Importance of the long chain omega-3 fatty acids in human milk to benefit an infant's immune development and risk of allergy

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https://www.howstuffworks.com/
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- Adviser/consultant for: CIHR, Dairy Farmers of Canada, International Life Science Institute, Second Science
Outline

- Allergy, and immune development & breast milk
- DHA and the immune system
- Should we be concerned about DHA status during lactation?
- Summary
Prevalence Food Allergies in the United States

- Food allergies are part of a group of atopic diseases
- 2-8% of children are affected
- Most common allergies are egg, milk, peanut, tree nuts, fish, shellfish & sesame
  → 40% of children with food allergies are allergic to > one food.
- IgE-mediated food allergies are the only food related chronic illness with a risk of life threatening anaphylaxis
Factors Affecting Infant’s Risk for Allergy Risk

- Diet
  - Mom’s diet during pregnancy & lactation
  - Breast-feeding
  - Food introduction

- Environmental Exposure

- Genetics

Allergy Risk
Immunity in the 1st year of life

- Infant survival depends on the ability to respond to environmental challenges
- Infant has a ‘different’ immune system than an adult
Immunity in the 1st year of life

- Compared to an adult... infant has
  - ↓ ability of T cells to respond to immune challenges (i.e. proteins, pathogens, toxins)
  - Reliance on their innate immune system
  - In the process of developing tolerance to proteins in the environment

→ Compared to adults, infants have a delayed immune response and ↑ risk of infection, ↑ inflammatory response & ↑ risk of atopic diseases
Development of Oral Tolerance (OT)

- Food allergies are a failure to develop OT to a dietary antigen

- What is OT?
  - *Immunological ignorance?*
  - **No** this is an active learned response by the immune system

Nature Mar 24, 2014
Breast feeding associated with a ↓ risk of food allergies

Studies have consistently found that breast-feeding is protective against atopic diseases/allergies:

- Exclusive breast feeding for at least 4 mos reported to prevent or delay atopic dermatitis, cow milk allergy and wheezing early in life
- A definite improvement in infant eczema and associated gastrointestinal complaints when baby is exclusively breast-fed
Immunological compounds in human milk

- Immunoglobulins- sIgA
- Lactoferrin
- Free secretory component
- Lysozyme
- Oligosaccharides
- Lactoperoxidase
- **Fatty acids**
- Nucleotides
- Nucleotide-hydrolyzing antibodies
- Maternal leukocytes
  - Macrophages
  - Neutrophils
  - B and T cells
- Cytokines
  - TGF-β1
  - IL-10, -4,-6,-12,-13,-16, -18, -ira
  - IFN-γ
  - TNF-α
- Chemokines
- Hormones: insulin, leptin, adiponectin
- sCD14
- α-lactoglobulin
- κ-caseins
- Platelet activating factor
- Complement & complement receptors
- Haptocorrin
- β-defensin-1
- Mucins
- Toll-like receptors
- Bifidus factor
- Anti-secretory lectins
- Bioactive peptides
- Antioxidants
- Prostaglandins, leukotrienes and other eicosanoids

Breast milk Fat

- Fat globules
- 98-99% fat is triglycerides
- Small amounts of diglycerides, monoglycerides, free fatty acids, phospholipids, gangliosides, cholesterol and cholesterol esters
- Fatty acid composition:
  - SFA (45%) 
  - MUFA (40%)
  - PUFA (15%):
    - 0.2-0.4% DHA
    - 0.3-0.6% ARA
Outline

- Allergy background, immune development & breast milk
- **DHA and the immune system**
- Should we be concerned about DHA status in lactating moms
- Summary
Essential Fatty acids

- North American intake of EPA & DHA is low
- This pathway is not straightforward
- Although people can convert ALA to EPA & DHA, the conversion rates are very low, due to Δ6-desaturase enzyme
  - To EPA: ~0.2-8% (as high as 21%)
  - To DHA: ~0.13-6% (as high as 8%)

**n-3**

- α-linolenic acid (ALA, C18:3)
- Stearidonic acid (SDA, C18:4)
- Eicosatetraenoic acid (ETA, C20:4)
- Eicosapentaenoic acid (EPA, C20:5)
- Docosapentaenoic acid (DPA, C22:5)
- Docosahexaenoic acid (DHA, C22:6)
Our clinical trials in infants who were not breast fed and found:

- that adding DHA(+Ara) to full (and preterm) formula:
  - modifies type of immune cells in blood closer to that of the breast-fed infant
  - facilitated the maturation of peripheral T helper cells (CD4$^+$) cells
  - improved the ability of T cells to respond to an immune challenge
  - increases the ability of immune cells to produce the regulatory cytokine (IL-10) when challenged
  - Improves ex vivo tolerance to dietary proteins

→ Suggests improved/faster immune development and facilitated development of OT

(Field et al., 2008, 2009, 2010)
1) Review the evidence from epidemiological studies assessing the association between the amount of DHA (+ Ara) in mom’s breast milk and immune development in her baby.

2) Review the evidence for the essentiality of DHA (+ Ara) in the postnatal infant diet for immune development.

3) Review the evidence for DHA supplementation in the postnatal maternal diet (breast-feeding) and the impact on the infant’s immune system development early in life.
Epidemiological studies suggest an inverse association between breast milk DHA content and the development of atopic disease in children with family history of atopic disease.

Evidence from observational studies:

- Maternal DHA intake influences breast milk DHA content.
- Breast milk DHA (and Ara) content negatively associated with the development of atopic diseases in children at risk of atopic disease.
Nutritional intervention studies suggest that supplementing the maternal diet with fish oil (late pregnancy and/or lactation) or feeding infant formula enriched in DHA/Ara alters markers of immune function in a direction that is thought to be beneficial.

<table>
<thead>
<tr>
<th>DHA in maternal diet (n=3)</th>
<th>DHA in infant diet (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All were RCTs</td>
<td>• RCTs (4), observational open label (2)</td>
</tr>
<tr>
<td>• 2.2 to 4 months postpartum</td>
<td>• 4 wk to 12 months.</td>
</tr>
<tr>
<td>• Daily fish oil EPA (range: 195-1600mg/d) and DHA (900-1100mg/d)</td>
<td>• 5 studies provided infant formula enriched in AA (range 0.34-0.72%) and DHA (range 0.2-0.36%); 1 provided fish oil supplement (110 mg EPA &amp; 280 mg DHA)</td>
</tr>
<tr>
<td>• Immune function or incidence of allergic and atopic diseases were 1° or 2nd outcome</td>
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</tbody>
</table>
Turn to the Animal Models
Feeding a DHA diet to dams increases the n-3 LCPUFA content of breast milk

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control diet (N=11)</th>
<th>DHA Diet (N=7)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of total fatty acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C20:4 n6 (AA)</td>
<td>0.44 ± 0.05</td>
<td>↑ 0.69 ± 0.03</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C18:3 n3 (ALA)</td>
<td>1.60 ± 0.05</td>
<td>↑ 2.99 ± 0.10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C20:5 n3 (EPA)</td>
<td>0.09 ± 0.02</td>
<td>0.07 ± 0.01</td>
<td>0.59</td>
</tr>
<tr>
<td>C22:5 n3 (DPA)</td>
<td>0.03 ± 0.01</td>
<td>↑ 0.05 ± 0.00</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C22:6 n3 (DHA)</td>
<td><strong>0.24 ± 0.18</strong></td>
<td>↑ <strong>1.09 ± 0.03</strong></td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

<sup>a</sup>Values are presented as mean ± SE. AA, Arachidonic acid; ALA, α-Linolenic acid; EPA, Eicosapentaenoic acid; DPA, Docosapentaenoic acid; DHA, Docosahexaenoic acid.

<sup>b</sup>P value from the main effect of dams diet in the Mixed model.

Animal Study Design

Dams

Birth (0 wk)

(N=12)
Control Diet
0% DHA, 0.4% AA

(N=8)
DHA Diet
0.9% DHA, 0.4% AA

Pups =10/dam

Lactation period

Mucosal OT

Placebo

OVA

Termination (3 wks)

Weaning period

Vaccination OVA

Termination (6 wks)

Control Diet
0% DHA, 0.4% AA

Control Diet
0% DHA, 0.4% AA

Placebo

OVA

Placebo

OVA
Feeding DHA during suckling reduces plasma OVA-specific IgE concentrations in 3 and 6 weeks old pups.

Control diet
DHA diet
Suckling diet:

\[ P_{interaction} = 0.030 \]

This improved tolerance to vaccination with a dietary protein was maintained after suckling, even when a diet without DHA was fed.

* Statistically significant change between the DHA diet and the control diet, \( P < 0.05 \).

Richard et al. Nutrients 2016
Feeding DHA during suckling differentially affects the response of splenocytes to a dietary antigen (OVA)

**Suckling diet:**  
- Blue: Control diet
- Green: DHA diet

*Statistically significant change between the DHA diet and the control diet, $P < 0.05$. 

Richard et al. Nutrients, 2016
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Kaplan et al., *Maternal & Child Nutrition*, 2014)
Variation in DHA content in human milk between countries

0.26 ± 0.25 (APrON cohort)

FIG. 2. DHA as weight percent of total FA in mature human milk of women from nine countries. Values are means ± SEM with 44 to 54 samples per group. Means with different superscripts are statistically different (P < 0.05).

Yuhus et al., 2006
Diet recommendations for DHA during pregnancy/lactation

- Consensus recommendations on behalf of the European Commission research projects Perinatal Lipid Metabolism and Early Nutrition Programming developed jointly with representatives of:

the Child Health Foundation, the Diabetic Pregnancy Study Group, the European Association of Perinatal, the European Society for Clinical Nutrition and Metabolism, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, the International Federation of Placenta Associations and the International Society for the Study of Fatty Acids and Lipids

200 mg/d of DHA during pregnancy & lactation
Association between DHA intake & DHA in breast milk

Unpublished data demonstrating the relationship between dietary intake of DHA and the content of DHA in breast milk of APrON women at 3 months post-partum (Graph removed)
Proportion of APrON Women Below DHA Recommendations

Average intake of DHA from diet was 120 mg/d

Jia et al. APNM, 40(5):474-81, 2015
What did we learn from APrON women

- Breast milk content of DHA in Albertan women was below global average
- If the ideal breast milk DHA range (0.30-0.64%):
  - Requires a dietary intake of DHA: 340-1600 mg/day
- To get that
  - At least 3 servings of fatty fish a week
  - Take a daily supplement containing DHA
The incidence of food allergies are highest in the first 3 years of life when the immune system is developing.

Research suggests:

- The nutrient DHA is important for:
  - Ensuring women’s breast milk content of DHA
  - Development of the infant’s immune system
  - Ability of the infant to develop tolerance to food proteins

- Women should ensure they consume DHA during breast feeding (and pregnancy) we estimate that they require 340-1600 mg/day while they are providing breast milk to their infant.
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