The Role of Omega 3's in Pregnancy

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Do pregnant and lactating women need omega 3s? And how much?

Omega 3's in Pregnancy systematic reviews

- Effect of pregnancy fish oil supplementation:
  - Mean duration of gestation was increased by 2.5 days
  - No prevention of preterm birth <37 weeks GA,
  - significantly reduced the risk of **early** preterm birth (<34 weeks GA)
- No consistent benefit during pregnancy and/or lactation on child neurodevelopment visual acuity

DOMInO – DHA to Optimize Mother Infant Outcome

- Designed to assess postnatal depression in women and neurodevelopmental outcome in early childhood
- Largest trial of n-3 LCPUFA supplementation with **2399 women**
- Australian women consume low DHA (~100mg/d)
- DOMInO included more women than systematic review
- Also assessed pregnancy outcomes

Makrides, Gibson, McPhee et al, JAMA 2010;304:1675-83

Study Design

- Randomized controlled trial
- Women with singleton pregnancy at <20 weeks gestation, general population
- DHA group – 3x500mg capsules of DHA-rich fish oil concentrate providing **800mg of DHA/day**
- Control group – 3x500mg capsules containing a blend of 3 vegetable oils (to match Australian diet) with **no DHA**
- Intervene from study entry to birth

DHA and pregnancy outcome

DOMInO Gestation Duration (800mg DHA, 100mg EPA)

	DHA (n=1197)	Control (n=1202)
Duration of gestation, d	282	281 p=0.05
Birth <37 weeks'	5.6%	7.3% p=0.09
Birth <34 weeks'	1.1%	2.3% p=0.03
Post-term induction/ post-term pre-labour C-section	18%	14% p<0.01

Makrides, Gibson, McPhee et al, JAMA 2010;304:1675-83

Birth anthropometrics

	DHA (n=1197)	Control (n=1202)	Adjusted effect (95% CI)
Birth weight (g)	3475	3407	68 (23, 114)
Birth weight <2500g (%)	3.4	5.3	0.65 (0.44, 0.96)
Birth weight >4000g (%)	16.3	12.8	1.27 (1.05, 1.55)
Birth weight z-score	0.28	0.22	NS
SGA for weight (%)	6.1	6.8	NS
LGA for weight (%)	17.1	14.4	1.19 (0.99, 1.43)

Makrides, Gibson, McPhee et al, JAMA 2010;304:1675-83
Zhou et al, AJCN 2012;95:1378-1384

DOMInO neonatal outcomes

	DHA	Control
Neonatal hypoglcaemia	70/1197, 5.8%	58/1202, 4.9%
Oxygen for CLD	2/1184, 0.17%	4/1179, 0.34%
Neonatal convulsion	0/1184	5/1177, 0.42%*
Admission to NICU	21/1197, 1.8%	37/1202, 3.1%*
Brain injury	0/1184	5/1176, 0.43%*
NEC	1/1184, 0.08%	0/1177
Sepsis	3/1184, 0.25%	2/1177, 0.17%
Perinatal death (stillbirth or death in the first 28 days)	3/1197, 0.25%	12/1202, 1.00%*

*p<0.05

Zhou et al, AJCN 2012;95:1378-1384

Gestational Diabetes (GDM) and Pre-Eclampsia (PE)

	DHA (n=1197)	Control (n=1202)	Adjusted effect (95% CI)
GDM based on GTT	5.8%	5.6%	1.04 (0.75, 1.44)
GDM clinical diagnosis	8.1%	8.3%	0.97 (0.74, 1.27)
PE based on PIH and proteinuria	5.0%	4.9%	1.03 (0.72, 1.48)
PE clinical diagnosis	4.3%	4.9%	0.87 (0.60, 1.25)

PIH=pregnancy induced hypertension

Zhou et al, AJCN 2012;95:1378-1384

Kansas DHA Outcomes Study (KUDOS), Carlson et al, 2013

	Placebo N=154	DHA N=147	P-value
GA (d)	272.7	275.6	0.041
Preterm birth (<37 wks)	8.8%	7.8%	NS
Early preterm birth (<34 wks)	4.8%	0.6%	P=0.025
NICU admission	8.8%	8.4%	NS
Days in NICU (mean #)	38.4	7.8	P=0.034

Randomized to 600 mg DHA/d or placebo at a mean of 14 wks gestation

Carlson et al, AJCN 97;808-15 2013

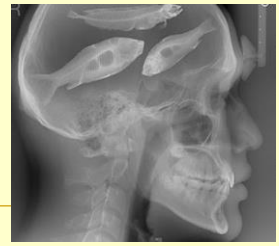
Updated Systematic Review

Variable	Cochrane review 2006	Updated Cochrane review (unpublished)
Mean Difference in Gestation Length (d)	**2.5 (95% CI 1.0 to 4.1) 1621 women, 3 trials**	**2.0 (95% CI 1.1 to 3.0) 4289 women, 5 trials**
Relative Risk of Preterm Birth (<37 w)	0.92 (95% CI 0.79 to 1.07) 1916 women, 5 trials	0.92 (95% CI 0.80 to 1.04) 5586 women, 8 trials
Relative Risk of Early Preterm Birth (< 34 w)	**0.69 (95% CI 0.49 to 0.99) 860 women, 2 trials**	**0.60 (95% CI 0.44 to 0.81) 3560 women, 4 trials**

No effect in Mexico study (400mg DHA)

What about the brain? Does DHA play a role in:

- Post natal depression?
- Cognitive development in infancy?



DHA and Risk of postnatal depression

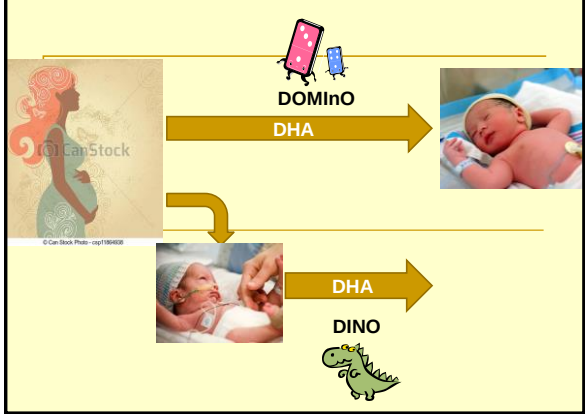
Variable	DHA n=1197	Control n=1202	Adj. RR (95% CI)
All women EPDS>12, %	**9.67**	**11.19**	**0.85 (0.70,1.02)**
6 wk	9.61	10.88	0.87 (0.68,1.10)
6 mo	9.74	11.50	0.83 (0.66,1.05)
New medical diagnosis during study, %	3.39	4.12	0.80 (0.62,1.02)
Subgroup, hi-risk women	N=298	N=287	
EPDS>12, %	**20.9**	**24.2**	**0.87 (0.68,1.12)**
6 wk	21.2	22.1	0.96 (0.71, 1.30)
6 mo	20.8	26.2	0.81 (0.60, 1.08)

Note: Effect size much smaller than suggested by cohort studies

Summary

- There is consistent evidence that n-3 LCPUFA given in the 2nd half of pregnancy will extend the mean gestation
- The DHA dose > 600mg/d for women consuming Western diets
- While there is no evidence that n-3 LCPUFA, in the range of levels tested, causes direct harm, the fact that normal gestation is extended could be a problem

What about the infant?



DINO and DOMInO

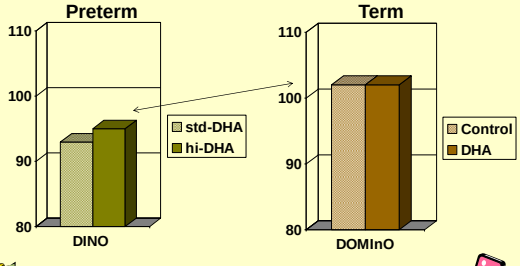
- **D**HA to **I**mprove **N**eurodevelopmental **O**utcome
- 657 infants born <33 weeks gestation
- >95% follow-up
- Test dose: 900mg/day largely to lactating women
- Intervention to 40 w PMA
- JAMA 2009;301:175-82

- **D**HA to **O**ptimise **M**other **In**fant **O**utcome
- 2399 pregnant women from 20 weeks gestation
- >95% follow-up
- Test dose: 800mg/day to pregnant women
- Intervention to delivery
- JAMA 2010;304:1675-83

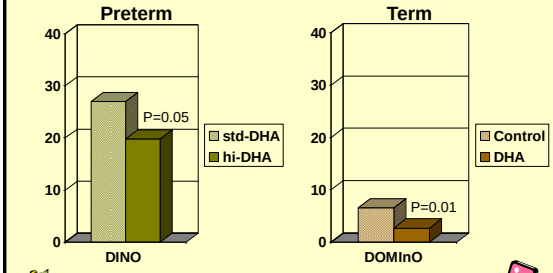
Development in DINO and DOMInO

- Cognitive (and Motor) Development assessed using the Bayley Scales of Infant Development at 18 months
- Provide standardized developmental quotient (DQ) scores

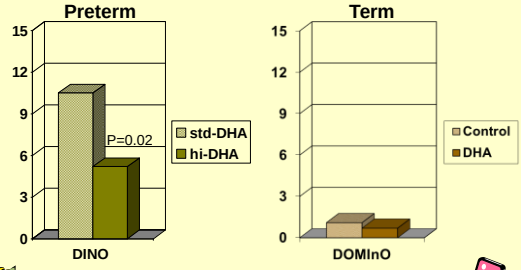
Mean DQ from Bayley mental/cognitive scales



Percentage with DQ < 85 (mild cognitive delay)



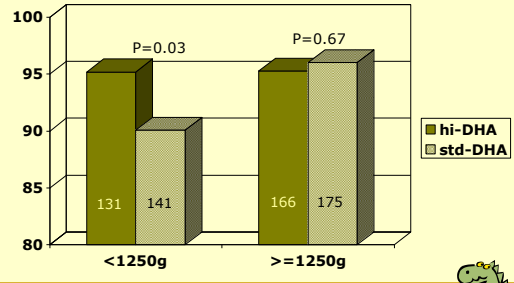
Percentage with DQ < 70 (major cognitive delay)



Who are the susceptible children?

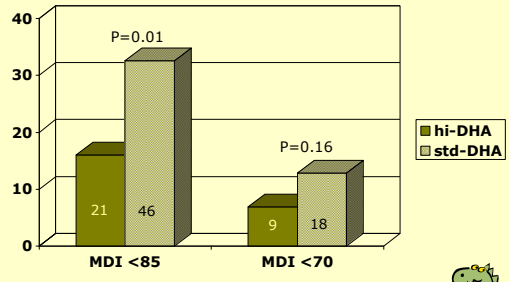
- Preterm infants with the lowest gestational age or lowest birth weight
- The sickest infants

Bayley mental DQ by birth weight strata



Makrides, Gibson, et al, JAMA 2009;301:175-82

Percentage of Infants <1250g with Mild and Significant Mental Delay



Makrides, Gibson, et al, JAMA 2009;301:175-82

Summary: the tail of preterm infants

- Significant interaction effect by the pre-specified randomisation strata (birth weight <1250g or ≥1250g)
- Differences between the groups were evident in infants born <1250g but not those born weighing ≥1250g
- Consistent with hypothesis that infants born at earliest gestations are the most vulnerable to DHA insufficiency

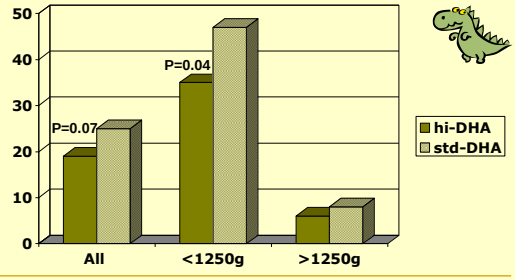
Growth

DOMInO: No Effect of DHA on Growth

- At 3 and % years -1531 children (92.2%)
- No difference in:
  - BMI z-score and
  - % body fat mass
  - overweight or obese
  - Body weight
  - height z-scores
  - waist and hip circumferences
  - Total and % lean mass

Respiratory

DINO: Percentage of infants requiring oxygen at 36 weeks



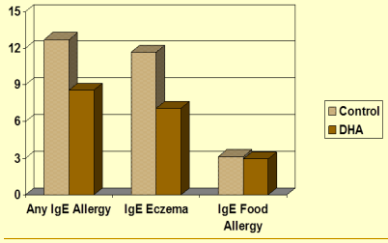
Manley B et al. *Pediatrics* 2011;128;e71

Allergy

DOMInO: Allergy at 1 year

- 706 families with high hereditary risk
- Assessed for IgE mediated allergies at 1 year

Palmer et al, BMJ, 2012;344:e184



The effect had disappeared by age 3

Summary

- There is consistent evidence that n-3 LCPUFA given in the last trimester either *in utero* or *ex utero* results in a range of clinical benefits to the child
- Dose for preterm infants ~ 60mg/kg/d
- Dose for term infants not clear
- There is no evidence that n-3 LCPUFA, in the range of levels tested, causes harm

The CNRC/FoodPlus Team