower ascorbate intake in early pregnancy, although recall bias could not be excluded.[50]

There is extensive evidence for oxidative stress in the intervillus space of women with preeclampsia (Table 1) (see earlier hypothesis). However, products of oxidative stress are quite transient. The question then arises of how molecules able to provoke oxidative stress can be transferred successfully to the mother's systemic circulation. Certain products of oxidative stress (eg, malondialdehyde) are reasonably stable and could be involved. Additionally, the activation of neutrophils and monocytes as they are exposed to oxidative stress while traversing the intervillus space results in another source of free radical transport to maternal tissues. Certain cytokines such as tumor necrosis factor α and leptin are increased by hypoxia. Tumor necrosis factor α and leptin are increased in preeclampsia and have the capacity to increase free radical production by endothelial cells. It is also likely that the microvillus particles that are shed in increased quantity in preeclampsia contain lipid oxidation products. There is in vitro evidence that these particles can alter endothelial function, alter vascular function, and activate inflammatory cells.[51]

Antioxidants to Prevent Disease

The extensive support for oxidative stress in the genesis of atherosclerosis led to preventive trials with antioxidants. However, several recently completed, large, randomized, controlled trials have not shown beneficial effects of antioxidants to prevent cardiovascular disease.[52] Objections have been raised about these studies including questions of antioxidant choice, dose used, and patient selection.[52] Whether these negative results are relevant to preeclampsia are open to question. Although preeclampsia and atherosclerosis share many pathophysiologic features, the unique feature of preeclampsia is its rapid appearance and disappearance. In atherosclerosis, which likely has been present for many years before the onset of antioxidant therapy, it is quite possible that irreversible (perhaps structural) changes are present.

What are the appropriate antioxidants with which to attempt to prevent diseases? The vast majority of trials in the past did not include ascorbate. Based on theoretical considerations, this linch-pin antioxidant should be included. Interestingly, one of the few randomized trials to prevent cardiovascular disease progression successfully included vitamin C.[53] A lipid-soluble antioxidant also should be included and vitamin E is a reasonable choice. It is important to remember that vitamin E defines a family of tocopherols, with the active forms of the vitamin limited to the naturally occurring (RRR-α tocopherol and the synthetic 2R stereoisomeric) forms.[54] The tocopherols are found in lipoprotein particles and increase with increased lipids.

There are, of course, special considerations for the use of antioxidants in pregnancy. The experience with antioxidants in cardiovascular disease prevention and theoretical considerations direct the use of a combination of vitamins C and E as preventive therapy for preeclampsia. Are these drugs safe for the mother and fetus? Vitamin C at doses greater than 1,000 mg/d minimally further increase circulating ascorbate levels and 1,000 mg was the dose used in most trials. Vitamin C crosses the placenta and in the 1960s there was a report of a rebound reduction in ascorbate levels in neonates. This has not been confirmed since this time and a recent report from the Institute of Medicine discounts this finding and considers 2,000 mg to be the maximum safe dose for pregnancy.[54] Vitamin E, when given to neonates in very high doses, can interfere with the ability of neutrophils to release superoxides to kill microbes. This results in an increased risk for sepsis.[55] Vitamin E, however, crosses the placenta very poorly and it is extremely unlikely that concentrations sufficient enough to interfere with neutrophil function can be achieved by placental transfer of the doses of vitamin E used in most trials, 400 IU.[56] Nonetheless, the final evidence of safety of these agents must come from randomized trials.

Antioxidants to Prevent Preeclampsia

Antioxidant therapy (vitamin C, vitamin E, and allopurinol) was tried unsuccessfully to improve outcomes in women with manifest preeclampsia.[57] This is consistent with all other therapies of preeclampsia that at best are palliative in women with overt disease. This contrasts with reports of successful therapy with calcium or aspirin begun in early pregnancy. Although larger trials have not supported benefit, a meta-analysis of the known trials and systematic reviews have suggested a benefit (albeit small) for both calcium supplementation therapy in populations deficient in calcium[58] and for low-dose aspirin (in over 30,000 pregnancies) when prophylactic agents were begun before manifest preeclampsia (see article, "Strategies to Prevent and Treat Preeclampsia: Evidence From Randomized Controlled Trials", in this issue).[59] It is likely that by the time preeclampsia is clinically evident that irreversible changes are present and therapy must be begun before this time.

Chapell et al used this strategy, testing the efficacy of antioxidant therapy before clinically evident disease.[60] They identified some high-risk women by history (previous preeclampsia, preexisting hypertension) but identified most by abnormal uterine artery Doppler measurements at 20 and 24

weeks gestation. The study, limited in size, was powered to determine whether evidence of endothelial activation could be decreased in these high-risk women by therapy with 1,000 mg of vitamin C and 400 IU of vitamin E. The uterine artery Doppler assessment they used has a positive predictive value of 20% when there is evidence of increased resistance at 20 and 24 weeks gestation. The investigators chose not to wait until 24 weeks to begin therapy and women were randomized on the basis of an abnormal Doppler at 20 weeks gestation, but if subsequent Doppler assessment at 24 weeks was normal, therapy was discontinued. The study analyzed as an intent-to-treat trial was successful because there was a significant decrease of markers of endothelial activation in the women assigned to the vitamin group. Surprisingly, in view of the small number of subjects, there also was a significant decrease in the diagnosis of preeclampsia in the treatment group. Preeclampsia occurred in 24 of 142 (17%) of the placebo group, but only 11 of 141 (8%) of the treated group (odds ratio, .39, 95% confidence interval (CI) .17-.90, P = .02). When the women who remained on placebo (81) or treatment (79) were compared, the results were even more impressive (odds ratio .24; CI 0.08-0.70, P = .002).

These 95% CI, although impressive, remain to be confirmed with a larger number of patients and it also is important to determine the safety of these large doses of vitamins for the mother and fetus (obviously not established in a trial limited to 80 patients). Furthermore, whether these findings from England, where only 17% of women took prenatal vitamins,[60] can be extended to a US population, where the vast majority of women take prenatal vitamins, remains to be established.

Antioxidant Studies to Prevent Preeclampsia Currently in Progress

There are several large trials of antioxidant therapy to prevent preeclampsia currently in progress worldwide. These include studies of high-risk women in England (that also encompasses World Health Organization network centers in developing nations), low-risk women in Canada and Mexico, and in the United States. The study in the United States includes 10,000 women and is being conducted by the National Institute of Child Health and Human Development Maternal Fetal Medicine Network for clinical trials with support from the National Heart, Lung & Blood Institute.

The National Institute of Child Health and Human Development/National Heart, Lung & Blood Institute trial is randomizing women to treatment with 1,000 mg of vitamin C and 400 IU of vitamin E at 8 to 16 weeks gestation and adds several interesting features to prior and current trials. The study is powered to see differences in maternal and fetal outcomes, rather than merely a decrease of the frequency of the diagnosis of preeclampsia. Thus, the primary outcome in the study is gestational hypertension and markers of a maternal morbidity (severe hypertension, or eclampsia or thrombocytopenia, or hepatic or renal dysfunction, or neonatal mortality or morbidity: stillbirth, indicated preterm birth, or small for gestational age [<3rd centile]). The study also includes a pathophysiology/prediction component in which 4,000 women (2,000 placebo and 2,000 treated) will have biological samples obtained before randomization and intermittently throughout pregnancy. This component of the study hopefully will identify predictors of preeclampsia and information on the early pathophysiology of the disorder. It also may determine if subset(s) of women are more or less likely to benefit from antioxidant therapy as well as what components of the pathophysiology of preeclampsia are modified by this therapy. All of the studies in progress should be completed in the next 3 years.

Summary

The current concept of the pathophysiology of preeclampsia proposes a two stage model, reduced perfusion and a maternal syndrome, that are somehow linked. Oxidative stress is an attractive candidate for the linkage and has considerable support. Antioxidant therapy offers the possibility to modify this linkage. Whether the encouraging results of the first small trial will be supported will be answered by several randomized controlled trials now in progress.

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