Improving Maternal Outcomes with Omega-3 Docosahexaenoic Acid (DHA)

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Objectives
Participants will be able to:
• Identify benefits of optimal omega-3 DHA intake during pregnancy and lactation upon infant visual, social, cognitive and psychomotor development.
• Identify best sources of omega-3 DHA and be able to discuss safe seafood consumption during pregnancy.

Essential Fatty Acid Metabolism

<table>
<thead>
<tr>
<th>N-6 Fatty Acids</th>
<th>N-3 Fatty Acids</th>
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<tbody>
<tr>
<td>LA (18:2 n-6)</td>
<td>ALA (18:3 n-3)</td>
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<tr>
<td>GLA (18:3 n-6)</td>
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<tr>
<td>ARA (20:4 n-6)</td>
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<td>Plant Sources</td>
<td>Delta-6 Desaturase</td>
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<td>Elongase</td>
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<td>Animal Sources</td>
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Benefits of Omega-3 DHA and Seafood Consumption During Pregnancy and Breastfeeding

Benefits of DHA and Seafood Consumption During Pregnancy

Maternal Benefits
• Emerging Evidence: Prevention and/or management of perinatal depression
• Good evidence: Increase in gestational length
• Potential reduction of preterm birth
• Improved DHA content of breast milk

Benefits to Babies
• Strong Evidence: Optimal development of vision and processing of neural signals
• Strong Evidence: Enhanced cognitive development: stronger motor, social and communication skills and IQ in childhood
• Emerging evidence ???Decreased Body Fat in Infancy and Childhood

Seafood Intake and Gestational Length
Fish Consumption During Pregnancy May Decrease the Incidence of Preterm Birth

- (8,729 dietary questionnaires from pregnant women)

**Maternal – Fetal Medicine Network**

- ORadj PT Birth in women consuming fish >3 times/w compared to 1 time or less/month: 0.60 (0.38, 0.95)
- No additional benefit beyond 3 serv/week and no effect of FO supplements

**Clinical Trials: Omega-3 DHA or Fish Oil Supplementation and Gestational Length**

- DHA-enriched eggs = 137 DHA mg/day vs. Ordinary Eggs
- DHA increased gestation by 6.0 + 2.3 days (p=.009)

- Makrides, M et al JAMA 2010;304:1675
  - 1197 pregnant women supplemented with 800 mg DHA as FO during pregnancy
  - 1202 controls received vegetable oil
  - Preterm Delivery
    - <37w +DHA 5.6% - DHA 7.34% p = .09
    - <34w +DHA 1.09% - DHA 2.25% p = .03
  - Low birth weight <2500g
    - + DHA 3.41% - DHA 5.27% p = .03

- DHA Supplementation Increases Gestational Length
  - CSU/Denver Health Trial – Omega-3 Enriched Foods in Pregnancy
  - For each 1% increase in Maternal % Total DHA there is a corresponding 1.4 day increase in gestation (p = .0056)
DHA Supplements Increase Gestational Length
Carlson S. AJCN online February 2013
- 350 women supplemented with 600 mg DHA/day vs control
  - Increased gestational length by 2.9 days (p = .041)
  - Increased birth weight by 172 g (p = .004)
  - Increased birth length by .7 cm (p = .022)
  - Increased head circumference by .5 cm (p = .012)
- PT Birth < 34 Wks
  0.6% w DHA vs. 4.8% controls (p=0.025)

CSU Omega Smart Baby Study
115 women supplemented with 300 mg DHA/day from week 24 – 28 through 3 months lactation

Systematic Reviews DHA and PT Birth
Significant reduction in rate of early preterm birth (<34 wks) RR .39 (0.18,0.84)
Significant reduction in rate of PT birth < 37 wks 8.9% (DHA) vs 16.3%
RR .61 (0.40, 0.93)
<34 wks RR .32 (0.09, 0.95)

Summary of Current Evidence
- Fish intake or DHA supplements associated with increased gestational length in the order of 2 – 6 days
- Some question remains regarding the effect of fish oil fatty acids or DHA on preterm birth
  - Most significant effect is reducing early preterm birth
- The greatest effects in observational studies are seen in women who consume little or no fish compared to those who consume >2 serv/week
  - Little additional effect of supplements in women who consume large amounts of fish

Omega-3 DHA Supplementation During Pregnancy Increases Maternal Stores

Maternal DHA Supplementation Prevents Decrease in Maternal DHA Stores During Gestation
Women supplemented with 0, 300, or 600 mg DHA/d
% RBC Total FA

Maternal-Fetal Network Study
Harper et al Obstet and Gynecol 115:234,2010
Clinical Trials: Omega-3 DHA Supplementation During Pregnancy and Infant Neurocognitive Development

Role of Omega-3 DHA in Neurocognitive Development

- Essential component of neural membranes
- 40 – 60% of fatty acids in brain and retina
- Found mostly in growth cones during development
- Structures which give rise to axons and dendrites
- DHA essential for development of neurite elongation and branching

DHA Promotes Neurite Development in Rat Tissue Culture Study

Brain Omega-3 DHA Accumulation

Brain DHA increases from the 18th week of gestation to 2 years of age.
- Term babies are born at a rapid stage of brain development and DHA accumulation
- Preterm babies are born with low DHA stores

Low Brain DHA May Be Related to Neurocognitive Deficits in Preterm Infants

- Preterm babies are known to have lower brain and RBC DHA and have visual and cognitive delays compared to full term infants

Cod Liver Oil Supplementation During Pregnancy Influences Subsequent Cognitive Development

- Cod Liver Oil vs Corn Oil from 17-19 Weeks of Gestation Throughout Lactation 1.183 mg DHA 803 mg EPA
- + 4.1 Points Kaufman Assessment Battery at age 4 in infants born to mothers supplemented through 6 months of lactation (Helland, IB. Ped 2003; 111:e39)
- Maternal DHA Status During Pregnancy correlated with K-ABC at 7 y (Helland, IB. Ped 2008;122:e472)
- Others found no association of DHA status at birth on K-ABC at 4 and 7 y (Guys, A. Early Human Dev 2002;69:83 and Bakker,EC 2009;63:499)
Maternal DHA Supplementation and Infant Sleep State

- Supplementation with 300 mg DHA in Food Bar
- N=28 DHA 26 Control
- 3,5,or 7 x per week from 20 weeks until delivery


Maternal DHA Supplementation During Pregnancy and Sleep State Post-natal Day 1

- Arousals in Quiet Sleep
  - DHA 2.7 ± 2.6
  - Control 5.9 ± 5.8
  - p<.05

- Percent Time in Quiet Sleep
  - DHA 22.7 ± 5.7 min
  - Control 21.7 ± 4.8 min
  - p <.05


Maternal DHA During Pregnancy and Infant Problem Solving at 9 months

- Follow-up of infants
- Problem-solving improved
  - DHA CONTROL
  - solutions 2.5±1.3 1.6±1.5  (p = 0.01)
  - intentions 8.0±2.3 6.7±3.0  (p = 0.017)


DHA Supplementation During Pregnancy May Improve Neurocognitive Development

- F/U of infants
- Supplementation with 137 mg DHA/day from 24 – 28 Wks until Delivery
  - N = 31 DHA 38 Controls
- Measurements:
  - RBC DHA
  - 4,6,8 mo Preferential Looking
  - 12,18 mo Free Play Attention

Colombo, J et al Child Dev 75:1254, 2004

Maternal RBC DHA Status at Delivery Improves Infant Cognitive Development

- Preferential Looking (sec)
  - Latency to Turn (sec) Look Duration (sec)
  - Longer latency to turn when distracted and longer look duration indicates more mature concentration

Colombo, J et al Child Dev 75:1254, 2004

Maternal RBC DHA Status at Delivery Improves Infant Cognitive Development

Free Play Attention

- Longer latency to turn when distracted and longer look duration indicates more mature concentration

Colombo, J et al Child Dev 75:1254, 2004
Fish Oil During Pregnancy Improves Hand Eye Coordination at 2 ½ Years

Hand Eye Coordination Score – Griffiths Mental Development Scales

Correlations with RBC Lipids

- DHA: r = .308, p = .009
- EPA: r = .320, p = .007
- ARA: r = -.331, p = .005


CSU Omega Smart Baby Project

This project is funded by USDA CREES and AES

Infant 12 mo Bayley Scales of Infant Development (BSID III)

Maternal DHA Supplementation and Early Visual Acuity

- 135 women supplemented with 200 mg DHA/day from week 16 until delivery
- Infant Visual Acuity determined by Teller Cards
- Improved Visual Acuity at 60 days of age
- OR = 3.37 (SE 1.64)
- More infant girls in placebo group had VA below average compared to DHA group (p = .048)
- Suggests some mother might have been DHA deficient

Innis, S (Am J Clin Nutr 87:548, 2007)

Epidemiological Evidence: Seafood Consumption During Pregnancy and Cognitive Development

Infant 12 mo Bayley Scales of Infant Development (BSID III)
Data from the Danish Birth Cohort

Oken,E Am J Epidemiol, 2008

- 25,446 children
- Highest fatty fish intake during pregnancy and breastfeeding duration associated with higher child development scores at 18 mo

Adj OR = 1.29 (1.20, 1.38)

Project Viva

- Cognitive Development in 3 year olds (Oken, 2008)
- 341 mother:child diads from project VIVA
- Peabody Picture Test
- Wide Range Assessment of Visual Motor Ability (WRAVMA)
- Mean fish intake 1.5 +/- 1.4 servings/month
  40 women (12%) consumed > 2 servings/wk

Project Viva - Cognitive Outcomes at Age 3

- Improved visual motor skills and Peabody scores with >2 servings fish week compared to none
  - Net Effect Diminished Slightly By High Maternal Hair Hg Levels
  - Most Dramatic Effect in Those Consuming the Highest Amount and the Lowest Maternal Hair Hg
    *Peabody OR 2.2 (2.6, 7.0)
    *WRAVMA OR 6.4 (2.0, 10.8)
  *Highest fish intake/lowest maternal Hg vs. no fish

The Fish Paradox

Most studies have found that although fish contain MeHg, the positive benefits of fish outweigh any negative effects
Omega-3 DHA and Seafood Consumption in US Women Pregnancy

DHA & Fish Intake in Pregnancy

- DHA intake among women in U.S.
  - All women = 50-60 mg/day (NHANES, 2007-2008)
  - Pregnant U.S. women = 50-90 mg/day

- Fish intake among women in U.S.
  - All women = 2.9 ounces/week (NHANES 1999-2000)
  - Pregnant Women = 1.89 ounces/week (FDA 2008 survey)
  - Lactating Women = 2.1 ounces/week (FDA 2008 survey)

Omega Smart Baby Study: DHA Intake in Pregnant Women in Northern Colorado

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SEM</th>
<th>95% Confidence Interval</th>
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<tbody>
<tr>
<td>Total DHA (mg/day)</td>
<td>295.4 ± 22.5</td>
<td>(258.1, 332.8)</td>
</tr>
<tr>
<td>DHA from food sources (mg/day)</td>
<td>81.9 ± 5.8</td>
<td>(72.3, 91.5)</td>
</tr>
<tr>
<td>Servings of high DHA fish (servings/week)</td>
<td>0.649 ± 0.057</td>
<td>(0.564, 0.744)</td>
</tr>
</tbody>
</table>

Omega Smart Baby Study: Fish Intake in Breastfeeding Women in Northern Colorado

- Fish Servings/Week*
  - 2 Months: 0.78 ± 0.115 (3.9 oz)
  - 4 Months: 0.94 ± 0.136 (4.7 oz)
- Times Consumed Fish/Week
  - 2 Months: 1.2 ± 0.172
  - 4 Months: 1.4 ± 0.202
* Serving size defined as 5 ounces

Omega Smart Baby Study: DHA Intake in Breastfeeding Women

<table>
<thead>
<tr>
<th></th>
<th>2 mo</th>
<th>4 mo</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA mg/day</td>
<td>90</td>
<td>99</td>
<td>200</td>
</tr>
<tr>
<td>ALA g/day</td>
<td>1.0</td>
<td>1.01</td>
<td>1.3 (Al</td>
</tr>
<tr>
<td>ALA (% of total energy)</td>
<td>0.004</td>
<td>0.004</td>
<td>0.6-1.3 (AMDR</td>
</tr>
<tr>
<td>LA (g/day)</td>
<td>9.24</td>
<td>9.19</td>
<td>13 (Al</td>
</tr>
<tr>
<td>Omega-6: Omega-3 (n6:n3)</td>
<td>9.4:1</td>
<td>8.6:1</td>
<td>4.1 – 6:1</td>
</tr>
</tbody>
</table>

Omega Smart Baby Study: Breast Milk DHA at 2 Months

- Maternal Breast Milk 2 Month DHA
- 2 Month Breast Milk DHA

- P for trend = 0.045 * p<0.059
Omega Smart Baby Study: Breast Milk DHA at 4 Months

Factors Influencing the Intake of Fish in Women of Childbearing Age

- Fear of mercury
- Availability
- Unaware of benefits
- Lack ability to prepare fish

“What You Need to Know About Mercury in Fish and Shellfish”

Advice for Women Who Might Become Pregnant

US FDA/EPA
March 2004

Focus Group Data – Intake of Fish in Pregnant Women

- “Pregnant women would be willing to eat more fish if they were advised by their obstetricians or if they had an accessible reference regarding which fish to eat”

Oken, E. Am J Clin Nutr. 2010; 92:1234

Recommended Omega-3 DHA Intake During Pregnancy

- No Current U.S. DRI for DHA
- World Association of Perinatal Medicine
- March of Dimes
- 200 mg DHA per day

Forms and Formulations of Omega-3 DHA/EPA Supplements

- Fish Oil
  - Natural triglycerides (FO/FBO/CLO)
  - Reconstituted Triglycerides (rTG)
  - Free Fatty Acids (FFA)
  - Ethyl/Methyl Esters (EE/ME)
  - Emulsified Liquids
  - Algal Oils
    - 3 major producers have products with GRAS designation
    - US products high in DHA, little or no EPA
    - Australian product contains both EPA and DHA

Which Form of Supplemental DHA Do You Recommend for Pregnant and Breastfeeding Women??
**Bioavailability of DHA from Supplements**

**Omega-3 FO Capsules = Fish = DHA Fortified Food**

- Fish vs. Capsules vs Fortified Foods
  
  Kirkhus B, Br. J Nutr 2001

- Algal DHA vs Salmon
  
  Arterburn M, JADA 2008

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**Bioavailability of DHA from Supplements**

**Emulsified Oils = Standard FO Capsules**

- Emulsified Liquid Formula = significantly greater incorporation of EPA but non-significant increase in DHA into plasma phospholipids
  
  Raatz S, JADA 2009

- Emulsified Liquid Formula = significantly greater incorporation of both EPA and DHA into plasma triglycerides
  
  Garaiova J, Nutr J 2007

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**Comparative Bioavailability of Krill Oil**

- Krill Oil vs Reesterified TG vs Ethyl Esters
  
  Schuchardt J, Lipids in Health & Dis 2011

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**Bioavailability of DHA from Supplements**

**Mixed Results Comparing rTG or natural FO with EE**

- Natural fish oil DHA and EPA more rapidly incorporated into RBC than EE
  
  Neubronner J, Eur J Clin Nutr 2011

- Natural fish oil or rTG → quicker and greater increase in n-3 index than EE
  
  Schuchardt J, PG LT Ess FA 2011

- Natural FO = EE incorporation into RBC
  
  Harris W, AJCN 2007

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**Krill Oils**

- Krill Oil (KO)
  
  - Euphrasia suberba
  
  - DHA and EPA present as phospholipids
    
    - Primarily phosphatidylcholine
To Improve Tolerance in Pregnancy

- Freezing capsules may help
- Enteric coated capsules may help
  - One study showed ↓ absorption but bioavailability still good
- Pure liquid oil may be better tolerated
  - If Cod Liver Oil – should have Vitamin A removed
- High product quality MOST important factor

2010 Dietary Guidelines for Americans

**Women who are pregnant or breastfeeding**

Consume 8 to 12 ounces of seafood per week from a variety of seafood types.

Due to their high methyl mercury content, limit white (albacore) tuna to 6 ounces per week and do not eat the following four types of fish: tilefish, shark, swordfish, and king mackerel.


Thank You and Questions