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Micronutrient combination plus DHA during pregnancy

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The multicentre, parallel, randomised, controlled study assessed the impact of once-daily supplementation with 12 vitamins, 6 minerals and docosahexaenoic acid (DHA) on maternal biomarkers and child-specific parameters during pregnancy. The results indicated, among other things, improvement of the DHA and vitamin D status coupled with good tolerability and a high level of safety.

A mother's healthy diet during pregnancy including an adequate supply of energy, proteins, vitamins and minerals promotes the child's foetal development and helps prevent pregnancy complications. Even among women in high-income countries, the increased demand for nutrients during pregnancy can result in deficiencies [1]. The WHO recommends as standard the supplementation of iron and folic acid (0.4 mg/day) throughout the entire pregnancy to reduce maternal anaemia and to improve the health of the child [2].

This study is the first randomised, controlled study on the effects of supplementing a combination of several micronutrients and DHA during pregnancy.

Study on the combination of micronutrients and DHA during pregnancy

176 healthy, pregnant women were included in the randomised, controlled, parallel group study at two centres in Italy. Inclusion criteria were: a single pregnancy, a haemoglobin value of > 105 g/L and an intake of ≥ 400 µg folate/day [1].

The effects of once-daily nutritional supplementation with several micronutrients plus DHA (referred to below as Multiple Micronutrient Supplementation, MMS) on maternal biomarkers and anthropometric parameters of the children were compared to those of no supplementation during pregnancy. The study product was a softgel capsule with the following ingredients (Elevit® 2, Bayer): Vitamin A (beta-carotene) 2566 IU; Vitamin C 85 mg; Vitamin D 200 IU; Vitamin E 15 IU; Vitamin B1 1.4 mg; Vitamin B2 1.4 mg; Vitamin B3 18 mg; Vitamin B5 6 mg; Vitamin B6 1.9 mg; Folic acid 200 µg; L-methylfolate 226 µg; Vitamin B12 2.6 µg; Biotin 30 µg; Iodine 150 µg; Magnesium 57 mg; Zinc 10 mg; Selenium 60 µg; Copper 1.0 mg; Iron 14 mg; DHA 200 mg.

Recruitment of the women and determination of the baseline values took place in the 11th to 14th week of pregnancy (WoP). From WoP 13 to 15, the women started taking the study product once daily (n = 87, of which 65 completed the study) or were assigned to the control group without supplementation (n = 89, of which 76 completed the study). The study ended with the birth of the child and lasted an average of 24.5 ± 6.49 (1.0 to 30.9) weeks. The study duration in the study group was comparable with that of the control group.

Micronutrient level were determined – for example in the maternal blood – after 9 weeks and after 18 weeks of supplementation.

The primary endpoint was the change in the DHA levels in the maternal red blood cells (RBC), determined as a percentage by weight relative to the total fatty acid content (wt % TFA).

The secondary endpoints included, for example, the vitamin D status and additional biomarkers as well as anthropometric parameters of the children on delivery such as head circumference, body length, weight etc.

Significant increase in the mother's DHA value

Long-chain, polyunsaturated fatty acids are found in high concentrations in the brain and central nervous system. Docosahexaenoic acid (DHA) makes up the largest share of these fatty acids. It helps, among other things, to support

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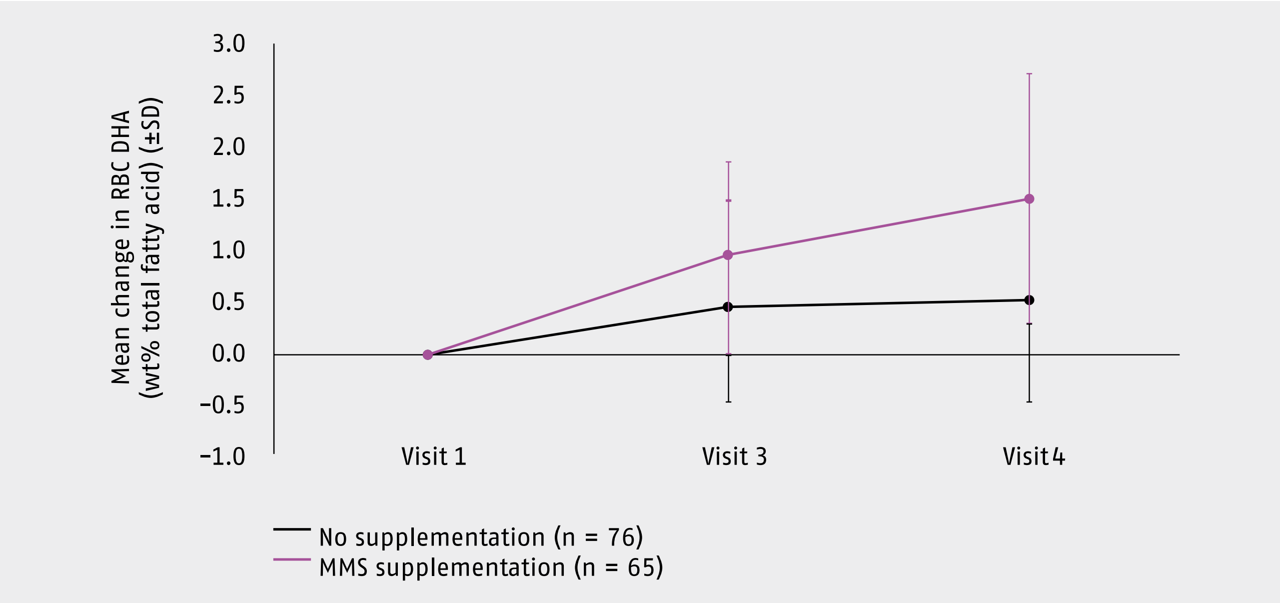

Fig. 1. Mean change (incl. standard deviation) between check-up visit 1 and check-up visit 4 of the maternal erythrocyte DHA (wt % TFA) ($p < 0.0001$ in favour of MMS)

foetal neuronal and visual development [3]. The levels of DHA available to the foetus during pregnancy are determined by the mother's diet [1].

The DHA content relative to the total fatty acid content (wt % TFA) in the maternal erythrocytes was regarded as an indication of the maternal status regarding long-chain polyunsaturated fatty acids. It increased at each check-up visit in both groups (**Fig. 1**). The mean change from check-up visit 1 to 4 was significantly larger in the MMS group than in the control group, with an estimated treatment difference of 0.96 (95% confidence interval [CI] 0.61–1.31; $p < 0.0001$). In addition, among women at the lower end of the measurement range the erythrocyte DHA levels (RBC DHA levels) increased more markedly in the MMS group (by 1.1 % at check-up visit 3 and 1.6 % at check-up visit 4 compared to check-up visit 1) than in the control group (increase of 0.2 % at check-up visit 3 and 0.5 % at check-up visit 4 compared to check-up visit 1) and reached the target RBC DHA level for pregnant women (5 %) at check-up visit 4 [1]. Although the average RBC DHA levels were above 6% at each check-up visit, there were women that fell below this value in both groups. However, among women in the lower ranges, the levels increased more strongly in the MMS group over the course of the study and reached the threshold value in the third trimester.

Significant increase in the mother's omega-3 index

The secondary endpoints included the improvement of additional maternal variables such as the increase in other

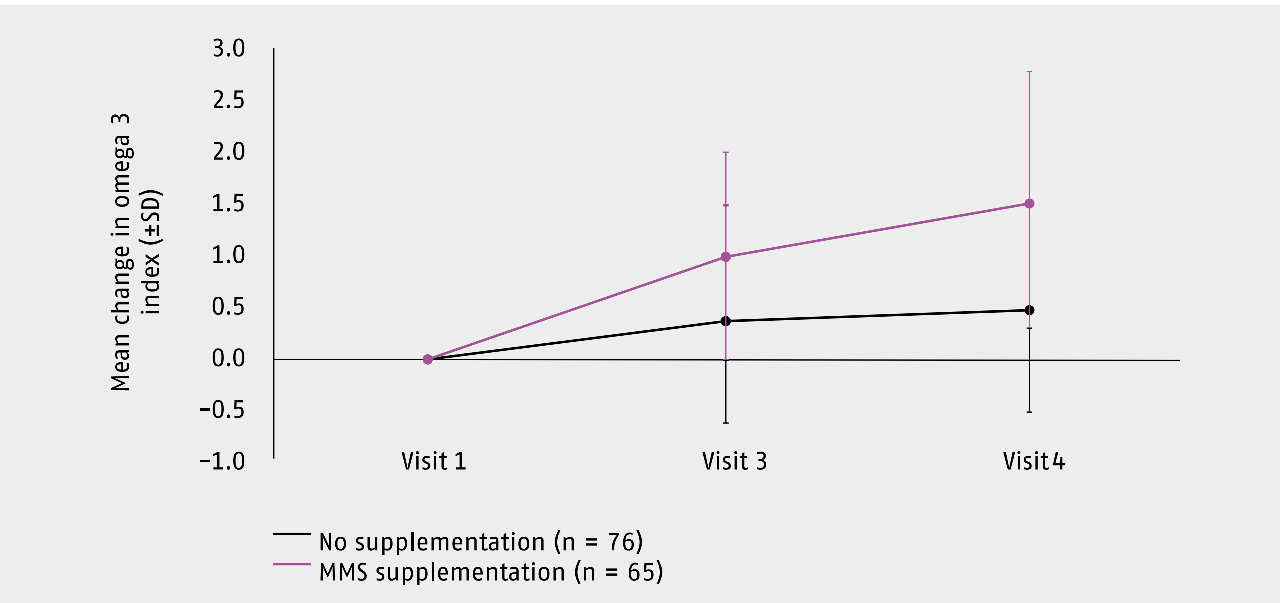

Fig. 2. Mean change (incl. standard deviation) between check-up visit 1 and check-up visit 4 of the omega-3 index ($p < 0.0001$ in favour of MMS). The omega-3 index is derived from the sum of DHA and EPA.

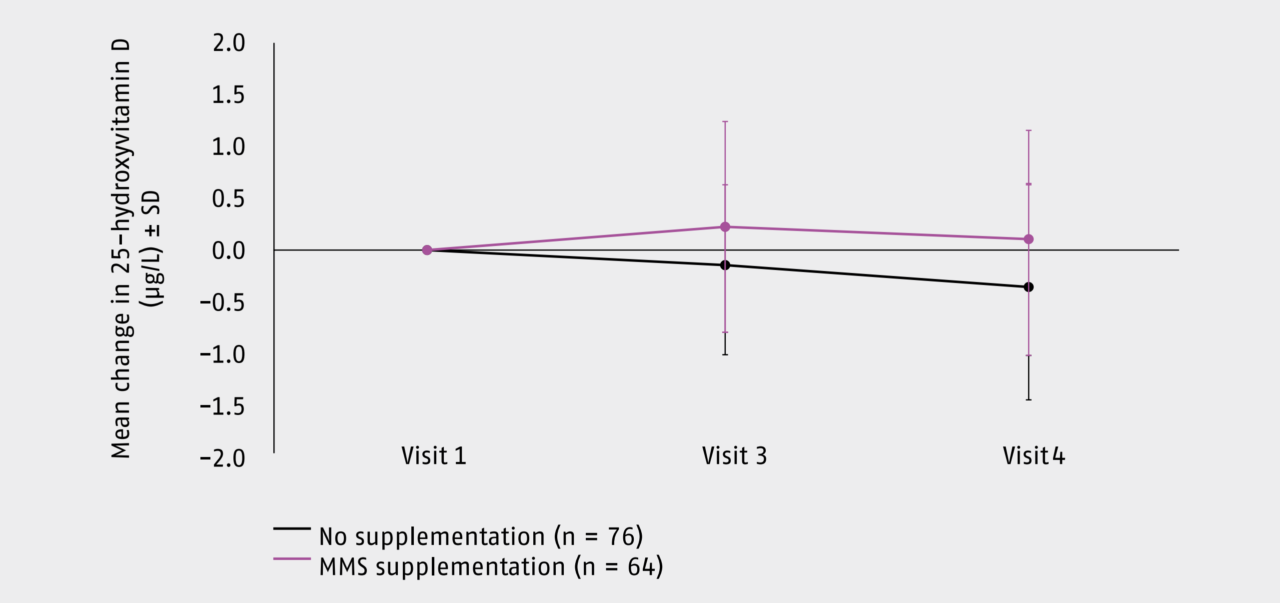

Fig. 3. Mean change (incl. standard deviation) between check-up visit 1 and check-up visit 4 of calcidiol (25-hydroxyvitamin D) (p = 0.0122 in favour of MMS)

fatty acid parameters in the red blood cells, such as the total fatty acid (TFA), eicosapentaenoic acid (EPA), the DHA/TFA ratio and the omega-3 index, which is calculated from the sum of DHA and EPA [1].

Significant differences in favour of MMS were revealed in the omega-3-index, the estimated difference was 1.00 (95% CI 0.64–1.37; $p < 0.0001$) (**Fig. 2**) [1].

According to the European Food Safety Authority (EFSA), EPA contributes to normal cardiac function, maintaining normal blood pressure and maintaining normal triglyceride concentrations in the blood [3, 4].

Stabilisation of the mother's vitamin D value

Among other things, vitamin D contributes to normal immune system function and to the physiological uptake and utilisation of calcium and phosphate. Consequently, it is important for bone health [3, 4]. Low levels of vitamin D in the blood of pregnant women have been associated with pregnancy complications [1].

The calcidiol level – which provides information about the body's vitamin D supply – was determined as an indicator of the vitamin D status.

In the test subjects who took MMS plus DHA supplements there was a significant increase in the calcidiol level compared to the control group (estimated difference 3.96 µg/L; 95 % CI 0.88–7.04; $p = 0.0122$), whilst in the control group there was actually a decrease in the vitamin D level (**Fig. 3**) [1].

MMS plus DHA proved safe and well tolerated

The number of adverse events was comparable for the MMS and the control group. None of the events were viewed by the investigators as having a causal link to the supplementation. Over and above this, no relevant changes to laboratory parameters were observed, and the physical and gynaecological examinations revealed no abnormalities.

Summary

The results of the study showed that for women from industrialised nations, taking a micronutrient supplement with DHA in the second and third trimesters was associated, among other things, with a significant increase in the maternal DHA value and a likewise significant stabilisation of the vitamin D status.

The supplement was well tolerated and the safety results were comparable for the study group and control group.

Despite the fact that, even in high-income countries, pregnant women often have an inadequate supply of micronutrients, the routine recommendation of food supplements is currently limited to iron and folic acid. Studies with larger study populations would be recommended to provide further evidence of the benefits of multinutrient supplements during pregnancy.

Literature

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