

**Topics:** Postnatal depression, cognitive and language development, infant neurodevelopment outcomes, docosahexaenoic acid (DHA), fish oil (FO)

**Objective:** To determine whether supplementing the mother with DHA during the last half of pregnancy reduces the incidence of depressive symptoms in the mother and enhances neurodevelopmental outcomes in their offspring.

**Background:** Population studies have shown that higher intakes of n-3 long-chain polyunsaturated fatty acids (LCPUFAs) from fish and seafood during pregnancy are associated with a reduced risk of depressive symptoms in the postnatal period, as well as improved developmental outcomes in the offspring. However, n-3 LCPUFA intervention trials in human pregnancy have reported mixed results and have not been conclusive largely because of methodological limitations.

**Method:** This multicentered, randomized, double-blind, placebo-controlled clinical trial, [DHA to Optimize Mother Infant Outcome (DOMInO trial)] was conducted in 5 Australian maternity hospitals, included 2,399 women with gestation of less than 21 weeks with singleton pregnancies and an 18 month follow up of 726 of their infants. Treatment included three 500 mg/day capsules of DHA –rich fish oil concentrate, providing 800 mg/day of DHA and 100 mg/day of EPA or three 500 mg/day vegetable oil capsules without DHA and comprised of equal proportions of rapeseed, sunflower and palm oils. The primary outcomes were as follows:

1. High levels of depression in the mothers as measured by the Edinburgh Postnatal Depression Scale (EPDS) with a score of more than 12 at 6 weeks or 6 months postpartum
2. Cognitive and language development in the infants as measured by the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) at 18 months

**Findings:** The results for primary outcomes on intent to treat basis were as follows:

1. No significant difference between high levels of depression in the DHA verses control group during the first 6 months postpartum (9.67% vs 11.19%; adjusted relative risk, 0.85; 95%confidence interval (CI), 0.70-1.02;p=0.009) - large improvements were measured in both groups. In fact, 9.74% of women in the DHA group suffered post natal depression compared to 15-16% in the general population, representing a major (35%) reduction. It must be noted that a 23% reduction, which masked to some extent the benefit from supplementation, was also seen in the placebo group demonstrating the benefit of care/attention/support in general in the prevention of postnatal depression.
2. Mean cognitive composite scores (adjusted mean difference, 0.01;95%CI, -1.36-1.37;p=0.99) and mean language composite scores (adjusted mean difference, -1.42;95% CI, -3.07 to 0.22; p=0.09) of children in the DHA group did not differ from children in the control group, but major benefits were seen in disadvantaged children officially classed as 'slow developing' . In all children 6.64% in the placebo group were classed as 'slow developers' compared to only 2.71% in the DHA group – a reduction of almost 60%. In boys only the reduction was even greater from 9.6% to 3.45%.

#### **Other Findings**

3. **Effects of birth weight and pre-term delivery:** Pre-term delivery and low birth weight are two of the major risk factors for ill health and poor development in children.
  - i) Supplementation with DHA significantly reduced the number of very early pre-term deliveries (less than 34 weeks) by more than 50% compared to placebo (1.09% vs 2.25%;adjusted RR, 0.49; 95% CI, 0.25-0.94; p=0.03).
  - ii) Mean birth weight was 68 g (95% CI, 23-114g; p=0.003 heavier and fewer infants were of low birth weight (3.41% vs 5.27%;adjusted RR,

0.65; 95% CI, 0.44-0.96;p=0.03) in the DHA group compared with the control group.

4. **Safety:** There were no differences between the DHA and placebo group for frequency of hemorrhage and antenatal hospitalization, maternal reports of nose bleeds, vaginal blood loss, constipation, nausea or vomiting at 28 and 36 weeks gestation. More women in the DHA group experienced gas and burping compared with the control group (43.6% vs 25.6%; adjusted RR, 1.68;95%CI, 1.50-1.89;p<.001) at 28 weeks gestation; however, fewer women from the DHA group reported diarrhea (13.4% vs 16.1%; adjusted RR, 0.83; 95% CI, 0.71-0.96; p=.01). There were more post term births requiring obstetric intervention (inductions or cesarean deliveries) in the DHA group compared with the control group (17.59% vs 13.72%; adjusted RR, 1.28; (%%CI, 1.06-1.54; p=.01). The following results indicate that DHA supplementation was safer or provided greater benefit than placebo:
- i) Only 3.01% of infants in the DHA group versus 4.49% in the placebo group experiencing at least one serious adverse event (defined as *admission to intensive care, major congenital abnormality or death*) (RR, 0.67; 95% CI, 0.44-1.01; p=0.06)
  - ii) Significantly less than half the number of infants in the DHA group required neonatal intensive care than in the placebo group (probably due to reduced number of pre-term births) (1.75% vs 3.08%; RR, 0.57;95%CI, 0.34-0.97; p=0.04).
  - iii) There were three times the number of fetal/infant deaths in the placebo group as compared to the DHA group reported as 4 fetal/infant deaths (0.33%) in the DHA group compared with 12 deaths (1%) in the control group at 18 months (RR, 0.33;95% CI, 0.11-1.03; P=.06).

**Conclusion:** DHA supplementation did not significantly reduce the levels of postnatal depression in the mother or improve cognitive and language development in their offspring as determined by the main outcome measures of the experiment. However, the results did highlight substantially fewer cases of postnatal depression relative to those expected in the general population and benefits to infant development following safe relatively high dose DHA supplementation during pregnancy.

**Relevance to:** Efanatal, Efalex Mother and Baby

**Reference:** Makrides M, Gibson R, McPhee A, Yelland L, Quinlivan J et al. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children. JAMA 2010;304(15):1675-1683.

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**PRESS RELEASE****DHA Supplementation During Pregnancy Benefits Mother and Infant.**

The largest clinical study ever providing DHA to pregnant women has reported a reduction in postnatal depression relative to in the general population and substantial health benefits to their infants. The study, supported by a grant from the Australian National Health and Medical Research Council and completed with capsules donated by Efamol Ltd., UK, was aptly named the DOMInO trial [DHA to Optimize Mother Infant Outcome].

The multicentered, randomized, double-blind, placebo-controlled clinical trial, conducted in 5 Australian maternity hospitals, included 2,399 women with gestation of less than 21 weeks with singleton pregnancies and 726 of their infants. The women took either three 500 mg/day capsules of DHA rich fish oil providing 800 mg/day of DHA and 100 mg/day of EPA or three 500 mg/day vegetable oil capsules without DHA that matched the fatty acid composition of the average Australian diet. Level of depression in mothers was measured with the Edinburgh Postnatal Depression Scale and cognitive and language development in the infants was assessed by the Bayley Scales of Infant and Toddler Development.

For the two primary outcomes, the results showed so significant difference between high levels of depression in the DHA versus control group during the first 6 months postpartum. However, improvements were measured in both groups compared to the incidence of post natal depression in the general population with a major (35%) reduction in the DHA group, but also a 23% reduction in the placebo group that masked the beneficial effects found in the DHA group. The reduction in the placebo group probably demonstrated the benefit of care/attention/support in general in the prevention of postnatal depression. Viewed in another manner, 9.74% of women in the DHA group suffered post natal depression compared to 15-16% in the general population.

Overall, cognitive and language development of infants in the DHA group did not differ from those in the control group. However, major benefits were seen in disadvantaged slow developing children where in all infants 6.64% in the placebo group were officially classed as 'slow developers' compared to only 2.71% in the DHA group – a reduction of almost 60%. In boys, the reduction was even greater at 64%. Based on Australia's birth rate this represents 10,000 children per year no longer being classed as slow developers.

Although as defined by the main outcome measures of the experiment, DHA supplementation did not significantly reduce the levels of postnatal depression in mothers or improve cognitive and language development in their offspring, it definitely achieved substantial improvement in postnatal depression incidence relative to that reported for the general population and provided a variety of benefits to infant health. In particular, supplementation with DHA significantly reduced the incidence of low birth weight babies by 35% and the number of very early pre-term deliveries by more than 50% compared to the control. This represents a major public health benefit, in countries such as Australia for example, where there would be more than 3000 fewer preterm births per year if women were supplemented with DHA during pregnancy. Pre-term delivery and low birth weight are two of the major risk factors for ill health and poor development in children.

A number of additional observations demonstrated not only the safety of DHA supplementation during pregnancy, but some also highlighted additional health benefits that were achieved relative to the control. For example, over 40% less infants in the DHA group required admission to intensive care; there were two thirds less infant deaths in the DHA group and one third less infants in the DHA group experienced a serious adverse event relative to control. These findings were all highly significant and show much better general health of the infants whose mothers were given DHA.

Overall, the results of this study provide a number of good reasons why women should supplement with DHA during pregnancy.

**References:**

Makrides M, Gibson R, McPhee A, Yelland L, Quinlivan J et al. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children. *JAMA* 2010;304(15):1675-1683.