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Does Supplementation of N-3 Fatty Acids Containing DHA Throughout Pregnancy and Breastfeeding Improve Child Cognition?

Bianca E. Parenti, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not the supplementation of N-3 fatty acids containing DHA throughout pregnancy and breastfeeding improve child cognition.

Study Design: Review of three double blind randomized controlled clinical trials (RCTs) published in 2003 and 2011.

Data Sources: Three peer-reviewed RCTs were found using PubMed and Medline. These studies compared DHA supplementation against various placebos.

Outcomes Measured: Enhanced child cognition was assessed via various exams, including the Kaufman Assessment Battery for Children (K-ABC) and Fagan tests. Significant outcomes were evaluated through the use of SD, Mean Scores, and p-values.

Results: Helland et al (2003) found significant cognitive differences between 4 year old children born to DHA and non-DHA supplemented mothers, via MPC scores on the K-ABC test (106.4[7.4] vs. 102.3[11.3]; P=0.049). Helland (2001) and Campoy (2011), however, did not note any significant differences between children on either the Fagan ((55.2[4.5] vs. 55.4[3.7]% at 6 months and 55.5[3.8] vs. 56.2[3.5]% at 9 months) or K-ABC tests (110[11] vs. 110[14.5] at 6.5 years old) respectively.

Conclusion: Conflicting results from these three RCTs demonstrate that the effects of supplementing pregnant and breast-feeding mothers with N-3 fatty acids containing DHA on child cognition is inconclusive.

Key Words: DHA supplementation, Pregnancy, Lactation, Cognition.
INTRODUCTION

Cognition is a multi-faceted entity formed from various contributing factors, but, in recent years, the role of Docosahexaenoic acid (DHA) in the developing brain has become a primary focus. Cognition has often been defined as an avenue for the processing of information and application of acquired knowledge, encompassing aspects such as awareness, understanding, learning, perception, reasoning, and judgment.¹² In short, it is an observable outward expression of intelligence. Evidence of this correlation is seen in both psychometric evidence and brain-imaging studies. “Factor-analytic studies have demonstrated that measures of working memory (cognition) correlate extremely highly (r’s >0.90) with the general intelligence factor.”² Furthermore, structural MRI’s have shown similar activations of the pre-frontal cortex and anterior cingulate gyrus when individuals are taking intelligence exams, such as the Raven’s Progressive Matrices Test, and during working memory tasks.² This paper will evaluate three randomized controlled trials (RCTs) that sought to compare the cognition of children born to mothers who did and did not take DHA supplementation throughout pregnancy and breastfeeding via various intelligence testing.

The relevance of cognition to both patients and healthcare providers alike is profound. Unlike disease states, which burden varying degrees of the population, cognition is a part of every individual’s life. In a world that emphasizes the importance of health, achievement, and success, the possibility of providing one’s unborn child with an edge in this arena, through the use of prenatal supplementation, will most certainly bring this issue to nearly every health care provider’s door. It is estimated that up to 95 percent of pregnant mothers take some type of prenatal supplement. On average, the cost
of taking the recommended supplementations of vitamins A through E, folic acid, iron, and calcium from three months before pregnancy through a year of breastfeeding totals nearly $220 per individual.\textsuperscript{3,4,5} Furthermore, a great number of healthcare visits accompany the birth process in order to assess fetal development and well being. Pregnant women are advised to see their obstetrician once each month for weeks 4 through 28, then twice a month for weeks 28 through 36, and weekly from weeks 36 to birth.\textsuperscript{6}

Cognition is a complex entity with both genetic and environmental components. Fetal brain development undergoes its most rapid period of growth from the third trimester through the second year of life.\textsuperscript{7} During this critical time, neurologic development is heavily dependent on the energy it derives from the mother’s diet via placental transfer and breast milk; long-chain polyunsaturated fatty acids play a particularly important role. More specifically, it is the N-3 fatty acid, DHA, which makes up nearly 30\% of brain structure and aids in neuronal cell formation and signaling in the gray matter of the cerebral cortex.\textsuperscript{7} DHA also plays a role in the ongoing structure of the adult brain, where it serves as the most abundant fatty acid in cell membranes, altering permeability and enhancing protein activity.\textsuperscript{7} “Pregnant and lactating women require at least 300mg of daily DHA intake to promote optimal nervous system development in their children.”\textsuperscript{7} By measuring DHA levels in the umbilical artery and vein of infants at birth, researchers have correlated low concentration levels to neurologic abnormalities and even stillbirths.\textsuperscript{8}

Cognitive disparities from child to child have prompted the development of various interventional techniques, such as early brain training programs, remediation
techniques, and compensatory strategies, to narrow the gap. These strategies, however, have proven to be of limited value.\textsuperscript{9} Due to its relative safety, efficacy, tolerability, and known role in neurologic development, DHA supplementation is now being proposed as an alternative treatment resource.

**OBJECTIVE**

The objective of this selective EBM review is to determine whether or not the supplementation of N-3 fatty acids containing DHA throughout pregnancy and breastfeeding improves child cognition.

**METHODS**

Three double blind randomized controlled studies were used in this review. Each study’s population followed a group of women from pregnancy through lactation, as the intervention of N-3 fatty acids containing DHA were introduced to the experimental groups. The specific concentration and source of DHA intake varied across the studies, as did the structure of each control group; the commonality, however, was the absence of DHA in whichever prenatal supplement the comparison control group was instructed to take. After birth, the transfer of DHA from mother to fetus was confirmed by obtaining levels in either blood, the umbilical cord of infants, or maternal milk. Cognitive function was then later assessed using various tests, including the Fagan and Kaufman Assessment Battery for Children (K-ABC).

Key words used in the search included DHA, pregnancy, breastfeeding, and cognition. The chosen articles were all written in English and published in peer-reviewed journals between 2003 and 2011. Each was found through the PubMed and Medline databases, and selected based on its relevance to my initial clinical question and its ability
to be correlated to the outcome in question. The inclusion criteria consisted of randomized controlled trials and a population of healthy pregnant women with uncomplicated singleton pregnancies. Pregnant women who had previously taken any prenatal supplements before the start of the trial were excluded, as were infants suffering from premature births, infections, asphyxia, and congenital abnormalities. Summary statistics were reported using standard deviations, means, medians, and p-values.

Table 1: Demographics & Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>#Pts</th>
<th>Age (yrs)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campoy et al¹⁰  (2011)</td>
<td>Double Blind, RCT</td>
<td>270</td>
<td>18-40</td>
<td>Healthy women, Uncomplicated Singleton Pregnancies, weight: 50-92 kg, intention to breast feed</td>
<td>No prior supplementation during pregnancy, premature births, infections, asphyxia, congenital anomalies</td>
<td>109</td>
<td>N-3 long chain poly unsaturated fatty acids containing 500mg/d DHA and 0.5% formula DHA (from the 20&lt;sup&gt;th&lt;/sup&gt; wk of pregnancy until birth and from birth until 6 mo after delivery, respectively)</td>
</tr>
<tr>
<td>Helland et al¹¹ (2001)</td>
<td>Double Blind, RCT</td>
<td>590</td>
<td>19-35</td>
<td>Healthy, null or primi parous women, singleton pregnancies, intention to breast feed</td>
<td>No prior supplementation during pregnancy, premature births, infections, asphyxia, congenital anomalies</td>
<td>245</td>
<td>Cod liver oil with DHA (1183mg/10mL/d) from the 17&lt;sup&gt;th&lt;/sup&gt; wk of pregnancy until 3 mo after delivery</td>
</tr>
<tr>
<td>Helland et al¹² (2003)</td>
<td>Double Blind, RCT</td>
<td>590</td>
<td>19-35</td>
<td>Healthy, null or primi parous women, singleton pregnancies, intention to breast feed</td>
<td>No prior supplementation during pregnancy, premature births, infections, asphyxia, congenital anomalies</td>
<td>506</td>
<td>Cod liver oil with DHA (1183mg/10mL/d) from the 17&lt;sup&gt;th&lt;/sup&gt; wk of pregnancy until 3 mo after delivery</td>
</tr>
</tbody>
</table>
OUTCOMES MEASURED

Each child, whose mother successfully adhered to all experimental procedures, was invited to complete either the Fagan or K-ABC test at various ages post-birth. These tests successfully measure cognition by evaluating a child’s ability to process information and correlating it to a quantitative exam score. In the Fagan Test, this processing is measured on the theory that an infant tends to “look longer at new targets, such as a picture of a woman’s face, than at one previously seen.” An infant’s “preference for novelty” tells us that the infant has the ability to acquire knowledge, process stimuli, and make discriminations. A specific computer program then derives novelty scores, which are simply “the amount of fixation devoted to the novel picture divided by the total fixation time to both the novel and familiar picture, multiplied by 100.” Individual novelty preference scores are then compared to the mean, where higher scores indicate higher levels of cognitive function.

The K-ABC test, which is comprised of four scores from sixteen subtests, including sequential processing, simultaneous processing, achievement, and mental processing scales, was also used to assess cognition. “The sequential processing scale measures short-term memory and problem solving skills, such as recalling numbers and arranging items. The simultaneous processing scale examines skills that require a child to process several stimuli at once, such as facial recognition. These two scores comprise the mental processing composite (MPC), which is a global measurement of the child’s cognitive ability. Finally, the achievement scale focuses on applied skills and facts, such as naming famous people and solving riddles.” Standard K-ABC scores have a mean score of 100 and a standard deviation of 15 and individual scores are compared to these
values accordingly. Both the Fagan and K-ABC tests have known efficacy and are widely recognized.

RESULTS

Three double blind randomized controlled trials compared the cognitive function of infants born to mothers supplemented with varying levels of DHA throughout pregnancy and breastfeeding to cognitive levels of children born to mothers whose controlled supplements contained no DHA. Helland’s (2001 and 2003) control group received corn oil and assessed child cognition at 6 and 9 months and 4 years of age respectively, while Campoy et al’s control group received a placebo and assessed child cognition at 6.5 years of age. The inclusion and exclusion criteria of all three studies were similar (Table 1). All enrolled mothers were young, healthy, adults whose supplementation began in the second trimester and continued through, at least, 3 months of breastfeeding. Premature infants and multiple gestations were excluded because they are more vulnerable to DHA deficiencies, as they have less time or opportunity to draw on stores from the mom. 

Data from all trials were reported as continuous data and could not be converted into a dichotomous format; therefore, calculations evaluating tolerability, adverse events, and treatment effects could not be computed. Participants in all three studies did however receive written information and consented to participate in each trial, all of which were approved by regional ethics committees. The women were also free to withdraw without giving a reason, however, 43.1% and 38.7% of participants in the cod liver and corn oil groups, respectively, from the Helland studies withdrew because of “feelings of discomfort” the supplements gave them, and Campoy et al stated that “no illness or
disability interfering with normal neurologic development was observed amongst its
participants.”  

Across all studies, participants also submitted pregnancy records, food frequency
questionnaires, birth records, and blood and milk sampling. No significant variations in
dietary intake, maternal age, smoking, or parental education levels existed.\textsuperscript{10,11,12} Maternal blood or milk sampling was used to evaluate the transfer of DHA from mother
to fetus and confirm higher levels in the experimental groups.\textsuperscript{10,11,12} All trials
demonstrated this transfer, hence the validity of separating the groups into a experimental
and control population was confirmed.

In Helland et al (2001) 590 pregnant Norwegian mothers were recruited from the
National Hospital and Baerum Central Hospital in Oslo between December 1994 and
October 1996.\textsuperscript{11} They were randomized into both a control and experimental group by a
computer program and instructed to take 10mL/day of either cod liver oil (containing
DHA) or corn oil. The lack of compliance was 9.5% in the cod liver oil group and 16.1% in the corn oil group.\textsuperscript{11} 115 controls and 130 women receiving DHA completed the
intervention through the third month after delivery and allowed the cognitive Fagan test
to be performed on their children at both 6 and 9 months of age.\textsuperscript{11}

In this particular version of the exam, the infants received the same 10 novelty
problems on both occasions; all problems involved comparison of familiar and new
digitized faces on a computer monitor.\textsuperscript{11} Scores were computed as above described in the
methods section; A 2-tailed student t-test was used to examine differences between the
control and experimental groups, based on mean scores and standard deviations; a p value
of $<0.05$ was considered significant. \textsuperscript{11} “No significant differences in novelty preference
between the cod and corn oil groups at either 6 or 9 months of age were found” (55.2[4.5] vs. 55.4[3.7] and 55.5[3.8] vs. 56.2[3.5] respectively).  

Table 2: Treatment v. Control Fagan Test Data at 6 and 9 months of age, Mean[SD]

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children born to mother’s supplemented with cod liver oil containing DHA (N=130)</td>
<td>55.2[4.5]</td>
<td>56.2[3.5]</td>
</tr>
<tr>
<td>Children born to mother’s supplemented with corn oil lacking DHA (N=115)</td>
<td>55.4[3.7]</td>
<td>56.2[3.5]</td>
</tr>
</tbody>
</table>

In Helland et al (2003), the same children, born to mothers in the very population above described, were followed up with at 4 years of age. 48 children born to mothers who had taken cod liver oil and 36 children born to mothers who had taken corn oil participated in cognition assessment via the K-ABC test. “In a backward stepwise regression model with Mental Processing Composite as the dependent variable, maternal intake of DHA was found to be an independent variable of clinical significance” (r2=0.07; P=0.03).  

T-tests then measured differences between continuous variables, and p values <0.05 were considered significant. Children in the cod liver oil group had significantly higher MPC scores than the children in the corn oil group (106.4[7.4] v. 102.3[11.3]; P=0.049).  

Table 3: Treatment v. Control MPC Scores at 4 Years of Age, Mean[SD]

<table>
<thead>
<tr>
<th></th>
<th>MPC Scores from K-ABC Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children born to mother’s supplemented with cod liver oil containing DHA (N=48)</td>
<td>106.4[7.4]</td>
</tr>
<tr>
<td>Children born to mother’s supplemented with corn oil lacking DHA (N=36)</td>
<td>102.3[11.3]</td>
</tr>
</tbody>
</table>
Campoy et al (2011) recruited healthy pregnant women, at less than 20 weeks of gestation, from three different European antenatal care clinics. “Blockwise randomization” was performed at each center and the women were separated into four groups. For the purpose of this analysis, however, we will focus only on the groups of women who received either supplements containing only 500 mg of DHA or a placebo from pregnancy through 6 months of breastfeeding. Infants born to DHA supplemented mothers who could no longer breastfeed were still allowed to remain in the study and received either a formula containing 0.5% DHA until 6 months of age or a formula lacking DHA. 37 children from the DHA supplemented group and 45 children from the control group complied with the experiment and took the K-ABC test at 6.5 years of age. No compliance percentages from the mother’s were reported. The Kruskal-Wallis test was performed to assess the effects of supplementation based on median values and ranges obtained from K-ABC scores; p values <0.05 were considered significant. No significant differences in the MPC scores on the K-ABC test were found between the DHA supplemented and placebo groups (110[11] vs. 110[14.5] respectively).

Table 4: Treatment v. Control MPC Scores at 6.5 years of Age, Median[Range]

| Children born to mother’s supplemented with cod liver oil containing DHA (N=37) | MPC Scores from K-ABC Test |
| Children born to mother’s supplemented with a placebo (N=45) | 110[11] |
| | 110[14.5] |

DISCUSSION
Using three double blind RCT’s, this meta-analysis reviewed the affects of DHA supplementation, to pregnant and breastfeeding mothers, on the cognition of their yet unborn children. Each article selected healthy mothers whose children were not at any predetermined risk for cognitive deficits, however, recent studies have suggested running similar experiments in at risk children. The validity and blinding of each RCT was without error, however drop out rates were high, as follow up required years of compliance, leaving the sample sizes relatively small. Furthermore, child cognition was only assessed using two exams and many other options for evaluation exist.

DHA is a relatively safe supplement when used as directed (amounts under 3 grams per day). Its supplementation is contraindicated in patients taking blood pressure and anticoagulant medications as it may cause pressure to drop too low and also slows clotting.\(^\text{15}\) Under the Dietary Supplement Health and Education Act of 1994, the Food and Drug Administration regulates DHA by requiring its manufacturers to ensure its safety before marking and intervenes if any harmful product does reach stores.\(^\text{16}\) Since the start of its widespread use, only minimal adverse affects, such as nausea, intestinal gas, and bruising, have been noted.\(^\text{15}\) No black box warnings exist. Insurances do not cover DHA supplements yet its availability and use is widespread.

DHA supplementation has, for example, begun to be implemented in the treatment of various disease states. In the Rotterdam studies, researches noted protective and reductive effects of DHA on the incidence of Alzheimer’s; DHA has even been shown to improve age related memory loss.\(^\text{7}\) Another study measured the impact of DHA on visual development in infants. Those who received DHA-enriched egg yolks had greatly enhanced retina and visual cortex maturation.\(^\text{7}\) Other less common uses include
the treatment of Coronary Artery Disease, ADHD, and, when given along with EPA, Psoriasis.\textsuperscript{7}

CONCLUSION

The supplementation of N-3 fatty acids containing DHA, to pregnant and breastfeeding mothers, has shown inconclusive affects on child cognition. Helland et al (2003) was the only RCT that detected a significant difference in cognitive scores between experimental and control groups. Noting that this is the same population a previous trial tested (at an earlier age using a different cognitive assessment) with insignificant results, DHA supplementation’s effects remain conflicting at best.

The administration of DHA in all studies relied solely on the mother’s compliance and honest reporting of intake. In the future, the reliability of such intake should be standardized and controlled. The known correlation between DHA and brain structure warrants future investigation on this matter. Continuing research should consider enhancing the dose of DHA supplementation, testing children at later stages of life, and even implementing new tests to assess cognition, as this matter will continue to be of great importance in the coming years.
References


