Powerhouse Nutrients for Optimal Growth and Development: Evidence Based Guidelines for Optimum Growth and Development

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Powerhouse Nutrients for Prepregnancy, Pregnancy and Lactation

- Folic Acid
- Iron
- Vitamin D
- Calcium
- Energy/Protein for Optimal Weight Gain
- Omega-3 DHA
Folic Acid Recommendations

- **CDC**
  - Women with a Hx of NTD should consume 4 mg folic acid per day (1991) from the 1\textsuperscript{st} month prior to conception through the first 3 months of pregnancy
  - All women of childbearing age in the US who are capable of becoming pregnant should consume 400 mcg folic acid per day (1992)

- **IOM**
  - Women capable of becoming pregnant should consume 400 mcg folic acid per day from supplements, fortified foods and a varied diet

- **DRI**
  - Pregnant women 600 mcg folic acid per day: 400 mcg from supplements and fortified foods and 200 mcg from food sources

- **2010 Dietary Guidelines**
  - 400 mcg from supplements plus 200 mcg from food sources for women of childbearing age
Folic Acid

• Numerous benefits to women before, during and after pregnancy
  • Well Documented
    • Decreased risk of NTDs
    • Prevention of macrocytic anemia
  • Emerging Science
    • Possible decreased incidence preterm birth
    • Possible decreased risk preeclampsia
Folic Acid and Neural Tube Defects

• In majority of NTDs, the primary defect is abnormal utilization of folic acid
  • Several gene variants have been identified that result in low activity of enzymes involved in folic acid metabolism
    • N5,N10 MTHFR gene and/or methionine synthase reductase (MTTR) gene
  • High levels of folic acid restore enzyme activity
  • Greatest predictor of risk of NTDs is low plasma and RBC levels of folate
• Estimated 40 - 60% NTDs Preventable with Folic Acid Supplements
Flour Fortification Program

Flour fortified with 140 mcg folic acid /100 g

- Amount estimated to increase folic acid intake an average of 100 mcg/day
  - Actually doubled that (about 220 mcg/day increase)
- Theoretically expected to decrease NTDs 50 – 70%
- Since fortification program in U.S. → decreased NTDs almost 40%
- World wide reduction in NTDs with folic acid supplements reported to be between 20 – 50%
Issue: Should the Level of Folic Acid Fortification Be Increased?

• Justification
  • 50% of all pregnancies are unplanned and only 30 – 40% of women of reproductive age take supplements

• Problem with increasing supplemental level of folic acid
  • Public health approach exposes everyone to high levels
  • Expected additional benefit of reducing CHD was not realized
    • Framingham data show ↑ serum folate ↓ Hcys but no ↓ in CHD mortality
  • Since genetics and other risk factors (DM, Obesity) play a role in NTDs, it is unlikely to get a further reduction by increasing folic acid intake
In 2010, CDC named folic acid fortification as one of the top 10 great public health achievements in the last 10 years.
Ethnic Disparity in NTD Reduction

Increased Prevalence Hispanic 1.22 (1.11-1.31)
Nat’l Birth Defects Prevention Study

- Largest ongoing birth defect study in US
  - Report of 565 NTD cases 3691 controls
- Failed to show linear decrease in NTDs with folic acid at stratified levels of intake
- About half of DFE came from diet, half from supplements
- DFE between cases and controls similar

Mosley, B Am J Epidemiology 169:9,2009
Risk: Benefit of Folic Acid Fortification

• Benefit
  • 2009 estimate of medical costs for the first year of life for a child with spina bifida was $52,415
  • Lifetime medical cost for a person with spina bifida estimated to be $460,923
  • Lifetime non-medical cost for a child with spina bifida, which includes education and developmental services such as early intervention services and counseling, estimated to be $56,511

• Potential Risk
  • Some recent evidence that high folic acid levels increase risk of recurrence of colon cancer (at 1000 mcg/d 3x risk) and hypermethylation (5000mcg/d) of DNA (a condition associated with development of cancers of all types)
Emerging Benefits of Folic Acid in Pregnancy
Folic Acid Supplements Throughout Gestation May Reduce Preterm Birth

National Birth Defects Prevention Study

- Survey of periconceptional intake of folate and folic acid
  September 1998 – December 2005
- OR for PT birth 1.44 (1.01, 2.04) in those with lowest quartile of folic acid intake compared to highest
Folic Acid Supplements in Early Second Trimester May Reduce Preeclampsia

- Prospective cohort study
- 2945 Pregnant women with singleton pregnancies
- Folic acid alone or multivitamin
  - 0.1 – 2.0 mg/day (79% were 1 mg/day)
  - 62% took supplement prior to conception, 38% post-conception
- Decreased risk preeclampsia RR 0.37 (0.18,0.75)

Wenn SW et al  Am J Obstet Gynecol 2008;198:45e1
Food Sources of Folate Compared to one slice of enriched bread (37 mcg)

<table>
<thead>
<tr>
<th>Food</th>
<th>DFE /serv</th>
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<tbody>
<tr>
<td>½ c spinach/asparagus</td>
<td>130</td>
</tr>
<tr>
<td>½ c broccoli</td>
<td>39</td>
</tr>
<tr>
<td>1/2 c peas</td>
<td>50</td>
</tr>
<tr>
<td>1/2 c lentils</td>
<td>179</td>
</tr>
<tr>
<td>1 oz cold cereal</td>
<td>100 – 400</td>
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<tr>
<td>½ c oatmeal</td>
<td>80</td>
</tr>
<tr>
<td>1/2 c orange juice</td>
<td>37</td>
</tr>
<tr>
<td>1 c strawberries</td>
<td>26</td>
</tr>
</tbody>
</table>
Folic Acid

• FREE PATIENT AND PROVIDER EDUCATION MATERIALS

http://cdc.gov/ncbddd/folicacid/freematerials.html
Vitamin D
Prevalence of Suboptimal Vitamin D in US

- Prevalence of Vit D Deficiency (< 50 nmol/L) in North Eastern US
  - Pregnant white women 15%
  - Pregnant black women 29%

- Prevalence of vitamin D insufficiency in North Eastern US (< 75-80 nmol/L)
  - 66 – 100%

- IOM estimates of inadequate intake of Vitamin D among pregnant women in US
  - 5 – 29%
Evidence is inconclusive but Vitamin D may be protective against preeclampsia, diabetes, infectious disease

Vitamin D and preeclampsia

- ↑ risk preeclampsia in Vit D deficient women (serum 25-OH D3 < 37.5 nmol/L)
  OR 2.4 (1.1, 5.4)
- Conversely, two recent studies (one unpublished) showed no differences in first and second trimester 25-OH D3 levels in women at low or high risk for preeclampsia who did or did not develop preeclampsia
  Shand et al BJOG 2010;117:1593
- Two small recent studies show ↑ risk early/severe preeclampsia with low plasma 25-OH D3
  - aOR severe preeclampsia with low 25-OH D3 5.41 (2.02,14.52)  Baker et al 2010
  - Each 25 nmol/L increase in serum 25-OHD3 →63% reduction in odds for severe preeclampsia  Robinson 2010
Vitamin D and Gestational DM

• Inconclusive

• Conflicting results in 4 observational studies of vitamin D status and gestational DM
  • Low 25-OH D3 in 1st trimester associated with ↑ risk gestational DM
    (Clifton-Bligh RJ et al 2008 Diabet Med 25:678-84)

• More recently, studies show no relationship between 1st or 2nd trimester 25-OH D3 and glycemia/insulin sensitivity during pregnancy
  (Makgobad 2011, Diabetes Care:1091-3)
• Dietary Recommend Intake (DRI) 600 IU/day for pregnancy and lactation (revised 2010)

• IOM position “limited evidence for maternal and fetal benefits and concerns about toxicity”

• DRI increased ONLY in response to pressure from the scientific community
• NO need for routine screening of plasma levels of 25-OH D3 in pregnancy
• Screening may be indicated for women considered to be at high risk
• To correct severe Vitamin D deficiency during pregnancy, 1000 IU – 2000 IU/day is considered safe
• Recommended intakes beyond that contained in prenatal vitamins should await results of ongoing RDBPCT
Exclusively breastfed babies should receive a supplement of 400 IU/day (APACON)

• Maternal vitamin D is poorly transferred to breast milk to achieve optimal levels of plasma 25-OH D3 levels in infants

• Achievement of adequate 25-OH D3 levels from breast milk would require maternal supplement of 4,000 IU/day

• Maintenance of optimal maternal plasma 25-OH D3 levels during lactation requires 1000 IU/day
Fish and Omega-3 Fatty Acids
Benefits of DHA and Seafood Consumption During Pregnancy

Maternal Benefits

• Prevention and/or management of perinatal depression
• Increase in gestational length and potential reduction of preterm birth
• Improved DHA content of breast milk

Benefits to Babies

• Improved visual acuity
• Enhanced cognitive development leading to stronger motor, social and communication skills, later IQ
• Emerging evidence ??? lower body fat in Infancy and childhood
Nutrient Contributions of Fish

• Rich Source of Omega-3 DHA and EPA

• Rich source of Vitamin D
  – 1 oz salmon provides the same amount of Vitamin D as 1 cup of milk

• Rich Source of Selenium
Fish Consumption During Pregnancy May Decrease the Incidence of Preterm Birth


(8,729 dietary questionnaires from pregnant women)
Maternal – Fetal Medicine Network

- Klebanof MA et al
- 40% reduction in aOR for PT Birth in women consuming fish >3 times/week compared to 1 time or less/month
  \[ OR = 0.60 (0.38, 0.95) \]
- No additional benefit beyond 3 serv/week and no effect of added FO supplements
DHA Increases Gestational Length
Denver Health Trial – Omega-3 Enriched Foods In Pregnancy

• For each 1% increase in Maternal RBC DHA there is a corresponding 1.4 day increase in gestation (p = .0056)

* Signif Different From Control  p<.05
DHA-enriched eggs = 137 DHA mg/day vs. Ordinary Eggs

DHA increased gestation by 6.0 + 2.3 days (p=.009)


Systematic Review

Significant reduction in rate of early preterm delivery (<34 wks)
RR .39 (0.18,0.84)

Other studies showed no effect of fish oil on prevention of preterm birth in populations with high baseline intakes of seafood

Helland IB. Ped 108:e1, 2001
Knudsen V. BJOG 113:536, 2006
Summary of Current Evidence

- Some question remains regarding the effect of fish oil or DHA supplementation on preterm birth
- The greatest effects are seen comparing women who consume little or no fish to those who consume 2 or more serv/week
- Little additional effect of supplements in women who consume large amounts of fish
Maternal DHA Supplementation Prevents Decrease in Maternal DHA Stores During Gestation

Women supplemented with 0, 300 or 600 mg DHA/d

Women supplemented with fish oil = 800 mg DHA and 1200 mg EPA/d

% Total FA - RBC

Change in % Total FA- RBC

Omega-3 for Baby and Me

Harper et al Obstet and Gynecol 115:234, 2010
Fish Consumption During Pregnancy and Breastfeeding is Associated with Optimal Cognitive 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
• DHA essential for development of neurite elongation and branching
DHA Promotes Neurite Development in Rat Tissue Culture Study

Control

+ DHA

Calderon and Kim, J. Neurochem. 2004
DHA Accumulation in Human Brain

Brain DHA increases from the 28th 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.


Slide courtesy of J. Hibbeln
Low Brain DHA May be Related to Neurocognitive Deficits in Preterm Infants

• Preterm babies are known to lower brain and RBC DHA and have visual and cognitive delays compared to full term infants
ALSPAC Study: Low maternal omega-3 consumption from seafood and Associated with low verbal IQ among children

Slide Courtesy of J. Hibbeln

Data from the Danish Birth Cohort

• 25,446 children

(Oken, E Am J Epidemiol, 2008)

• 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, E  Am J Epidemiol April 1, 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 serv/month
  
  40 women (12%) consumed > 2 serv/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
Most studies have found that although fish contain MeHg, the positive benefits of fish outweigh any negative effects.
FDA/EPA Advisory On Seafood In Pregnancy  March 2004

What You Need to Know About Mercury in Fish and Shellfish

Advice for
Women Who Might Become Pregnant
Women Who are Pregnant
Nursing Mothers
Young Children

from the
U.S. Food and Drug Administration
U.S. Environmental Protection Agency
THE FACTS

“Fish and shellfish are an important part of a healthy diet. Fish and shellfish contain high-quality protein and other essential nutrients, are low in saturated fat, and contain omega-3 fatty acids. A well-balanced diet that includes a variety of fish can contribute to heart health and children’s proper growth and development. So, women and young children in particular should include fish or shellfish in their diets due to the many nutritional benefits”
FDA/EPA Advice (2004)

- Eat Up to 12 ounces (2 average meals) a week of a variety of fish and shellfish that are lower in mercury
  - Which includes up to 6 oz per week of albacore tuna

- Avoid:
  - Shark
  - Swordfish
  - King Mackerel
  - Tile Fish
What Pregnant Women Heard........

“Better Safe Than Sorry”
DHA & Fish Intake in Pregnancy

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

• DHA intake among women in U.S.
  • All women = 50-60 mg/day (NHANES, 2007-2008)
  • Pregnant U.S. women = 50-90 mg/day
<table>
<thead>
<tr>
<th></th>
<th>Mean ± SEM</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total DHA (mg/day)</strong></td>
<td>295.4 ± 22.5</td>
<td>(258.1, 332.8)</td>
</tr>
<tr>
<td><strong>DHA from food sources (mg/day)</strong></td>
<td>81.9 ± 5.8</td>
<td>(72.3, 91.5)</td>
</tr>
<tr>
<td><strong>Servings of high DHA fish (servings/week)</strong></td>
<td>0.649 ± 0.057</td>
<td>(0.554, 0.744)</td>
</tr>
</tbody>
</table>
Omega Smart Baby Study: Fish Intake in Lactation

2 Months

Fish Servings/Week*

0.78 ± 0.115
(3.9 oz)

Times Consumed Fish /Week

1.2 ± 0.172

4 Months

0.94 ± 0.136
(4.7 oz)

1.4 ± 0.202

* Serving size defined as 5 ounces
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
Recommendations For Omega-3 DHA and Seafood Intake During Pregnancy and Lactation
Recommended Omega-3 DHA Intake During Pregnancy

• No Current U.S. DRI for DHA

• World Association of Perinatal Medicine
  • 200 mg DHA per day

Koletzko B, J Perinatal Med 2008
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.

Is Dietary DHA Essential?

- Conversion of plant based ALA (18:3n-3) to DHA is less than 0.1% to 1%
- Inadequate to provide for optimal accretion during periods of rapid growth
  - 60 mg DHA accreted in fetal brain each day in 3rd trimester
  - Another 70 – 80 mg/day in the first 6 months of life
- Up to 1/3 of women possess SNPs in the genes which code for the enzymes that convert ALA to DHA and have low blood, RBC and breastmilk DHA levels
- The US diet is high in omega-6 fatty acids, saturated and trans fatty acids which inhibit conversion
Gestational Diabetes May Increase Need for Long Chain Omega-3 DHA

• Diabetes impairs synthesis of long chain omega-3 and omega-6 fatty acids from 18C precursors
  
  Brenner R, 2000

• Infants born to mothers with gestational diabetes have low DHA levels
  
  Min Y, 2004
Use of Supplements for Women Who Can't Eat or Don't Like Fish

• Capsules should provide at least 200 mg DHA per day for pregnancy
• No real difference fish oil vs algal oil on bioavailability or pregnancy outcomes studied to date
• No reports of new Krill (Red Omega-3) supplements being used in pregnancy
• Levels up to 3000 mg/day (FDA GRAS limit) are safe for healthy adults
  • In pregnancy, up to 2700 mg (920 mg DHA +1300 mg EPA) /day have been used safely
Selection of FO/DHA Supplements in Pregnancy and Lactation

- **Cost**
  - OTC supplements less expensive than Rx prenatal multivitamin + DHA products
- **Amount of DHA and EPA per serving/serving size**
- **Stored in tight opaque container**
- **Presence of anti-oxidants (Vitamin E)**
- **Quality and Purity**
  - GOED membership or USP verified
  - Independent Third Party Testing
    - International FO Standards (www.ifosprogram.com)
    - Consumer Laboratories (www.consumerlab.com)
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
Thank You!

“Looks like Omega-3 Fish Oil really works”