**A novel dietary intervention to optimise vitamin E intake of pregnant women to 15mg/day.**

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**Abstract**

Associations have been reported between sub-optimal maternal vitamin E intake during pregnancy and childhood asthma. This pilot study conducted in 2008/9 investigated the feasibility and acceptability of a food based randomised controlled trial in pregnant women to optimise dietary vitamin E intake to 15mg/day. A food based intervention using ‘food exchanges’ to individually optimise dietary vitamin E intake to 15 mg/day was developed and included in an advice booklet. 43 pregnant women with a personal/partner history of asthma were recruited at 12 weeks gestation and randomised to food based intervention or a control group until 20 weeks gestation. A dietitian assessed the vitamin E intake of 22 women and provided tailored advice on food based exchanges to optimise their intake to 15mg/day. The 21 control women were not given dietary advice. The food based intervention was completed by 19 women and increased mean vitamin E intake: food diary data 7.13mg/day (95% CI 5.63-18.6) to 17.4mg/day (14.4-20.5), p<0.001, food frequency questionnaire (FFQ) data 10.9mg/day (8.50-13.3) to 15.9mg/day (12.4-19.4), p=0.008. Mean vitamin E intake did not change in the control women: FFQ data 12.3mg/day (10.4-14.1) to 12.4mg/day (10.1-14.8), p>0.1. This pilot study demonstrates the feasibility and acceptability of a food exchange based intervention to optimise dietary vitamin E intake during pregnancy. Further work is required to determine whether this intervention, if sustained for the rest of pregnancy, reduces the likelihood of childhood asthma. The methodology used in the design of this novel food based intervention could be transferred to other nutrients.

**Key words**: pregnancy, vitamin E, intervention, controls, dietary, asthma**Introduction**

It has been hypothesised that changes in diet have contributed to the recent marked increase in asthma (3,4) with a recent systematic review concluding that there is strong supportive evidence to prioritise trials of increasing maternal vitamin E intake during pregnancy as a potential population based intervention to reduce childhood asthma (10). In this article we describe the development of a novel food based intervention to optimise maternal vitamin E intake during pregnancy to 15mg/day and the results of piloting the intervention in a short term randomised controlled trial.

We are exploring the possibility of conducting a trial of vitamin E modification in pregnancy in relation to childhood asthma. Several considerations led us to choose a food based intervention to optimise maternal vitamin E intake to 15mg/day instead of vitamin E supplementation.

1). Previous antioxidant supplementation trials have failed to demonstrate beneficial effects on cardiovascular disease, cancer and all-cause mortality despite reports of beneficial associations from observational studies (15). Recently, a pre-eclampsia trial of vitamin E supplementation during pregnancy reported that vitamin E supplementation (133mg/day) during pregnancy does not reduce the incidence respiratory outcomes in children up to 2 years (16). These studies suggest that isolated maternal vitamin E supplementation during pregnancy is unlikely to have a beneficial effect on childhood asthma.

2). A food based intervention to enhance a dietary pattern that increases vitamin E intake embraces the complexity of diet by pragmatically accepting that the intervention not only increases vitamin E intake but also the intake of naturally associated nutrients. Indeed a strength of such an intervention is that other nutrients (e.g. PUFA, vitamin D) or the complex package of nutrients may be essential for any beneficial effect.

3). In the UK there are no explicit recommendations for vitamin E intake but in the US the recommended daily allowance for women is 15mg/day, and is unchanged by pregnancy (14).

Because of the innovative nature of such a food based intervention it was considered necessary to pilot the randomised controlled trial (RCT) of the food based intervention in pregnancy to assess the feasibility of a larger definitive RCT. A secondary aim was to confirm that the food based intervention not only increases vitamin E intake but also the intakes of other naturally associated nutrients.

**Methodology**

Participants

We envisage that a future RCT investigating whether vitamin E modification during pregnancy reduces the likelihood of childhood asthma would focus on women pregnant with a child at high risk of developing asthma. These women are likely to be more motivated to participate and comply with the intervention, a further advantage is that study size is minimised because of the higher incidence of asthma in their offspring. Therefore in this pilot study pregnant women with a personal and/or partner history of asthma attending the Aberdeen Maternity Hospital for routine antenatal care were recruited at 12 weeks gestation. We aimed to recruit and randomise 40 subjects; 20 intervention, 20 controls. Subjects were allocated in accordance with a pre-recruitment computer generated randomisation sequence. Vitamin E supplement use was an exclusion criterion. All participants provided written informed consent and ethical approval was granted by the North of Scotland Research Ethics Service (08/S0802/130).

Procedures

The pilot randomised control trial is summarized in figure 1. All participants had their dietary and serum vitamin E status assessed at 12 and 20 weeks gestation by validated semi-quantitative food frequency questionnaire (FFQ) (Scottish Collaborative Group version 6.5) (17) and measurement of serum α-tocopherol.

*Control group*

Control group participants received no dietary advice, they met with the dietitian at 12 and 20 weeks gestation for blood sampling and completion of FFQs.

*Intervention group*

In addition to the 12 and 20 week FFQ and blood sampling, the intervention group women received the food based intervention to individually optimize vitamin E intake to 15mg/day.

The study dietitian developed the dietary intervention by using food composition tables to identify vitamin E rich foods and the portion sizes containing 2mg vitamin E. It was also felt important that the intervention should be designed with the pregnant woman, her family and national recommendations in mind. An illustrated advice booklet was developed containing information on food portions with 2mg of vitamin E including breakfast cereals, spreads, cooking oils, vegetables, fruit, fish, sauces, snacks, nuts and seeds. Practical examples of breakfast, lunch and dinner options to increase vitamin E intake by 2mg were also included. At recruitment intervention group women were instructed on how to complete a 4 day non-weighed diet diary (3 weekdays, 1 weekend day) using photographic examples of food measures. The diary was analysed using WINDIETS (Univation Ltd, Aberdeen, UK) and in a subsequent face-to-face consultation the dietitian provided feedback on macro and micronutrient intakes and addressed any issues raised (e.g. body weight, intakes of iron, calcium). The diet diary was used to highlight existing dietary sources of vitamin E enabling the dietitian to suggest ways each woman could increase her vitamin E intake using foods already included in her diet. This tailoring of individual diets minimised the impact of the dietary intervention on the rest of the family. Suggested changes were reinforced by the advice booklet that contained pictures of ‘exchanges’ of foods containing vitamin E and the amount needed to provide 2mg of vitamin E (e.g. 1 tablespoon potato salad, 1 medium portion of Sultana Bran). The number of times per day any of these food exchanges should be eaten was tailored to increase the baseline intake to 15 mg/day, e.g. a woman consuming 7mg/day vitamin E would be advised to add four 2mg exchanges each day. Overweight or obese women were advised not to include high energy vitamin E sources in their diet. Common suggestions included changing/increasing breakfast cereals, changing brands of soft margarine and/or cooking oil, adding nuts/seeds to cereals, including coleslaw, crisps in lunches. Intervention group women were contacted by telephone at 15-16 weeks gestation to assess progress, identify problems and provide further advice. At 18 weeks gestation these women completed a second diet diary, the analysis of which was imparted at the 20 week scan visit by the dietitian.

*Qualitative subject study evaluation*

At the end of the study participating women were invited to take part in a semi-structured interview conducted by one of the researchers to discuss the study, the dietary intervention, any concerns about the study and suggestions to improve the study. Interviews were digitally recorded, transcribed and analysed for key themes.

*Statistical considerations*

Study statistical power was based on our previous study of pregnant women (8,9). With a mean (SD) vitamin E intake of 9.3mg/day (8.7), 20 intervention subjects were needed to detect an increase in vitamin E intake of 5.7mg/day (i.e. to 15mg/day) with 80% power at the 5% level of significance.

**Results and discussion**

Study recruitment is summarised in figure 2. 172 women were approached, 61(35%) had a personal and/or partner history of asthma. 18(30%) of these eligible women declined, 43 were randomised: 21 control, 22 intervention. Participants tended to be older than those declining [median age 29.0years (interquartile range 26.0-34.0) vs 25.5years (22.0-30.5)] and of higher socio-economic status (Scottish Index of Multiple Deprivation (20) [median decile 8(5-9) vs 5(3-9)]), none of these differences were statistically significant (p>0.2). 39(91%) women completed the study: 20(95%) control, 19(86%) intervention.

The results of the vitamin E analyses from the diet diaries, FFQs and serum are given in table 1.

*Diet diary (table 1).*

The food based intervention increased mean dietary vitamin E intake from 7.13mg/day (95% CI 5.63-18.6) at 12 weeks gestation to 17.4mg/day (14.4-20.5), at 18 weeks gestation, p<0.001. Energy adjusted dietary vitamin E intake increased from 6.41mg/day (5.30-7.52) to 17.0mg/day (14.0-20.0), p<0.001. Analysis on an intention-to-treat basis, assuming no dietary change for non-completers, mean vitamin E intake increased from 7.13mg/day (5.93-8.33) to 15.6mg/day (12.5-18.6) p<0.001 and mean energy adjusted vitamin E intake increased from 6.41mg/day (5.52-7.30) to 15.1mg/day (12.1-18.1), p<0.001. At 18 weeks gestation 4(21%) of participants had a vitamin E intake <14mg/day and 5(26%) >20mg/day. This finding suggests that any proposed pregnancy vitamin E RCT should include further diet diary assessments between 18 weeks gestation and delivery to ensure that the food based intervention is sustained throughout pregnancy, and to further tailor dietary intake to 15mg/day, thus optimising vitamin E intake and preventing excessive vitamin E intake.

In addition to vitamin E, associations have been reported between maternal polyunsaturated fatty acids (particularly n-3 PUFA), selenium and zinc status during pregnancy and childhood wheeze and asthma (5,9, 24-28). In our pilot study the food based intervention not only increased vitamin E intake but also increased the mean intakes of polyunsaturated fatty acids, 10.2g/day (8.7-11.7) to 23.1g/day (20.1-26.1) p<0.001, selenium 33.6ug/day (28.1-39.1) to 48.7ug/day (39.7-57.8), p=0.001 and zinc 7.30mg/day (6.36-8.34) to 8.58mg/day (7.37-9.78), p=0.014. This finding suggests that the previously reported associations between childhood asthma and maternal intake of these individual nutrients should not be viewed in isolation and that they may indeed reflect an association with a dietary pattern. It seems likely that an advantage of the novel food based intervention is that by promoting a dietary pattern it also increases the intake of other nutrients that have been reported to be associated with childhood wheeze and asthma. Indeed although the focus of the chosen dietary intervention was vitamin E it may be that any potentially beneficial effect of the dietary intervention is dependent on the complex mixture of naturally associated nutrients.

The qualitative study evaluation suggested that the food based intervention was more acceptable than a supplement intervention. Only 3 of 39 women commented that they would be happy to take a supplement, many women (21/39, 54%) mentioned needing reassurance that there would be no adverse effects to themselves or the baby preferring the more ‘natural’ option of changing their diet.

*Food frequency questionnaire (table 1).*

The FFQ data from the control group revealed no significant change in vitamin E intake (nor any other nutrients) between 12 and 20 weeks gestation suggesting that informing women of a vitamin E intervention study does not change dietary behaviour, a finding pertinent to any future RCT using a food based vitamin E intervention. In the intervention group the FFQ data were consistent with diet diary data showing increases in vitamin E and polyunsaturated fatty acid intakes.

Mean vitamin E intakes of the control and intervention groups did not differ at recruitment, 12.3mg/day (10.4-14.1) and 10.9mg/day (8.50-13.3), p=0.21. Between 12 and 20 weeks there were no changes in the macro and micronutrient intake of the control group. The food based intervention was associated with increased mean vitamin E intake from 10.9mg/day (8.50-13.3) to 15.9mg/day (12.4-19.4), p=0.008, mean energy adjusted vitamin E intake increased from 9.37mg/day (8.13-10.06) to 13.9mg/day (12.6-15.2) p<0.001. Analysis on an intention-to-treat basis demonstrated that the intervention was associated with an increase in mean vitamin E from 11.0mg/day (9.0-12.9) to 15.0mg/day (12.1-18.0) p=0.009 and mean energy-adjusted vitamin E intake from 9.8mg/day (8.7-10.8) to 13.5mg/day (12.4-14.6), p<0.001. The intervention increased mean polyunsaturated fatty (PUFA) acids from 15.1g/day (11.4-18.8) to 19.4g/day (14.9-23.9), p=0.047, there were no significant increase in the intake of other nutrients. Further analysis of the changes in n-6 and n-3 PUFA suggested that for energy unadjusted n-6 and n-3 PUFA intakes the food based intervention was associated with non-significant increases in n-6 PUFA [1.80 g/day (-1.22- 4.83)] and n-3 PUFA [0.39 g/day (-0.35-1.13)]. However, for energy adjusted intakes the food based intervention was associated with a significant increase in n-3 PUFA [0.28g/day (0.08-0.48), p<0.001) but not in n-6 PUFA [0.79 g/day (-0.26 – 1.85), p=0.30].

*Serum α-tocopherol (table 1)*.

There were no significant differences in serum α-tocopherol between control and intervention groups at 12 and 20 weeks gestation. Mean serum α-tocopherol increased in both groups between 12 and 20 weeks gestation: control 26.3μmol/L (23.0-25.6) to 29.4μmol/L (25.9-32.7) p=0.001, intervention 25.3μmol/L (23.5-27.7) to 28.7μmol/L (26.5-30.8) p=0.009. The increase in serum α-tocopherol between 12 and 20 weeks gestation did not differ between the control and intervention groups. As anticipated although the food based intervention increased vitamin E intake there was minimal effect on serum α-tocopherol. One of the limitations of vitamin E intervention is that there is no suitable biomarker that accurately reflects dietary intake or tissue stores of vitamin E (22). To illustrate this, a previous study that supplemented pregnant women with 133mg/day vitamin E resulted in about a 40% difference in plasma α-tocopherol between control and intervention subjects at 20 weeks gestation (21). Extrapolation to the present study suggests that a 10mg/day increase in vitamin E intake would increase serum α-tocopherol by about 3-5%. The current small pilot study was powered to detect changes in dietary vitamin E intake and consequently did not have the power to detect small changes in serum α-tocopherol. Any future vitamin E RCT would need to be of sufficient size and power to detect small changes in serum α-tocopherol or alternatively utilise an alternative biomarker of vitamin E status.

This pilot study demonstrates that pregnant women are willing and able to increase their dietary vitamin E intake between 12 and 20 weeks gestation. The qualitative study evaluation suggested that pregnant women would be willing to maintain the dietary changes until delivery with 17 of 19 women saying that they would have been willing to maintain the changes for a longer period, with the remaining 2 women saying they would have been willing to ‘try’ to maintain the changes for a longer period. However, any future RCT investigating the effects of vitamin E modification during pregnancy on childhood asthma would need the intervention to continue from 12 weeks gestation to delivery, therefore further studies are needed to confirm the sustainability of the food based intervention for the duration of pregnancy.

**Conclusion**

This study demonstrates that with the supervision and support of a dietitian, pregnant women with a personal and/or partner history of asthma are able to use a food based exchange intervention to increase their dietary vitamin E intake to the recommended 15mg/day. The study demonstrates the feasibility and acceptability of the food based intervention to increase dietary vitamin E intake but further work is required to ascertain the sustainability throughout pregnancy and if so whether it reduces the likelihood of childhood asthma. Although the focus of this pilot study has been vitamin E, the process of identifying exchanges of foods containing specified quantities of nutrients and the subsequent development of an individually tailored food based intervention could be transferred to other nutrients or combinations of nutrients for use in food based rather than supplement based intervention trials.

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Figure 1: Schematic outline of study

**Control Intervention**

12 week FFQ FFQ

scan visit Blood Sample Blood sample

4 day non-weighed diet diary

13-14 weeks Meet with dietitian

Dietary advice

Start to modify diet

Telephonecontact

with dietitian every two weeks

**Modify**

**Diet**

18 weeks Food diary

20 week FFQ FFQ

scan visit Blood sample Blood sample

Subject evaluation Subject evaluation

Figure 2: summary of numbers of women approached, recruited, randomised and who completed the study.

111 (65%)

no personal or partner

history of asthma

172 women invited **CONTACTED BY POST**

18 (30%)

Not interested

61 (35%)

personal and/or partner history of asthma

43 (70%)

recruited

22 intervention

21 control

19 completed

20 completed

Table 1: Summary of vitamin E parameters from food diaries, FFQ and serum for control and intervention groups at 12 and 18/20 weeks gestation as appropriate

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Control (n=20) | |  | Dietary Intervention (n=19) | |  |
|  | 12 weeks | 18/20 weeks | p value\* | 12 weeks | 18/20 weeks | p value\* |
| **Food Diary** |  |  |  |  |  |  |
| Vitamin E  mean (95% CI) mg/d |  |  |  | 7.13  (5.63-8.63) | 17.4  (14.4-20.5) | <0.001 |
| Energy  mean (95% CI) kcal/d |  |  |  | 1719  (1576-1863) | 2128 (1914-2342) | <0.001 |
| Energy adjusted vitamin E  mean (95% CI) mg/d |  |  |  | 6.41  (5.30-7.52) | 17.0  (14.0-20.0) | <0.001 |
| **FFQ** |  |  |  |  |  |  |
| Vitamin E  mean (95% CI) mg/day | 12.3  (10.4-14.1) | 12.4  (10.1-14.8) |  | 10.9  (8.50-13.3) | 15.9  (12.4-19.4) | 0.008 |
| Energy  mean (95% CI) kcal/day | 2400  (2133-2666) | 2339  (2008-2671) |  | 2375  (1998-2753) | 2529  (2060-2999) |  |
| Energy adjusted vitamin E  mean (95% CI) mg/day | 11.9  (10.6-13.2) | 11.8  (10.0-13.6) |  | 9.37  (8.13-10.06) | 13.9  (12.6-15.2) | <0.001 |
| **Serum** |  |  |  |  |  |  |
| α-tocopherol  mean (95% CI) μmol/L | 26.3  (23.0-25.6) | 29.4  (25.9-32.7) | 0.001 | 25.3  (23.5-27.7) | 28.7  (26.5-30.8) | 0.009 |
| Cholesterol  mean (95% CI) mmol/L | 4.90  (4.50-5.30) | 5.70  (5.19-6.21) | <0.001 | 4.59  (4.33-4.86) | 5.68  (5.43-5.93) | <0.001 |
| α-tocopherol/cholesterol  mean (95% CI) μmol/mmol | 5.34  (4.97-5.71) | 5.19  (4.69-5.69) |  | 5.54  (5.17-5.91) | 5.05  (4.72-5.37) |  |
| Change α-tocopherol 12 & 20 weeks mean (95% CI) μmol/L | 3.05  (1.48-4.62) | |  | 3.29  (0.95-5.64) | |  |

\*p values 12 vs 18/20 weeks, p>0.1 unless indicated.