Use of vitamin C and E to prevent preeclampsia

Andrew H Shennan and Suzy Duckworth

Centre for Fetal and Maternal Medicine, St Thomas' Hospital, London, UK

Summary: A review of the evidence exploring the effects of vitamin supplementation on pre-eclampsia and its co-morbidities.

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There is a wealth of basic science research supporting the role of oxidative stress in the pathophysiology of preeclampsia and, therefore, the potential of antioxidants to reduce the risks; a desirable goal given its associated co-morbidities. Preeclampsia is a hypertensive syndrome, with associated proteinuria, affecting up to 6% of pregnant women and represents a considerable proportion of the total obstetric workload, because of the need to monitor all suspected cases. Current management hinges around detection and timely delivery. The morbidity and expense of iatrogenic delivery is also considerable, in all societies. Any intervention that could impact on its prevalence or severity would be welcomed. The proposed link between oxidative stress explaining the pathophysiology of preeclampsia has been attractive, and antioxidants are a logical intervention.

Current evidence supports an inflammatory cascade resulting from incomplete remodelling of the maternal spiral arteries, presumably mediated via genetic and immunological influences. This is associated with a high resistance circulation, and reduced placentation, causing hypoxia and/or reperfusion, with a resulting rise in markers of oxidative stress. Intermittent ischaemia promotes production of superoxides and disrupts the pathway of protein synthesis, leading to inappropriate apoptosis. Analysis of maternal protein and lipid profile has confirmed oxidative modification in the presence of preeclampsia.

We tested the potential role of antioxidants in 1999,¹ by investigating the effect of early vitamin supplementation in women at high risk for developing preeclampsia (determined by abnormal uterine doppler waveform or previous preeclampsia.) We reported reduced cellular biomarkers of endothelial and placental function (plasminogen-activator inhibitor 1 and 2.) In addition, but as a secondary finding, we reported a significant reduction in the incidence of preeclampsia in the intention-to-treat group.¹ Enthused by these findings, we undertook a larger scale study² looking specifically at the development of preeclampsia (as the primary outcome) in over 2000 high-risk women, with a range of pragmatic risk factors. Results on this occasion were very different; not only did vitamin treatment have no impact on the primary outcome (incidence of preeclampsia), but also supplementation was

associated with adverse outcomes, powered for secondary endpoints, such as low birth weight.² Women taking antioxidants were more likely to be hypertensive.

In the meantime, numerous other investigators around the world commenced trials with the same intervention. These did not demonstrate any benefit and are summarized in a meta-analysis (including our studies) reported in 2009; seven trials in nearly 6000 women. Of concern, these showed a significant increase in gestational hypertension (relative risk [RR] 1.3; 95% confidence interval [CI] 1.08–1.57) and low birth weight (RR 1.13; 95% CI 1.004–1.27) associated with vitamin C and E intake.³

Three more key studies have been recently reported, all testing a similar intervention; 400 IU vitamin E and 1000 mg vitamin C supplementation, but in differing populations. A randomized placebo controlled trial by Spinnato *et al.*⁴ recruited subjects with a past medical history of hypertension or previous preeclampsia, enrolled between 12 and 20 weeks gestation. Despite effective follow-up and good compliance in 707 women, there was no indication of benefit; 13.8% of the treatment arm and 15.6% of the placebo group developed preeclampsia, resulting in the conclusion that vitamin treatment was not to be recommended.⁴ In a planned secondary analysis of the same data, there was a suggestion that this intervention may even increase the risk of premature rupture of membranes (PROM) and preterm premature rupture of membranes (PPROM).⁵

Earlier this year, these findings were supported by a randomized, multicentre trial⁶ involving 10,154 nulliparous women, with singleton pregnancies, treated before 16 weeks gestation. Subjects were considered low risk for preeclampsia and were randomly allocated to receive either daily vitamin C and E supplements or placebo. The primary outcome was that of severe pregnancy-induced hypertension (systolic >160 mmHg, diastolic >110 mmHg) and its associated pathology (elevated liver enzymes, thrombocytopaenia, seizure, deranged renal function, fetal death or deformity).⁶ Results, again, confirmed no significant beneficial effect of vitamin supplementation (7.2% preeclampsia in treatment group versus 6.7% with placebo) building evidence against its routine use in an otherwise healthy pregnant demographic. Furthermore, the authors warn against the potential adverse effects of low birth weight and gestational hypertension, requiring the need for prescribed antihypertensive medication (demonstrated in previous

Table 1 Summary of study findings

Study	n	Population	Gestation	PET placebo (%)	PET vitamin (%)	Relative risk	95% CI
Spinnato ⁴	707	High risk, past history	12–19 + 6 weeks	15.6	13.8	0.87	0.61–1.25
Roberts ⁶	9969	Nulliparous, low risk	9–16 weeks	6.7	7.2	1.07	0.93–1.24
Villar ⁷	1365	High risk, nutritionally deplete	14–22 weeks	23.3	24.1	1.00	0.9–1.3

PET = pre-eclampsia toxemia

studies) but could benefits be seen for those women who are nutritionally deplete at baseline?

We assisted the World Health Organization in evaluating whether women considered to be malnourished could benefit from these antioxidants. In a large-scale study of high-risk women, no overall advantage could be identified. By screening 1445 women in Indian, South East Asian and South African antenatal centres, between 14 and 22 weeks gestation, it was found that the incidence of preeclampsia was comparable between groups, despite subjects being from an under-nourished general population.⁷

Table 1 summarizes the findings of these latest studies. Clearly this dose of vitamin C and E cannot be recommended. Fortunately the suggestion of adverse effects has not been consistent in these latest trials.

Given the overwhelming evidence that oxidative stress is fundamental to the preeclamptic disease process, could amendments to dosing, and timing of supplementation (e.g. preconception) yield alternative outcomes? Or could different agents, or combinations thereof, be tried? The doses of vitamin C and E are derived from their synergistic action in diseases unrelated to pregnancy, meaning the response to vitamin E may be dependent on specific isoforms. Taking pure alpha tocopherol (as a pharmaceutical agent) is known to inhibit uptake of alternate isoforms: we demonstrated reduced gamma tocopherol in pregnant women taking 400 IU alpha tocopherol. Gamma tocopherol is a major component of dietary vitamin E and known to have an anti-inflammatory action, so it is plausible that we have unwittingly increased risk, by testing such a high-dose supplement. This may account for some of the detrimental results seen, such as the 30% increased risk of hypertension found in the meta-analysis.

Many expensive trials have failed. It is unlikely that further research can be justified with similar agents, given these findings. However, both statins and selenium supplementation warrant investigation. A global approach is needed; numerous trials of vitamin C and E, costing millions of pounds have all drawn similar conclusions. As the study's initial contributors, we were not surprised: preeclampsia was not a primary outcome in our first paper,¹ and we never advocated prescribing vitamins until further evidence was available. Many clinicians refuse to randomize women and this culture has to change. We should demand more robust evidence before giving pharmacologically active agents to pregnant women.

Funding bodies need stringently controlled trials to inform practice, in a step-wise approach, before large-scale indiscriminate finance is made available. Other avenues of prophylaxis warrant further research; calcium supplementation, perhaps, has the evidence to justify such expenditure on large-scale research.

We should not dismiss the role of oxidative stress in this important disease, nor ignore the potential of antioxidant agents to help. Clinical trials provide an invaluable resource to our scientists but more scientific support is necessary to explain findings, in tandem with practical studies. This ensures negative trials are not wasted, but provide possible avenues to pursue. In our global society, it is time to have a global approach to these devastating worldwide diseases. Working together to find the answer must take priority over academic self-interest and there are initiatives to try and achieve this, such as GONET (Global Obstetrics Network). We must learn from the vitamin C and E story; fragmented effort wastes money that could have been spent on other health priorities.

REFERENCES

- 1 Chappell LC, Seed P, Briley A, *et al.* Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet* 1999;**354**:810–6
- 2 Poston L, Briley A, Seed P, *et al.* Vitamins in Pre-eclampsia (VIP) Trial Consortium. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia: randomised placebo-controlled trial. *Lancet* 2006;**367**:1145–54
- 3 Rahimi R, Nikfar S, Rezaie A, *et al.* A meta-analysis on the efficacy and safety of combined vitamin C and E supplementation in pre-eclamptic women. *Hypertens Pregnancy* 2009;**28**:417–34
- 4 Spinnato J, Freire S, Silva J, *et al.* Antioxidant therapy to prevent preeclampsia. *Am Coll Obstet Gynecol* 2007;**110**:1311–8
- 5 Spinnato J, Freire S, Silva J, *et al.* Antioxidant supplementation and premature rupture of the membranes: a planned secondary analysis. *Am J Obstet Gynaecol* 2008;**199**:433.e1–433.e8
- 6 Roberts JM, Myatt L, Spong CY, *et al.* Vitamins C and E to prevent complications of pregnancy-associated hypertension. *N Engl J Med* 2010;**362**:1282–91
- 7 Villar J, Purwar M, Merialdi M, *et al.* World Health Organisation multicentre randomised trial of supplementation with vitamins C and E among pregnant women at high risk for pre-eclampsia in populations of low nutritional status from developing countries. *BJOG* 2009;**116**:780–8

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