

monitored appropriately. Second, Gattinoni et al. did not address the issue of how much potentially recruitable lung is sufficient for clinicians to consider the use of higher PEEP levels in a given patient. Third, even if a patient is found to have a large amount of recruitable lung, the study does not address how to decide which level of PEEP should be used. Finally, the use of CT is not a pragmatic solution to the calibration of PEEP in most clinical settings. The use of simpler clinical or physiological variables to predict or estimate recruitment has been suggested. In contrast to a previous report by Gattinoni et al.,¹² in the current study, the mode of injury — pulmonary (direct) or extrapulmonary (indirect) — was not helpful in predicting the potential recruitability of the injured lungs. However, data from the current study by Gattinoni et al. and another study¹¹ suggest that physiological variables (e.g., the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen) may be of greater practical value, even though the sensitivity and specificity of these findings may be less than those of CT. All these issues must be addressed before any of these approaches can come into wide clinical use.

A major message from Gattinoni et al. is that future studies investigating the optimal strategy for the setting of PEEP levels must take into account the degree to which the lungs can be recruited. In this postgenomic era, Gattinoni et al. demonstrate that sound physiological principles are still relevant to our understanding of disease processes. Such principles, along with advances in knowledge of cellular and molecular biology, should lead to improvements in the care of our critically ill patients.

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Antioxidants and the Prevention of Preeclampsia — Unresolved Issues

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Preeclampsia is a pregnancy-specific, multisystem disorder that can have considerable adverse effects on the mother and the fetus. In developing countries, preeclampsia is a major cause of death among pregnant women.¹ In the United States, 15 percent of premature births and their attendant complications are attributable to pre-

eclampsia.² Thus, numerous strategies intended to prevent preeclampsia — such as the use of antiplatelet agents and supplementation with calcium — have been studied, but without success.^{3,4}

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 preeclampsia⁵ and that increased oxidative stress, particularly in the placenta, may contribute to the endothelial dysfunction. Support for this concept comes from observations that markers of oxidative stress are increased and endogenous antioxidant capacity is reduced in women with preeclampsia.⁶ 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 of endothelial cells, and prevent or reduce the severity of preeclampsia.^{7,8}

Until recently, the data supporting the efficacy of supplementation with vitamin C and vitamin E for the prevention of preeclampsia have been limited.^{9,10} Published trials have focused on the use of antioxidants in pregnant women at high risk for developing preeclampsia. In one 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, women receiving antioxidant therapy had a lower rate of preeclampsia than controls (8 percent vs. 17 percent) and a significant improvement in markers of endothelial and placental function (the ratio of plasminogen-activator inhibitors type 1 to type 2), as compared with controls.⁹ Another small trial involving 109 women at high risk for preeclampsia — on the basis of a history of the disease or the presence of chronic hypertension, preeclampsia, or multifetal gestation — failed to demonstrate a benefit of antioxidant therapy; however, this study was stopped early because of a loss of funding and therefore was not adequately powered.¹⁰ A recently completed placebo-controlled trial in a diverse group of high-risk women demonstrated that supplementation with antioxidants did not reduce the risk of preeclampsia but was associated with a significantly higher incidence of complications — including low birth weight, fetal acidemia, gestational hypertension, and the need for intravenous antihypertensive and magnesium sulfate therapies — than in the placebo group.¹¹ The risks of some of these complications were particularly increased in women with diabetes.

In this issue of the *Journal*, Rumbold et al.¹² report the results of a large randomized trial to

assess whether supplementation with antioxidant vitamins during pregnancy reduces the risk of preeclampsia. The authors studied 1877 nulliparous pregnant women without medical or obstetrical complications who were randomly assigned to daily supplementation with vitamin C (1000 mg) and vitamin E (400 IU) or to placebo. There were no significant differences between the vitamin group and the placebo group in the risks of the three primary outcomes: preeclampsia (6.0 percent and 5.0 percent, respectively), death or a serious outcome in the infant (9.5 percent and 12.1 percent), or delivery of an infant with a birth weight below the 10th percentile for gestational age (8.7 percent and 9.9 percent).

Among the numerous secondary outcomes evaluated by Rumbold et al., antioxidant therapy was associated with a significant reduction in the risk of the respiratory distress syndrome in the infant (relative risk, 0.17; 95 percent confidence interval, 0.04 to 0.75). But the therapy was also associated with increases in the risk of hospitalization of the woman for hypertension (relative risk, 1.54; 95 percent confidence interval, 1.00 to 2.39) and the use of antihypertensive therapy (relative risk, 1.67; 95 percent confidence interval, 1.03 to 2.69). The authors also noted a higher frequency of elevated aminotransferase levels in the vitamin group than in the placebo group; however, liver-function tests were performed only in the subgroup of women with clinical indications.

Rumbold et al. concluded that the results of their study do not support the routine use of antioxidant vitamins by nulliparous, low-risk pregnant women to prevent preeclampsia or to improve perinatal morbidity. This conclusion is reasonable; however, it should be noted that this trial was powered to detect only a reduction of 50 percent or more in the risk of preeclampsia, given the incidence of this outcome of 5 percent in the placebo group. Thus, the possibility of a smaller benefit in these women cannot be ruled out.

The study by Rumbold et al. leaves open important questions about possible harmful effects of supplementation with vitamin C and vitamin E. Certain adverse maternal outcomes were more common in the antioxidant group than in the placebo group. Because multiple comparisons were made, the findings of potential harm could be explained by chance alone. The observation

that some adverse outcomes in this study were similar to those reported in the recently published trial involving pregnant women at high risk for preeclampsia,¹¹ however, is certainly of concern. The high-risk population in the latter study was heterogeneous, and it remains unclear whether some subgroups of women may be at particular risk for adverse effects of supplementation with antioxidants and whether there might still be a role for supplementation with antioxidants in low-risk women.

The Maternal–Fetal Medicine Units Network of the National Institute of Child Health and Human Development is currently conducting a multicenter trial in the United States of supplementation with vitamin C and vitamin E for the prevention of preeclampsia, with an anticipated sample of 10,000 low-risk women. 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.

Until more data are available, given the scant evidence of benefit and the potential for harm, supplemental antioxidant therapy for the prevention of preeclampsia should be limited to women enrolled in randomized trials and should not be prescribed as part of routine practice.

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