Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial

Lucy C Chappell, Paul T Seed, Annette L Briley, Frank J Kelly, Rosalind Lee, Beverley J Hunt, Kiran Parmar, Susan J Bewley, Andrew H Shennan, Philip J Steer, Lucilla Poston

Summary

Background Oxidative stress has been implicated in the pathophysiology of pre-eclampsia. This randomised controlled trial investigated the effect of supplementation with vitamins C and E in women at increased risk of the disorder on plasma markers of vascular endothelial activation and placental insufficiency and the occurrence of pre-eclampsia.

Methods 283 women were identified as being at increased risk of pre-eclampsia by abnormal two-stage uterine-artery doppler analysis or a previous history of the disorder and were randomly assigned vitamin C (1000 mg/day) and vitamin E (400 IU/day) or placebo at 16–22 weeks' gestation. Plasma markers of endothelial activation (plasminogen-activator inhibitor 1 [PAI-1]) and placental dysfunction (PAI-2) were measured every month until delivery. Pre-eclampsia was assessed by the development of proteinuric hypertension. Analyses were done by intention to treat, and in the cohort who completed the study.

Findings Supplementation with vitamins C and E was associated with a 21% decrease in the PAI-1/PAI-2 ratio during gestation (95% CI 4–35, p=0·015). In the intention-to-treat cohort, pre-eclampsia occurred in 24 (17%) of 142 women in the placebo group and 11 (8%) of 141 in the vitamin group (adjusted odds ratio 0·39 [0·17–0·90], p=0·02). In the cohort who completed the study (81 placebo group, 79 vitamin group), the odds ratio for pre-eclampsia was 0·24 (0·08–0·70, p=0·002).

Interpretation Supplementation with vitamins C and E may be beneficial in the prevention of pre-eclampsia in women at increased risk of the disease. Multicentre trials are needed to show whether vitamin supplementation affects the occurrence of pre-eclampsia in low-risk women and to confirm our results in larger groups of high-risk women from different populations.

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Introduction

Pre-eclampsia is an important cause of maternal morbidity and mortality[1] and accounts for more than 40% of iatrogenic premature deliveries.[2] Despite the high cost to families and health-service resources, there is no effective management strategy other than elective delivery, and no therapeutic intervention has been proven to prevent or delay the onset of this disease.[3]

The underlying pathogenetic mechanisms of pre-eclampsia are much debated. The toxaemia theory, which proposes that the compromised placenta produces substances leading to the maternal syndrome of pre-eclampsia, remains the favoured hypothesis. Trophoblast invasion is defective in pre-eclampsia,[4] and the uteroplacental circulation remains in a state of high resistance. Persistent placental underperfusion is thought to stimulate release of pre-eclamptic factors that, on gaining access to the maternal circulation, lead to vascular dysfunction. Underlying maternal vascular disease[5] and unidentified maternal[6] or paternal[7] genetic influences may confer susceptibility. Several studies have shown that the maternal vascular endothelium is the ultimate target, and there is incontrovertible evidence that the normal protective role of this cell layer becomes severely compromised.[8] Likely contributors to the maternal syndrome include lower than normal endothelial prostacyclin synthesis, decreased bioavailability of nitric oxide, greater cell permeability, and increased endothelial expression of cell adhesion molecules and prothrombotic factors.[9] All these changes are consistent with endothelial-cell activation.

Free radicals have emerged as likely promoters of maternal vascular malfunction. Reactive oxygen species, particularly superoxide anions, evoke endothelial-cell activation through many pathways.[10] Markers of lipid peroxidation, including malondialdehyde[11] and 8-epiprostaglandin-F2α[12] are increased in the plasma of women with pre-eclampsia, and the low concentrations of water-soluble and lipid-soluble antioxidants in the plasma[13] and the placenta[14] further suggest a state of oxidative stress. These observations led us to hypothesise that early supplementation with antioxidants may be effective in decreasing oxidative stress and improving vascular endothelial function, thereby preventing, or ameliorating the course of, pre-eclampsia. We therefore carried out a double-blind, randomised controlled trial of early supplementation with vitamins C and E in women at increased risk of pre-eclampsia.

This study was primarily designed to assess the potential benefit of antioxidant supplementation on markers of endothelial and placental function. Plasminogen-activator inhibitor 1 (PAI-1) is synthesised predominantly by endothelial cells and is a marker of endothelial-cell activation. PAI-1 concentrations increase progressively in the maternal plasma in normal pregnancy and are even higher in pre-eclampsia.[15] PAI-2 is synthesised by the placenta; plasma concentrations also increase progressively

in normal pregnancy but decrease with reduced placental function.[15] The ratio of PAI-1 to PAI-2 decreases in normal pregnancy, as the placental mass increases, but is high in pre-eclampsia owing to endothelial-cell activation and placental insufficiency. Reith and colleagues have suggested that the ratio may be useful as a discriminator between normal and pre-eclamptic pregnancies.[16] We therefore chose it as an index of the disease process for this study. Our secondary outcome measure was the occurrence of pre-eclampsia.

There is no widely accepted test for the prediction of pre-eclampsia. In this study we used two methods of assessment. The first, uterine-artery doppler waveform analysis provides a surrogate marker of placental perfusion[17] and has been correlated with trophoblast invasion.[18] In early pregnancy the uterine-artery waveform is characterised by a high resistance profile; in normal pregnancy the profile transforms by 24 weeks' gestation to one of low resistance. With two-stage uterine-artery doppler screening at 20 weeks and 24 weeks of gestation, a persistent high-resistance waveform is predictive of subsequent pre-eclampsia, intrauterine growth restriction, and placental abruption.[19] The women whose waveforms became normal by 24 weeks were classified as being at low risk[19] and in our study design were withdrawn from further treatment. The second criterion adopted in our trial for assessment of increased risk was a previous history of pre-eclampsia, which is associated with a significant recurrence rate; the earlier the onset of pre-eclampsia in the index pregnancy, the higher the recurrence risk.[20]

Methods

Participants

Eligible participants had an abnormal doppler waveform in either uterine artery at 18–22 weeks' gestation (defined as a resistance index ⩾95th centile for gestation or the presence of an early diastolic notch) or a history in the preceding pregnancy of pre-eclampsia necessitating delivery before 37 weeks' gestation, eclampsia or HELLP (haemolysis, elevated liver function tests, low platelets) syndrome. Reasons for exclusion were heparin or warfarin treatment, an abnormal fetal-anomaly scan, and multiple pregnancy. Uterine-artery doppler screening was done at one centre (St Thomas' Hospital) by two members of the research team (LCC and ALB). Women with a previous history were recruited from St Thomas' Hospital and the high-risk antenatal clinic at the Chelsea and Westminster Hospital. The study was approved by the local ethics committees, and all women gave informed written consent. Since we believed that early intervention was essential to achieve maximum benefit, women were randomly assigned the combination of vitamins C and E or placebo at 18–22 weeks' gestation on the basis of previous history or abnormal doppler scan. The women with a previous history who were identified at an earlier stage were randomised at 16 weeks' gestation.

Design and procedures

Tablets containing 1000 mg vitamin C were manufactured specifically for this study by Peter Black Healthcare Ltd (Swadlincote, Derbyshire, UK) and coated so that the characteristic tart taste of ascorbic acid was masked. Similarly coated placebo tablets of identical appearance, containing microcrystalline cellulose, were manufactured by the same company. Women were given instructions to swallow the tablets whole without chewing or crushing them. Levine and colleagues[21] reported an improvement in endothelium-dependent vasodilation after administration of 2000 mg/day ascorbic acid, but kinetic studies show that plasma saturation occurs at 1000 mg/day.[22] We therefore chose the lower dose for this study. Capsules containing 400 IU natural-source vitamin E and placebo capsules of identical appearance (containing soya-bean oil) were provided by Henkel

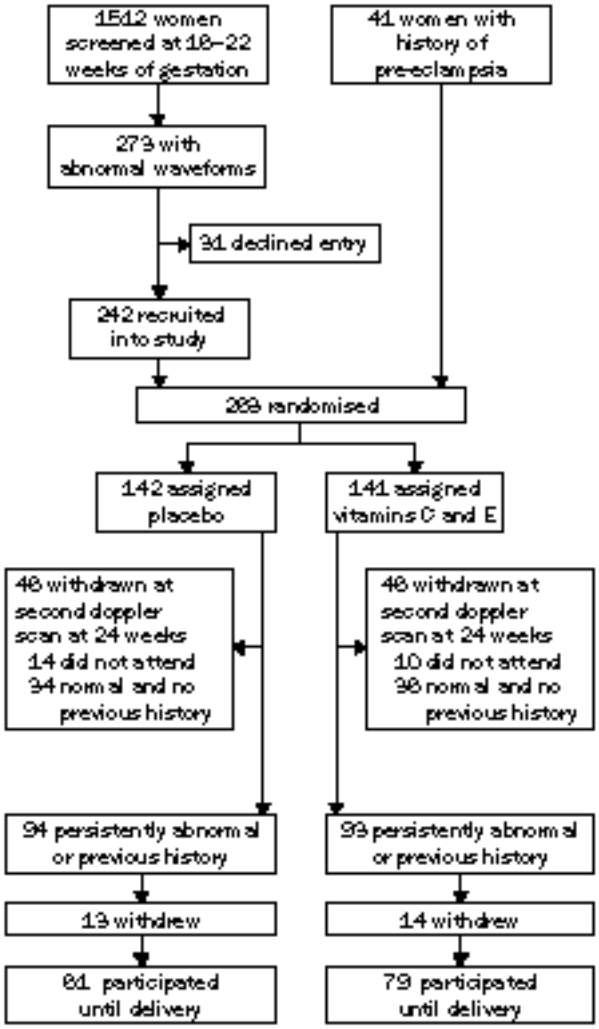

Figure 1: **Trial profile**

Ireland Ltd. 400 IU α-tocopherol effectively decreases oxidation of LDL,[23] and beneficial effects of this dose have been shown in patients with established coronary-vessel disease.[24] We chose to use the combination of vitamins, because vitamin C, a water-soluble antioxidant, and vitamin E, a lipid-soluble antioxidant, act synergistically in vitro.[25,26] All tablets and capsules were kept in the pharmacy departments and dispensed by their staff.

Women were assigned on an individual basis to both vitamins C and E or to both placebo treatments. They remained on the same allocation throughout the pregnancy if they continued in the study. A computer-generated randomisation list was drawn up by the statistician (PTS), with randomisation in blocks of ten, and given to the pharmacy departments. The researchers responsible for seeing the pregnant women (LCC and ALB) allocated the next available number on entry into the trial (in the ultrasound department or antenatal clinic), and each woman collected her tablets direct from the pharmacy department. The code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete.

All women with abnormal results of doppler waveform analysis were asked to return for a second scan at 24 weeks' gestation; those with a normal waveform at 24 weeks' gestation stopped treatment and were withdrawn from the study. The remaining women (with persistently abnormal waveforms) and those with a previous history of pre-eclampsia were seen every 4 weeks through the rest of pregnancy. Blood samples were taken at each visit. These visits were additional to the routine antenatal care arranged for the women. A record of the uterine-artery doppler results, the woman's participation in the research study, and each visit to the research team was made in the antenatal notes. If any pregnancy

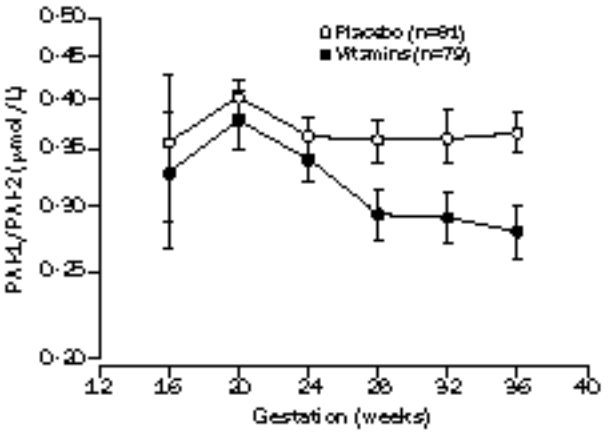

Figure 2: **Mean PAI-1/PAI-2 during gestation in completed-study cohort**

Values at 16 weeks' gestation are from women recruited on previous history at this stage (n=11). PAI-1/PAI-2 is expressed on a logarithmic scale. Error bars show SE.

complications arose, the woman was referred to her obstetric team for further management.

At each visit, venous blood was drawn from an uncuffed arm into two tubes, one containing trisodium citrate (ratio one to nine), for measurement of PAI-1 and PAI-2, and the other containing lithium heparin, for measurement of ascorbic acid and α-tocopherol. The tubes were placed immediately on ice, and centrifuged at 4°C within 3 h of sampling. Samples of the supernatant were removed and stored at -70°C until analysis. Two volumes from each heparinised sample were mixed with cold 2% metaphosphoric acid and centrifuged at 4°C. Volumes of the supernatant were removed and stored at -70°C.

PAI-1 and PAI-2 antigen concentrations were measured by ELISA (Tintelize, Biopool International, Umeå, Sweden). The lower limits of detection were 0·5 μg/L (PAI-1) and 6·0 μg/L (PAI-2). The within-assay coefficients of variation were 3·3% (PAI-1) and 3·7% (PAI-2) and the between-assay coefficients of variation were 2·9% and 3·0%. Ascorbic acid was measured by means of reverse-phase high-performance liquid chromatography with electrochemical detection.[27] The lower limit of detection was 5 nmol/L and the coefficients of variation within and between assays were 2·2% and 3·5%. α-tocopherol was measured by means of reverse-phase high-performance liquid chromatography with spectrophotometric detection at 292 nm.[28] The lower limit of detection was 10 nmol/L and the coefficients of variation within and between assays were 2·1% and 3·9%.

The primary outcome measure was the ratio PAI-1/PAI-2 and the secondary outcome measure the frequency of pre-eclampsia, which was defined prospectively according to the guidelines of the International Society for the Study of Hypertension in Pregnancy.[29] Gestational hypertension was defined as two recordings of diastolic blood pressure of 90 mm Hg or higher at least 4 h apart, and severe gestational hypertension as two recordings of diastolic blood pressure of 110 mm Hg or higher at least 4 h apart or one recording of diastolic blood pressure of at least 120 mm Hg. Proteinuria was defined as excretion of 300 mg or more in 24 h or two readings of 2+ or higher on dipstick analysis of midstream or catheter urine specimens if no 24 h collection was available. Women were classified as previously normotensive or with chronic hypertension before 20 weeks' gestation. For previously normotensive women, pre-eclampsia was defined as gestational hypertension with proteinuria and severe pre-eclampsia as severe gestational hypertension with proteinuria. For women with chronic hypertension, superimposed pre-eclampsia was defined by the new development of proteinuria. For this study, all women were allocated to an outcome category on the basis of their blood pressure before delivery.

Other adverse perinatal outcomes were: placental abruption (the presence of retroplacental clot at delivery and abdominal pain, bleeding, or both immediately before delivery); spontaneous preterm delivery (before 37 weeks' gestation); intrauterine death; and small-for-gestational-age infants (on or below the 10th centile for gestation and sex, corrected for maternal height, weight, parity, and ethnic origin by customised centile charts[30]).

	Placebo (n=142)	Vitamins C and E (n=141)
Mean (SD) age (years)	29·8 (5·6)	28·9 (6·4)
Smokers	14 (10%)	22 (16%)
Mean (SD) body-mass index (kg/m²)	25·6 (5·6)	25·3 (6·0)
Mean (SD) blood pressure (mm Hg)		
Systolic	110 (12)	112 (15)
Diastolic	68 (10)	67 (11)
Parity		
0	87 (61%)	91 (65%)
1	42 (30%)	39 (28%)
2	8 (6%)	9 (6%)
>2	5 (4%)	2 (1%)
New partner (If multiparous)	11/55 (20%)	12/50 (24%)
Ethnic origin		
European	87 (61%)	97 (69%)
African	30 (21%)	14 (10%)
Caribbean	21 (15%)	24 (17%)
Other	4 (3%)	6 (4%)
Previous history of pre-eclampsia	21	20
Coexisting disease		
Essential hypertension	7 (5%)	10 (7%)
Lupus/antiphospholipid syndrome	1 (1%)	4 (3%)
Diabetes	3 (2%)	2 (1%)
Medication before 20 weeks' gestation		
Methyldopa	6 (4%)	6 (4%)
Aspirin	7 (5%)	8 (6%)
Multivitamins	8 (6%)	11 (8%)
Doppler analysis		
Mean (SD) resistance index	0·64 (0·10)	0·65 (0·10)
Unilateral notch	44/121 (36%)	42/121 (35%)
Bilateral notch	77/121 (64%)	79/121 (65%)

Table 1: **Baseline characteristics of intention-to-treat cohort**

Statistical analyses

No longitudinal data on PAI-1/PAI-2 were available. The initial power calculation was based, therefore, on cross-sectional values for PAI-1 in pregnancy:[15] a mean of 79·2 μg/L (SD 19·7) for normotensive women and 122·0 μg/L (SD 34·4) for women with pre-eclampsia. A sample size of 38 women in each group would be required to detect a clinically useful 30% reduction in PAI-1 (α=0·05, β=0·10). The predictive value of the combined screening tests was estimated at 20%; therefore, a sample of 209 women in each group would be needed (this estimate allows for a 10% drop-out rate). The protocol planned one interim analysis on the primary outcome measure of PAI-1/PAI-2 when full data to delivery were available for half the intended sample, with an O'Brien and Fleming rule.[31] The trial would be stopped only if p was less than 0·005 for the difference in rate of change of PAI-1/PAI-2. At this interim analysis, the main treatment effect was significant at p=0·002. Therefore, recruitment was stopped but women already entered continued on randomised treatment.

Data were collected and laboratory analyses carried out without awareness of the randomisation. Three clinicians assessed the masked data and assigned an outcome based on blood pressure to each participant. Log transformations were used to give normal distribution of PAI-1/PAI-2 and α-tocopherol concentrations. Inspection of data for each individual showed that log PAI-1/PAI-2 and α-tocopherol were approximately linear during gestation. By standard techniques,[32] each woman's values of PAI-1/PAI-2 were summarised as the weekly rate of change, by least-squares regression. Analysis of covariance (ANCOVA) was used to produce unbiased estimates of the treatment effect at each visit, with correction for PAI-1/PAI-2 at randomisation. Adjustment was made for baseline variables by linear regression.[33] Robust SEs[34] were used to correct for non-normality in estimating SE and CI. Ascorbic acid and α-tocopherol data were summarised as arithmetic and geometric means, respectively.

	Intention to treat		Completed study	
	Placebo (n=142)	Vitamins C and E (n=141)	Placebo (n=81)	Vitamins C and E (n=79)
Total with pre-eclampsia	24 (17%)	11 (8%)	21 (26%)	6 (8%)
Women previously normotensive				
Total	135	131	74	74
Normal blood pressure	103	104	50	56
Gestational hypertension	13	16	8	14
Mild pre-eclampsia	13	5	12	3
Severe pre-eclampsia	5	3	3	1
Lost to follow-up	1	3	0	0
Women with chronic hypertension				
Total	7	10	7	5
No change in blood pressure	0	4	0	2
Severe gestational hypertension	1	3	1	1
Superimposed pre-eclampsia	6	3	6	2

Table 2: **Occurrence of pre-eclampsia in intention-to-treat and completed-study cohorts**

Because some women were withdrawn from the trial by design, the clinical outcomes were analysed both by intention to treat and by completion of the study. The longitudinal analysis of the biochemical markers was done only for women who continued in the study, with adjustment for baseline measurements (ANCOVA). Forward stepwise regression with $p<0{\cdot}1$ for entry was used to select the baseline variables that were related to the final value of PAI-1/PAI-2. Adjustment was made with these four variables (diastolic blood pressure, smoking, ethnic origin, and chronic hypertension) by logistic regression. All computing used the statistical package Stata (version 5.0). Birthweight centiles were calculated with Gestation-Related Optimum-Weight software (Queen's Medical Centre, Nottingham, UK).

Results

Doppler screening was done on 1512 women (figure 1); 242 women with abnormal uterine-artery doppler waveforms and 41 with a history of pre-eclampsia in a previous pregnancy were recruited. 72 (30% of the 242 women with abnormal waveforms) were withdrawn at 24 weeks' gestation because they had normal uterine-artery scans at the second stage of screening; 24 women did not attend for the second scan. A further 27 women withdrew from the trial after 24 weeks' gestation: seven transferred their antenatal care to another area; nine did not want to continue taking tablets throughout pregnancy; and 11 women did not return for further visits despite several reminders.

The intention-to-treat cohort included all 283 women randomised at their first visit, although this cohort included the women subsequently withdrawn from the study on the basis of normal doppler waveform. The baseline characteristics of these women are shown in table 1. The completed-study cohort consisted of 160 women who participated in the study until delivery (figure 1); these women were the group in whom PAI-1/PA1-2 was assessed longitudinally.

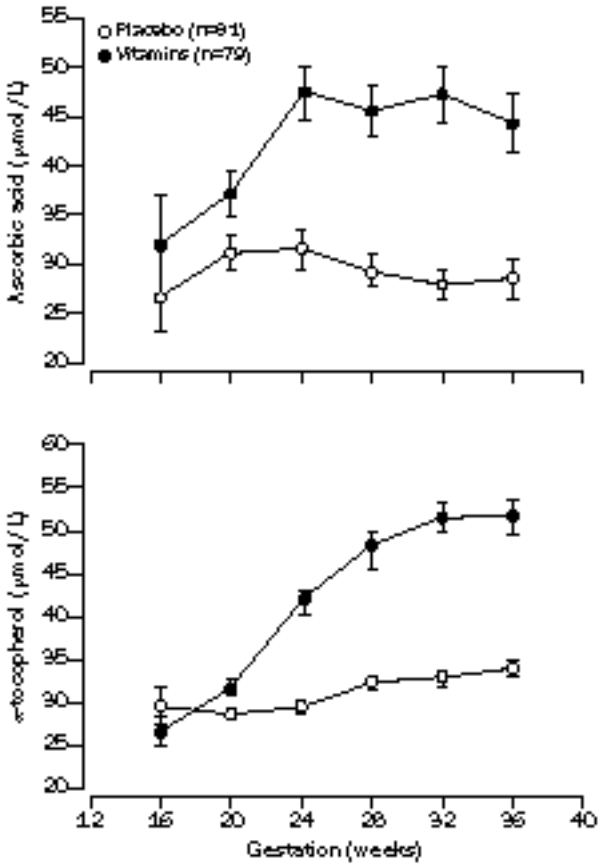

Figure 3: **Mean plasma ascorbic acid and α-tocopherol concentrations during gestation in completed-study cohort**
Values at 16 weeks' gestation are from women recruited on previous history at this stage (n=11). Error bars show SE.

Vitamin supplementation was associated with a 21% (95% CI 4–35, $p=0{\cdot}015$) reduction in PAI-1/PAI-2 over gestation compared with the placebo group (figure 2). Within the treated group, plasma ascorbic acid concentration increased by 32% (20–44) from baseline values and plasma α-tocopherol concentration increased by 54% (45–63) from baseline (figure 3). At 36 weeks' gestation, plasma concentrations of ascorbic acid were 34% (24–44) higher and α-tocopherol concentrations 41% (34–49) higher in the vitamin group than in the placebo group.

In intention-to-treat analysis, the number of women who developed pre-eclampsia differed significantly between the

	Intention to treat		Completed study	
	Placebo (n=142)	Vitamins C and E (n=141)	Placebo (n=81)	Vitamins C and E (n=79)
Adverse perinatal outcome				
Placental abruption	3	1	3	1
Spontaneous preterm delivery	5	6	2	3
Intrauterine death	2	1	2	1
Small-for-gestational-age infants	45 (32%)	33 (23%)	29 (36%)	20 (25%)
Mean (SD) maximum blood pressure before delivery (mm Hg)				
Systolic	131 (22)	133 (19)	138 (25)	134 (18)
Diastolic	84 (16)	86 (17)	88 (17)	87 (18)
Median (IQR) perinatal characteristics				
Gestational age at delivery (weeks)	39·7 (38·5–40·9)	39·4 (38·2–40·7)	39·3 (38·0–40·7)	39·4 (37·5–40·6)
Birthweight (g)	3160 (2760–3464)	3100 (2765–3430)	3060 (2750–3400)	3020 (2450–3474)
Birthweight (centile)	25 (7–51)	29 (11–55)	28 (8–54)	20 (7–42)

Table 3: **Perinatal outcomes and characteristics in intention-to-treat and completed-study cohorts**

	Placebo group			Vitamin group		
	Normal outcome (n=94)	Gestational hypertension (n=13)	Pre-eclampsia (n=24)	Normal outcome (n=93)	Gestational hypertension (n=16)	Pre-eclampsia (n=11)
Mean (SD) maximum blood pressure before delivery (mm Hg)						
Systolic	120 (10)	145 (13)	164 (25)	124 (10)	148 (10)	163 (19)
Diastolic	75 (7)	101 (7)	107 (12)	77 (6)	101 (6)	109 (10)
Median (IQR) maximum urine protein excretion (mg/24 h)	0	0 (0–103)	890 (580–3050)	0	40 (0–195)	565 (380–1348)
Median (IQR) perinatal characteristics						
Gestational age at delivery (weeks)	40·1 (39·3–41·0)	39·6 (37·2–41·0)	37·5 (34·5–38·7)	40·1 (38·9–41·0)	38·6 (38·0–39·9)	36·1 (32·7–39·0)
Birthweight (g)	3285 (3000–3553)	3210 (2865–3540)	2670 (2073–3010)	3220 (2950–3588)	3060 (2640–3381)	2200 (1340–2940)
Birthweight (centile)	30 (11–56)	28 (7–60)	12 (3–30)	32 (14–56)	16 (7–43)	6 (1–51)

Table 4: **Perinatal outcomes and characteristics in the intention-to-treat cohort according to clinical outcome**

placebo and vitamin groups (24 of 142 [17%] *vs* 11 of 141 [8%]; adjusted odds ratio 0·39 [95% CI 0·17–0·90], p=0·02; table 2). The difference in outcome was more pronounced in analysis of the women who completed the study (21 of 81 [26%] *vs* six of 79 [8%]; adjusted odds ratio 0·24 [0·08–0·70], p=0·002; table 2).

Table 2 also shows subclassification of outcome in both cohorts, assessed on the basis of blood pressure. Table 3 describes other adverse events, maternal blood-pressure data, and perinatal characteristics. There were fewer small-for-gestational-age infants in the vitamin group than in the placebo group, but this difference did not achieve significance (p=0·12).

Table 4 shows a subanalysis of blood-pressure data and perinatal characteristics in the intention-to-treat cohort. Women with pre-eclampsia were compared with those who had gestational hypertension and those remaining in the trial who were normotensive and had a normal perinatal outcome (women with spontaneous preterm delivery, placental abruption, intrauterine growth restriction identified before delivery, or intrauterine death were excluded). Compared with those who had gestational hypertension, the women who had pre-eclampsia had babies at a significantly earlier gestational age (2·0 weeks [0·9–3·3]) and of significantly lower birthweight (560 g [230–932]). There was no significant difference in these variables in the pre-eclamptic women between the placebo and vitamin groups.

Discussion

In this randomised controlled trial, supplementation throughout the second half of pregnancy with vitamins C and E in women at increased risk of pre-eclampsia had significant beneficial effects on biochemical markers of the disease, and there was a significant reduction in the proportion of women with pre-eclampsia.

The doses of vitamin C and vitamin E chosen for the study resulted in significant increases in plasma concentrations of ascorbic acid and α-tocopherol. There are no reported contraindications of supplementation with vitamin C or vitamin E in pregnancy. Vitamin E is reported not to have any detrimental effects on preterm neonates[35] or pregnant women.[36] Numbers of adverse perinatal outcomes were small in this study, but were similar in the two groups.

Antioxidants have been proposed as a potentially advantageous prophylactic measure for pre-eclampsia.[37] Two previous studies of vitamin supplementation, both in women with established severe early-onset pre-eclampsia reported no substantial clinical benefit; Stratta and colleagues[38] used 100–300 mg/day vitamin E in a non-randomised trial, and Gulmezoglu and colleagues[39] used 1000 mg/day vitamin C, 800 IU/day vitamin E, and 200 mg/day allopurinol in a randomised controlled trial. However, Gulmezoglu and colleagues[39] reported a trend towards later delivery in the treated group. Since late intervention may have precluded maximum benefit, both reports proposed earlier initiation of therapy.

In view of the evidence that endothelial and placental dysfunction in pre-eclampsia results from oxidative stress, this trial was designed to address the hypothesis that antioxidants may lead to an improvement in these abnormalities. The occurrence of pre-eclampsia was a secondary outcome marker; we expected that improvement in biochemical function in this small study, if proven, would indicate a much larger multicentre study to investigate outcome. The ratio of PAI-1 to PAI-2 was adopted as the primary outcome measure because it reflects both endothelial and placental function. The results show clearly that supplementation with vitamins C and E lowered this biochemical indicator of disease in women at risk, thereby supporting the hypothesis. The associated improvement in clinical outcome strongly suggests a role for reactive oxygen species in the pathophysiology of the maternal syndrome.

This study did not directly address the mechanisms by which vitamins C and E decrease PAI-1/PAI-2 and reduce the risk of pre-eclampsia. Both antioxidants are inhibitors of reactive oxygen species, and a likely explanation of their effect is through this mechanism. Ascorbic acid is a potent scavenger of superoxide radicals,[40] and may thus have helped preserve nitric oxide. In addition, both α-tocopherol and ascorbic acid decrease LDL oxidation,[41,42] and ascorbic acid can help to maintain intracellular glutathione concentrations.[43] One, or more, of these mechanisms may underlie the lower PAI-1/PAI-2 in the supplemented group.

The use of screening methods to identify women at increased risk of pre-eclampsia had the result that 26% of the placebo group developed the disease. The estimated incidence in the general primigravid pregnant population with the definition of the International Society for the Study of Hypertension in Pregnancy is 2%.[44] We conclude therefore that a high-risk population can be successfully identified on the basis of uterine-artery doppler screening and previous history of the disease. This finding may be helpful in the design of future trials of preventive treatment. Although there is potential for treatment to affect transformation of the uterine-artery doppler waveform between 20 and 24 weeks of gestation, vitamins C and E are unlikely to have had any effect in our study, given the similar waveform normalisation rates in the placebo and treatment groups. Randomisation at 20 weeks rather than 24 weeks of gestation ensured that women at increased risk started taking vitamins or placebo at the earliest possible

stage of gestation. Late initiation of therapy after 24 weeks' gestation has been a criticism of some previous trials,[3] because pathophysiological processes are likely to begin many weeks before clinical manifestation of pre-eclampsia.

The definitions of gestational hypertension and pre-eclampsia must be carefully addressed in studies of this kind. There is still controversy over the criteria used to define pre-eclampsia and dissatisfaction with the use of two clinical endpoints (hypertension and proteinuria) in a disorder now accepted to be a multisystem disease. The definitions of the International Society for the Study of Hypertension in Pregnancy used in this study are a consensus statement and are widely used in studies of pre-eclampsia. The distinction between gestational hypertension and pre-eclampsia was emphasised by the clear differences in gestational age and birthweight centiles between these two groups.

Although the results of this study may have substantial implications for the future management of pregnancy, a multicentre clinical trial with large numbers of patients is needed before any decisions can be made about clinical management. Such a trial should include investigation of optimum dosing and timing of administration, and longer-term follow-up of the infants. Assessment of risk on the basis of uterine-artery doppler screening may not be feasible in all hospital settings. Any future multicentre trial should also consider the potential use and cost-benefit of supplementation with vitamins E and C in all pregnant women.

Contributors

Lucy C Chappell was the principal investigator and Lucilla Poston the principal supervisor. Paul T Seed, Frank J Kelly, Beverley J Hunt, and Susan J Bewley assisted in the design of the study and obtaining funding. Paul T Seed was responsible for the statistical analyses. Susan J Bewley, Andrew H Shennan, and Philip J Steer provided clinical supervision. All these investigators contributed to data interpretation and preparation of the paper. Annette L Briley assisted with recruitment and data collection. Rosalind Lee and Kiran Parmar did the laboratory analyses.

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Will to live in the terminally ill

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Summary

Background Complex biomedical and psychosocial considerations figure prominently in the debate about euthanasia and assisted suicide. No study to date, however, has examined the extent to which a dying patient's will to live fluctuates as death approaches.

Methods This study examined patients with cancer in palliative care. Will to live was measured twice daily throughout the hospital stay on a self-report 100 mm visual analogue scale. This scale was incorporated into the Edmonton symptom assessment system, a series of visual analogue scales measuring pain, nausea, shortness of breath, appetite, drowsiness, depression, sense of well-being, anxiety, and activity. Maximum and median fluctuations in will-to-live ratings, separated by 12 h, 24 h, 7 days, and 30 days, were calculated for each patient.

Findings Of 585 patients admitted to palliative care during the study period (November, 1993, to May, 1995), 168 (29%; aged 31–89 years) met criteria of cognitive and physical fitness and agreed to take part. The pattern of median changes in will-to-live score suggested that will to live was stable (median changes <10 mm on 100 mm scale for all time intervals). By contrast, the average maximum changes in will-to-live score were substantial (12 h 33·1 mm, 24 h 35·8 mm, 7 days 48·8 mm, 30 days 68·0 mm). In a series of stepwise regression models carried out at 12 h, 24 h, and 1–4 weeks after admission, the four main predictor variables of will to live were depression, anxiety, shortness of breath, and sense of well-being, with the prominence of these variables changing over time.

Interpretation Among dying patients, will to live shows substantial fluctuation, with the explanation for these changes shifting as death approaches.

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Introduction

A patient's state of mind is the single most important factor in understanding of a request for physician-hastened death. Euthanasia and physician-assisted suicide raise critical issues about the psychological underpinnings of death-hastening requests. This study is part of a programme of research that has addressed various psychiatric dimensions of palliative care.[1–4] The defining characteristic of this research has been that dying patients have served as the key informants. These studies have helped establish the prevalence of clinical depression among the terminally ill[1] and the extent to which dying patients may endorse a desire for death.[2] A limitation of the latter study was its largely cross-sectional design, with very little information on whether there are fluctuations in patients' will to live over the course of a terminal disease. Thus, although we now know that occasional or fleeting thoughts of a desire for death are common among the terminally ill and that some of these patients express a genuine desire for death, little is known about how these thoughts may change over the course of time.[2] Although the stability and determinants of will to live in a palliative-care setting are fundamental issues, they have received surprisingly little critical attention.

No previous studies have specifically examined the issue of will to live per se, but a few have addressed constructs that may serve as its proxy. Some studies, using responses to hypothetical scenarios before and after treatment, have documented the extent to which treatment of depression can favourably influence a patient's endorsment of life-sustaining therapy.[5,6] Other studies have shown a strong association between interest in physician-assisted suicide and depression,[2,4,7,8] pain,[2,7,9–11] and other distressing symptoms.[7,9–13] To date, only one small study reported that a desire for death may fluctuate over a brief period in a palliative-care setting.[2] Our study prospectively addressed the temporal stability of will to