



Maternal-Fetal Medicine and Perinatology Society of Turkey  
**X National Congress**

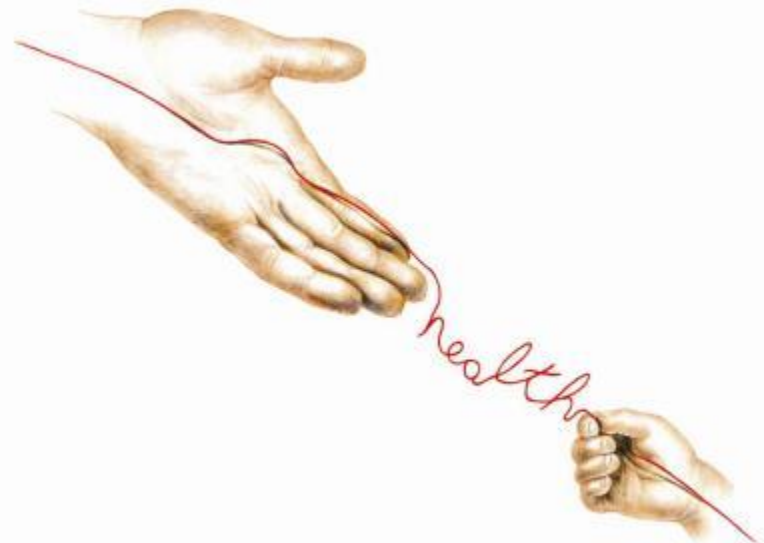
October 27-30, 2016 Harbiye Military Museum, Istanbul/Turkey



# Should we give Magnesium, Omega-3 and Iodine supplement in pregnancy? Recommendations of guidelines

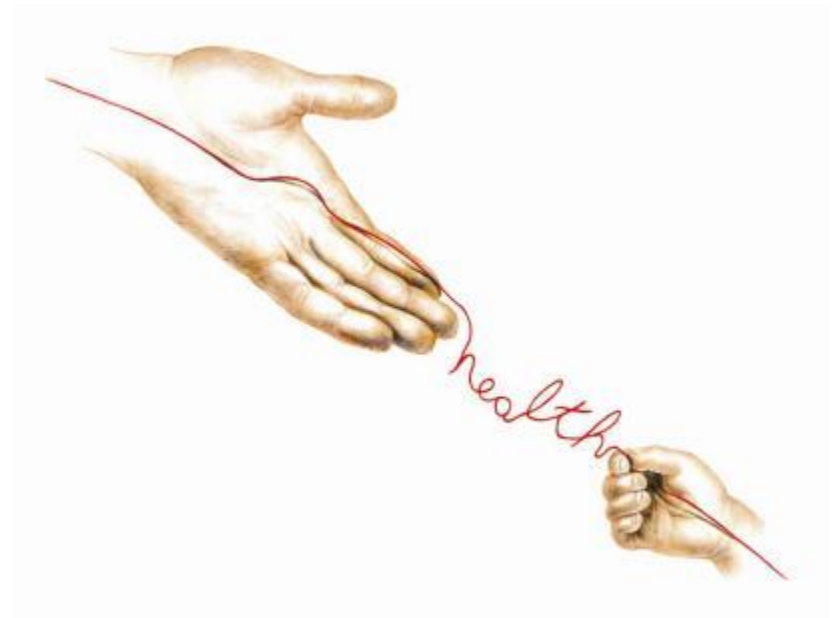
**Irene Cetin**

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University of Milano  
Hospital Luigi Sacco  
[irene.cetin@unimi.it](mailto:irene.cetin@unimi.it)*



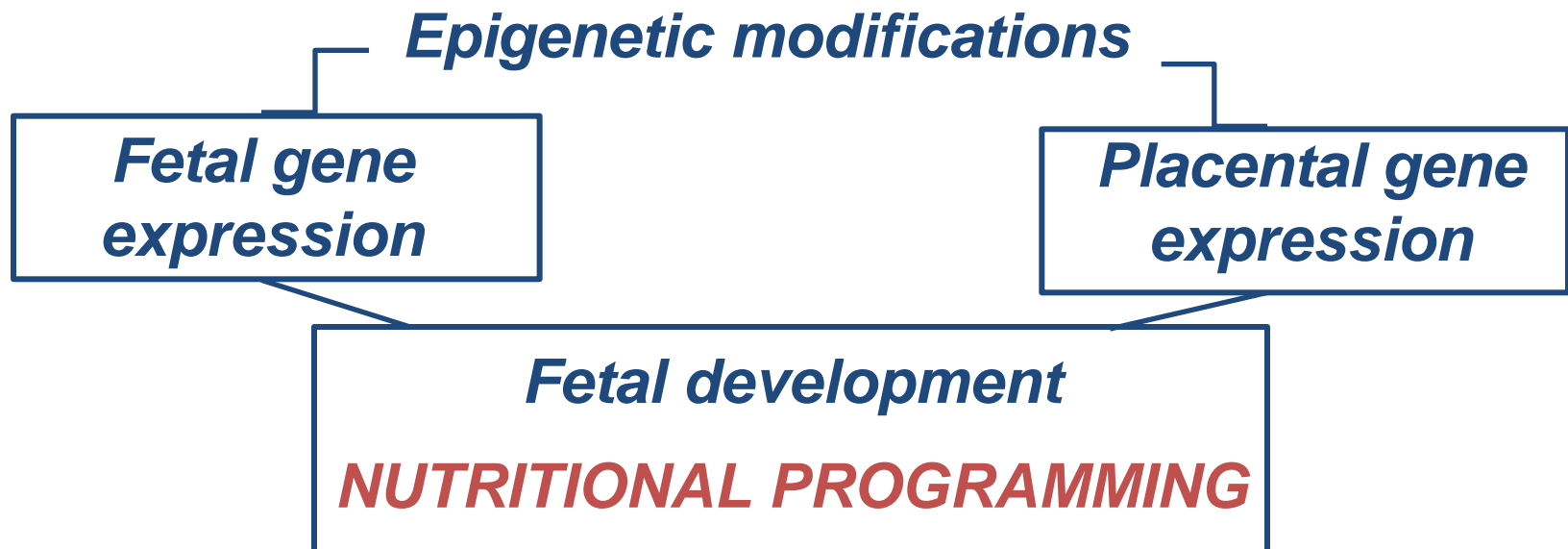
## *outline*

- ✓ **nutritional facts**
- ✓ omega 3 - DHA
- ✓ iodine
- ✓ magnesium
- ✓ key points

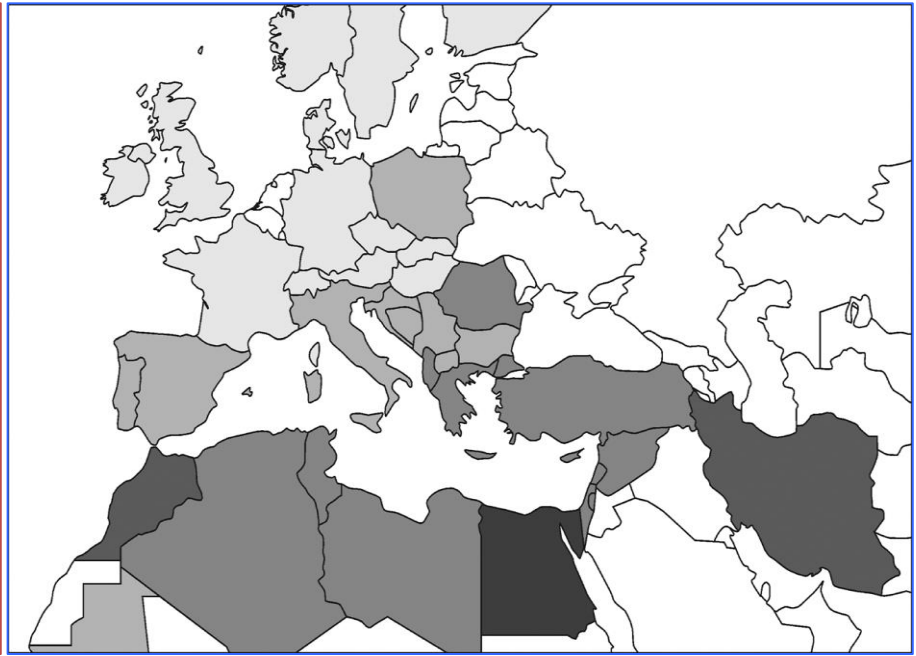


# Maternal nutrition and programming

- ***Maternal diet is one of the main players in intrauterine programming***, as macro and micronutrients are direct regulators of DNA stability and phenotypic adaptation, ***by influencing the availability of methyl donors and mechanisms promoting DNA stability***



# Dietary pattern change -Mediterranean Adequacy Index



Map of the adherence to the Mediterranean dietary pattern, comparing Mediterranean adequacy index value  
(□, 0.00–0.99; □, 1.00–1.99; □, 2.00–2.99; □, 3.00–3.99; □, 4.00–4.99; □, 5.00–5.99)

1961-1965

MAI Worldwide: 2.86

MAI Mediterranean Countries: 3.44

**MAI Italy: 3.30**

**MAI TURKEY: 5.03**

2000-2003

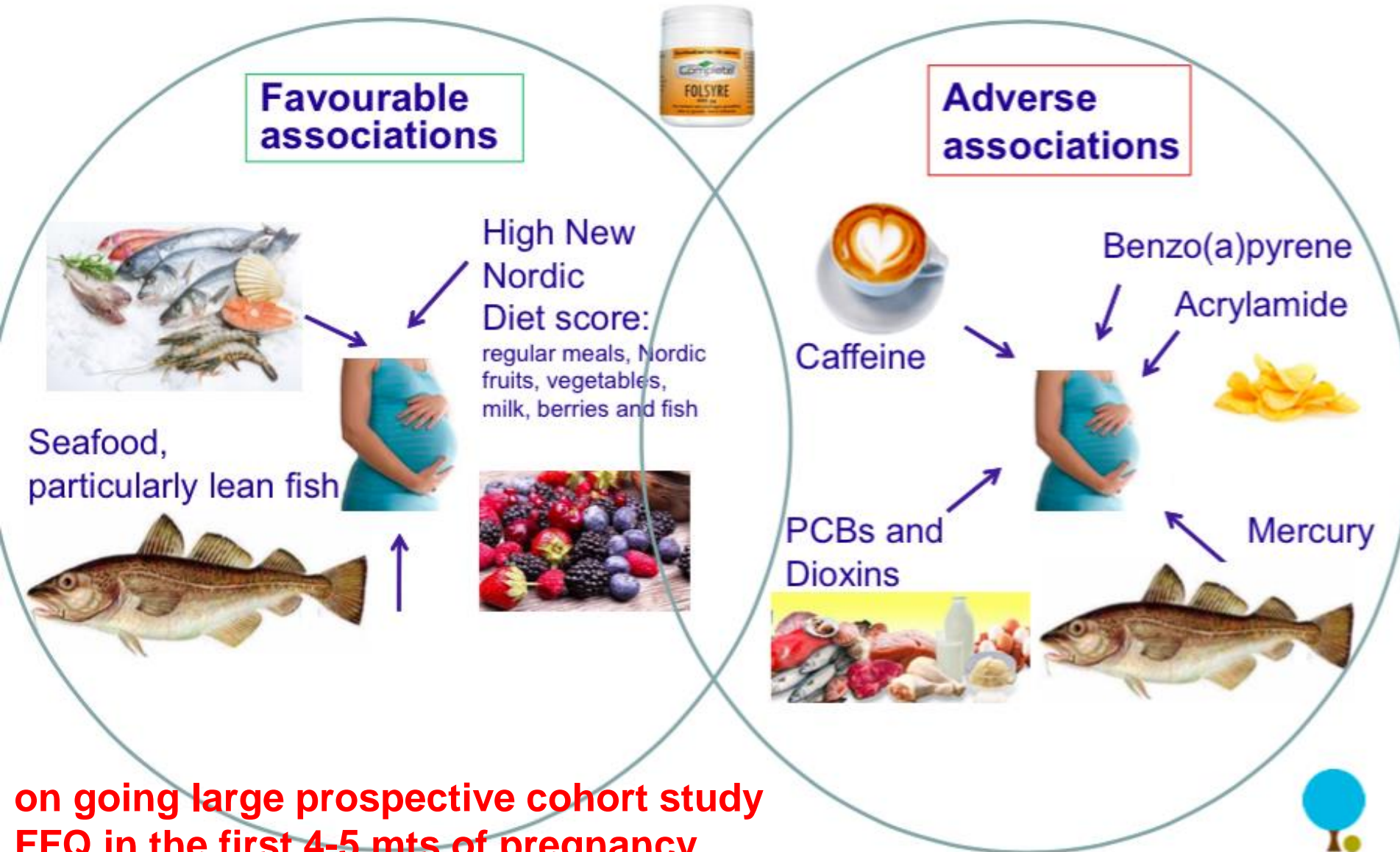
MAI Worldwide: 2.03

MAI Mediterranean Countries : 1.98

**MAI Italy: 1.62**

**MAI TURKEY: 2.80**

# Maternal diet and birth size





## *outline*

- ✓ nutritional facts
- ✓ **omega 3 - DHA**
- ✓ iodine
- ✓ magnesium
- ✓ key points



# Effects of **fish – omega 3** on pregnancy outcome

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BMJ. 2002 Feb 23;324(7335):447.

**Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study.**

Olsen SF<sup>1</sup>, Secher NJ.

**CONCLUSION:** Increased consumption of omega 3 can prevent low birth weight, pre-term labour and pre-eclampsia.

**Fish consuming populations** have on average:

- ✓ longer gestations (1.6 -2.6 days in mean);
- ✓ heavier neonates (47 –54g);
- ✓ less incidence of LBW
- ✓ less incidence of perinatal death

*Olsen SF et al . J Epidemiol Community Health 1985*

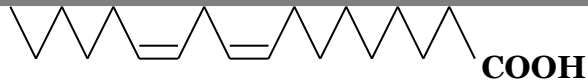
*Jensen CL. Am J Clin Nutr 2006*

*Berghella JMFNM 2015*

**omega 6**

# ESSENTIAL FATTY ACIDS

**omega 3**



**Linoleic Acid**

**18:2 n-6**



**Alfa-Linolenic Acid**

**18:3 n-3**

PGE1

PGF1

TXA1

LTA3

LTC3

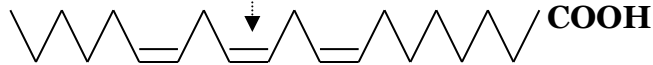
LTD3



*D5-6 desaturase*

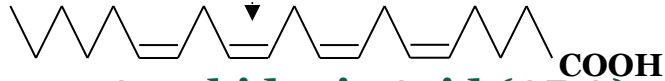


**SUBSTRATE  
COMPETITION**



**Diomogammalinolenic Acid**

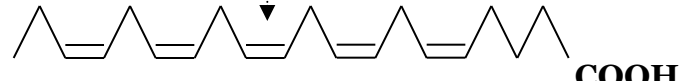
**18:3 n-6**



**Arachidonic Acid (ARA)**

**20:4n-6**

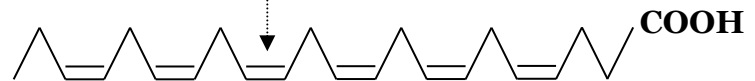
**-smooth muscle contraction  
(uterus, blood vessels)  
-ductus arteriosus persistency  
-coagulation**



**Eicosapentaenoic Acid (EPA)**

**20:5n-3**

**-blood fluidity  
-smooth muscle relaxation  
-antiarrhythmic effect  
-stabilization of plaques**



**Docosahexaenoic Acid DHA**

**22:6n-3**

**-SNC deposition (neuronal  
plasticity) - retina pigments**

PGD3

PGE3

PGF3

PGI3

TXA3

LTA3

LTB3

LTC3

PGD2

PGE2

PGF2

PGI2

TXA2

LTA4

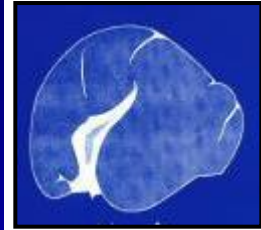
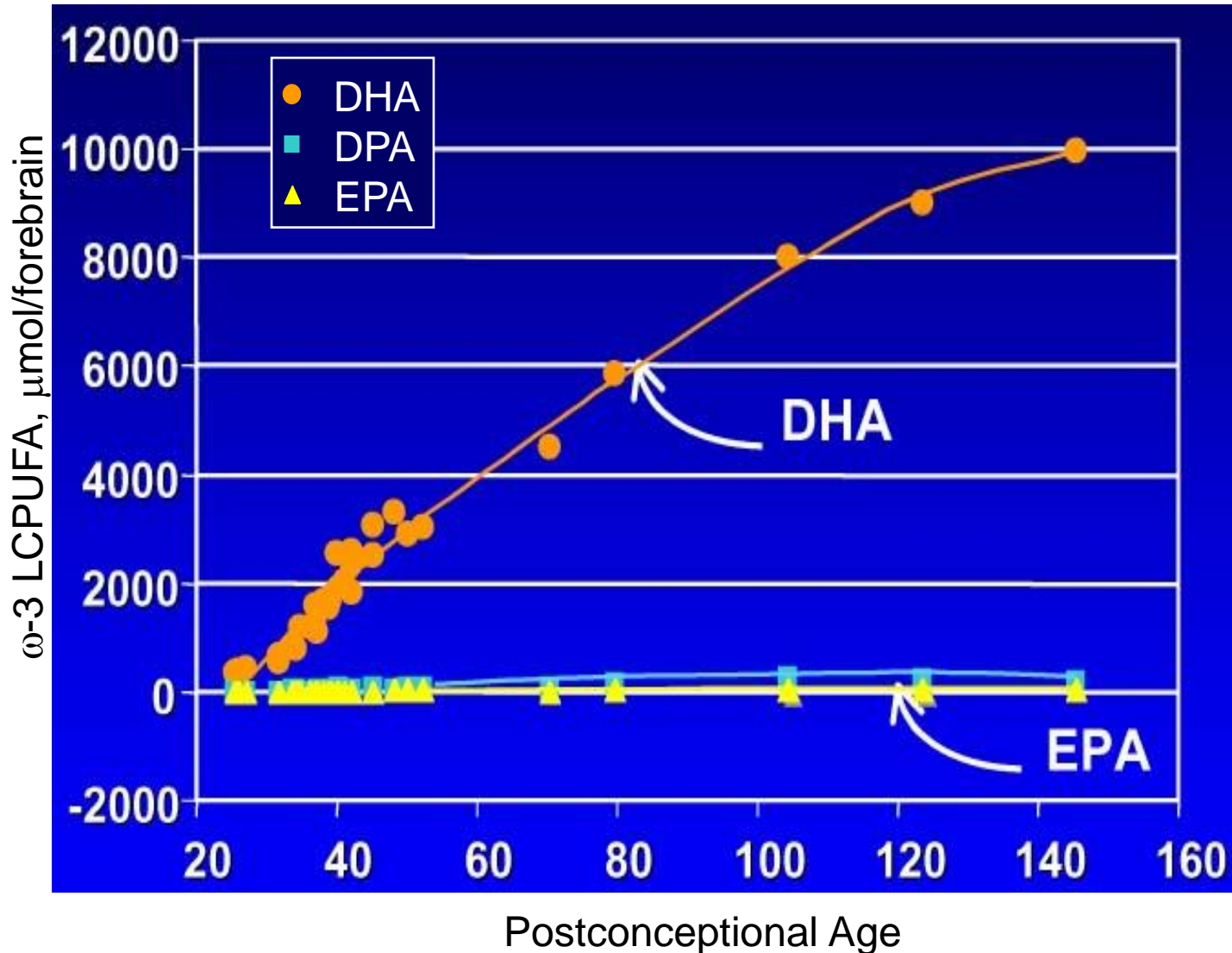
LTC4

LTD4

**LCPUFA**



# Early DHA deposition in brain



24 weeks,  
 $\approx 75$  g



40 weeks,  
 $\approx 400$  g

# Effects of $\omega$ -3 supplementation on offspring

Olsen et al. 2008: Am J Clin Nutr 88	Reduced hazard rate of asthma during 16-y follow-up of offspring	63% (95% CI: 8%, 85%; p= 0.03),
<b>IMMUNOLOGIC EFFECTS: ASTHMA</b>	Reduced hazard rate of allergic asthma during 16-y follow-up of offspring	87% (95% CI: 40%, 97%; p= 0.01)
Helland et al. 2003: Pediatrics 111	Children's mental processing scores ( <b>IQ</b> ) at 4-y aged	Mean IQ 106 vs 102 (p< 0.05). Significant correlation with maternal intake of DHA during pregnancy
Smithers et al. 2008: Am J Clin Nutr 88	Increased <b>visual acuity</b>	At 4 months, high-DHA fetuses = 1.4 cycle per degree higher than controls (p= 0.025)
Gale et al. 2008: J Child Psychol Psychiatry 49	<b>Reduced risk of hyperactivity</b> in fetuses	OR = 0.34 (95% CI: 0.15, 0.78)
Judge et al. 2007: Am J Clin Nutr 85	<b>Performance of problem-solving tasks</b>	Significant effects on total intention score (p=0.017) and solutions (p=0.011), number of intentional solutions on both cloth (p=0.008) and cover (p=0.004) steps

# Effects of $\omega$ -3 supplementation on pregnancy outcome

8

<b>Prolonged gestation</b> (Meta-analysis)	Szajewska et al. 2006: Am J Clin Nutr 83	1.57 days (95% CI: 0.35, 2.78) (6 RCTs, n=1278)
	Makrides et al. 2006: Cochrane Database	2.55 days (95% CI: 1.03, 4.07) (3 trials, n=1621)
<b>Pregnancy outcome</b> (Meta-analysis)	Berghella et al. 2015: JMFNM,	34 RCT: no effect on preterm, PE and IUGR, ↓73% perinatal death if started <20 wks
<b>Prevented preterm birth</b> (<34 weeks) in high risk patients (Systematic Review)	Horvath et al. 2007: Br J Nutr 98	RR = 0.39 (95% CI 0.18, 0.84) (2 RCTs; n= 291)
<b>Rate/Risk of pre- eclampsia</b>	Szajewska et al. 2006: Am J Clin Nutr 83.	No significant difference in the RR/rate of pre-eclampsia
	Makrides et al. 2006: Cochrane Database Syst Rev CD003402	

# Omega-3: effective in preventing early preterm delivery



Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

## European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: [www.elsevier.com/locate/ejogrb](http://www.elsevier.com/locate/ejogrb)

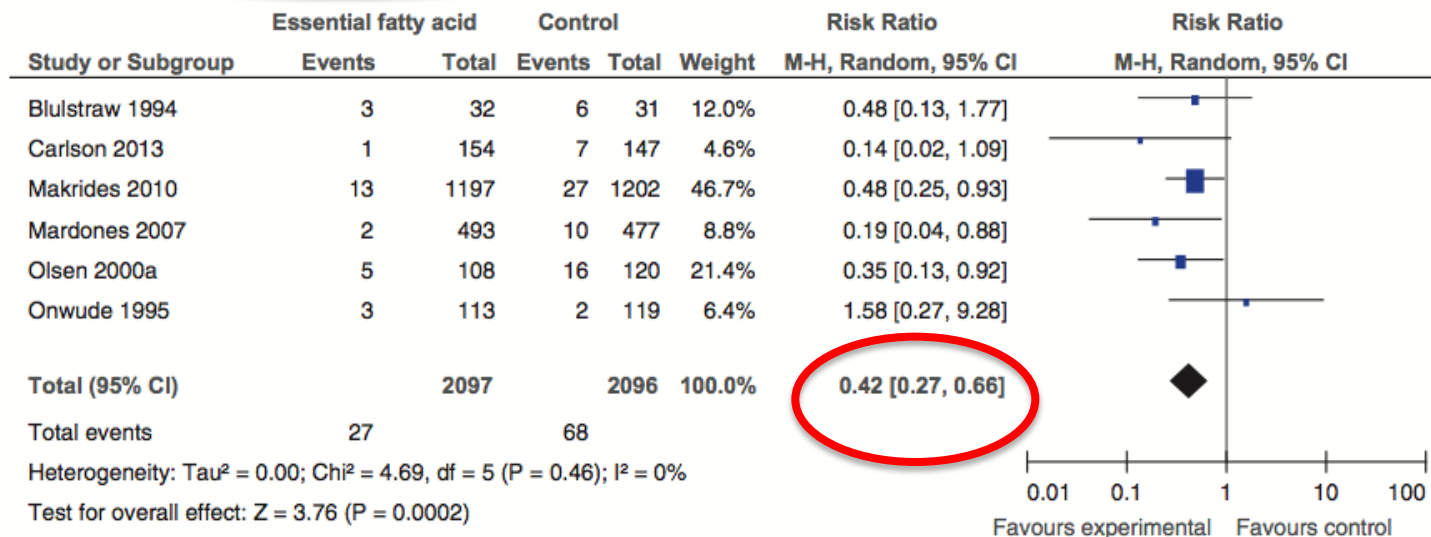


### Effects of omega-3 fatty acids in prevention of early preterm delivery: a systematic review and meta-analysis of randomized studies

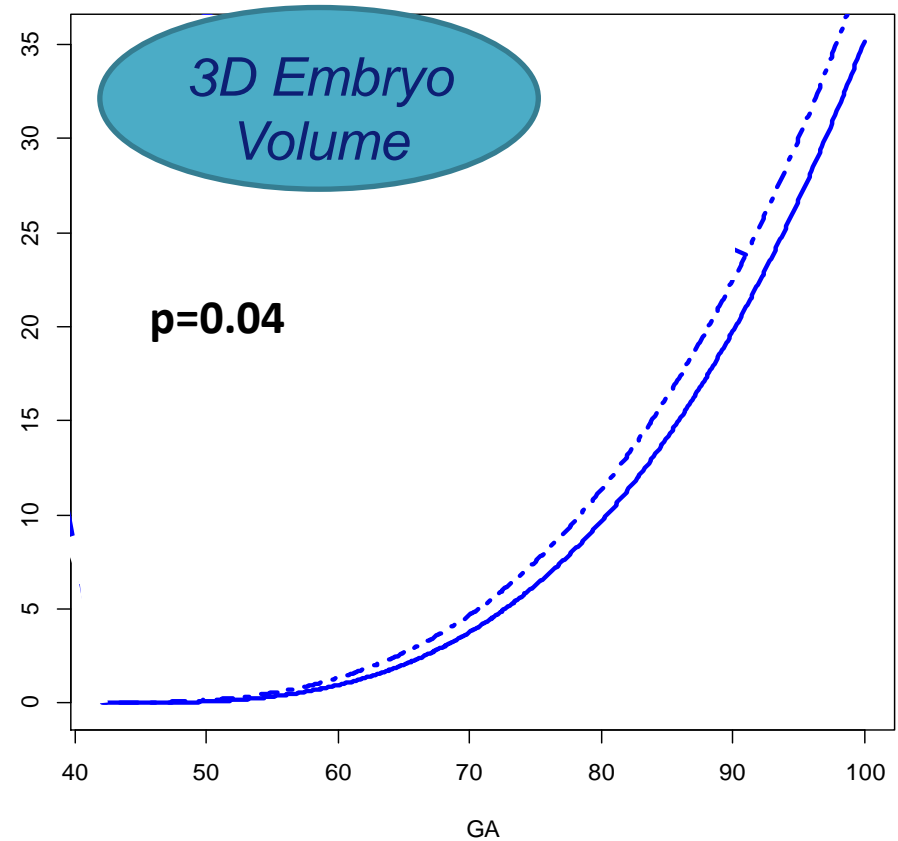
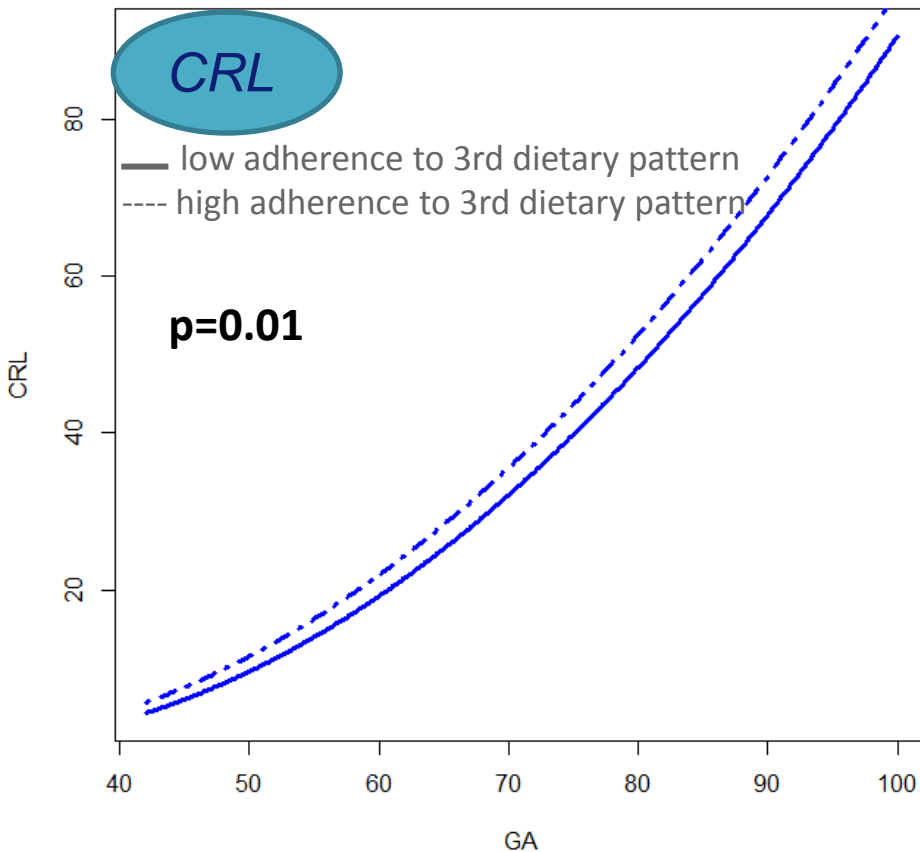


Sumit Kar<sup>a,\*</sup>, Min Wong<sup>b</sup>, Ewelina Rogozinska<sup>c</sup>, Shakila Thangaratnam<sup>a,c,d</sup>

#### a. Early preterm birth (< 34 weeks)



# Fish-related dietary pattern and embryonic growth



# CONSENSUS RECOMMENDATIONS

## DIETARY FAT INTAKE IN PREGNANCY AND LACTATION

Project supported by the European Union,  
Framework 5 programme,  
Quality of Life Key Action.



Koletzko B, Cetin I, Brenna J. B J Nutr 2007

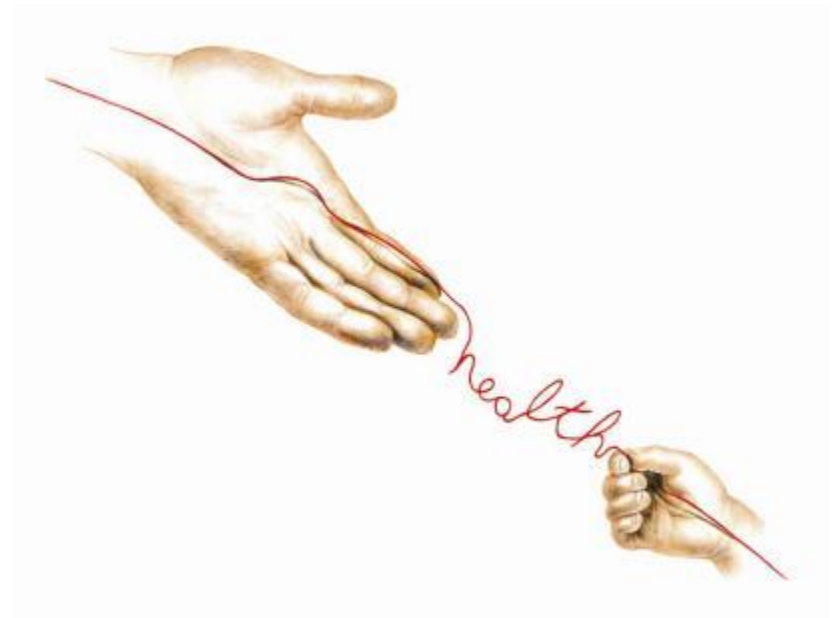


# RECOMMENDATIONS for LIPIDS and LC-PUFA

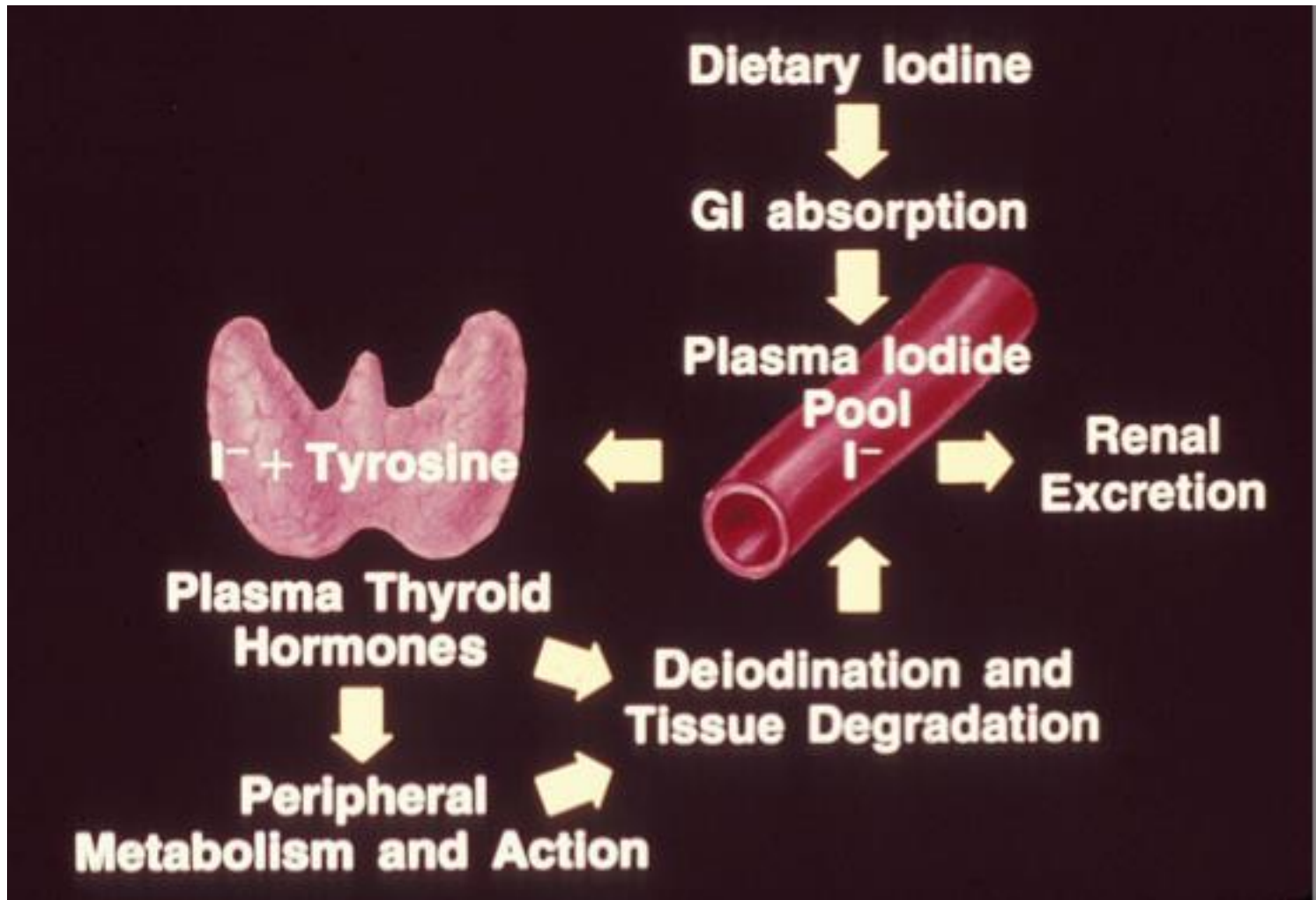
1. Lipid intake in pregnancy and lactation should not be different from the non pregnant state (as a proportion of total energy intake)
2. Women in pregnancy and lactation should reach the daily intake of 200mg/die of DHA with their diet. Amounts up to 1 g/die of DHA or 2.7 g/die of *n*-3 LCPUFA have been utilized in RCT without adverse effects.
3. Women in fertile age should be advised to consume 1-2 portions of fish per week (minimum dose of recommended DHA without excessive exposure to contaminants)

## *outline*

- ✓ nutritional facts
- ✓ omega 3 - DHA
- ✓ **iodine**
- ✓ magnesium
- ✓ key points



# Iodine



# Thyroid Hormone and Brain Development

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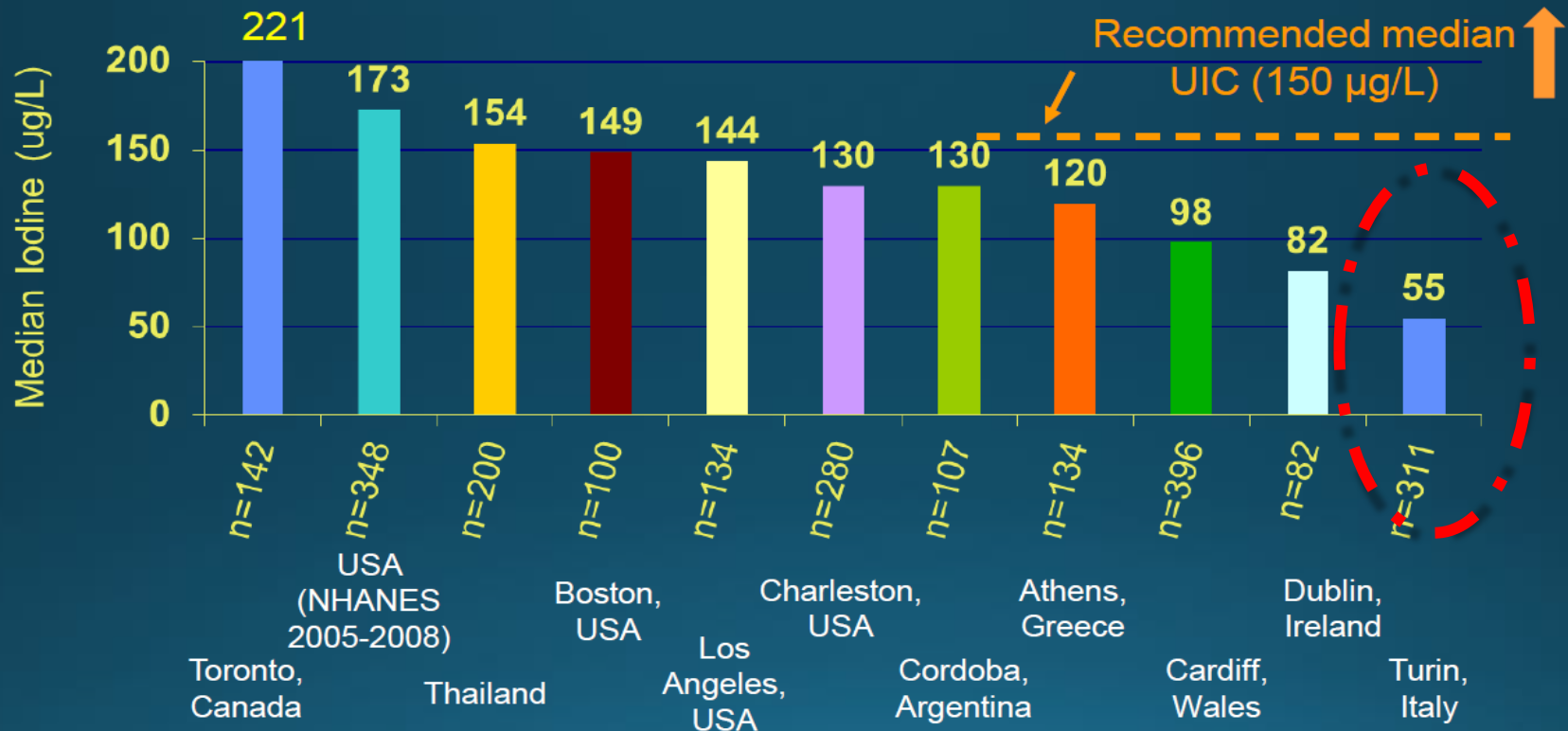
- Prenatal neocortical neurogenesis
- Growth of subventricular and subgranular zones
- Cell migration in cerebral cortex, hippocampus, cerebellum
- Axonal myelination
- Axon and dendrite formation
- Granule and other cerebellar cell proliferation; Purkinje cell maturation
- Postnatal neurogenesis

## ➤ ***Iodine intake < 20-25 µg/day → CRETINISM***

- Mental retardation, impaired growth, and neurological abnormalities
- Susceptible brain regions: cerebral neocortex, cochlea, basal ganglia; rapid growth in the 2<sup>nd</sup> trimester

# Iodine Deficiency

## Median Urine Iodine in Pregnant Women in Canada, USA, Thailand, Argentina, Wales, Italy, Ireland, and Greece



Pearce EN et al. *Thyroid* 2004

KL Caldwell KL et al. *Thyroid* 2005

Pearce EN et al. *J Clin Endo Metab* 2010

Pearce EN et al. *Endo Pract* 2011

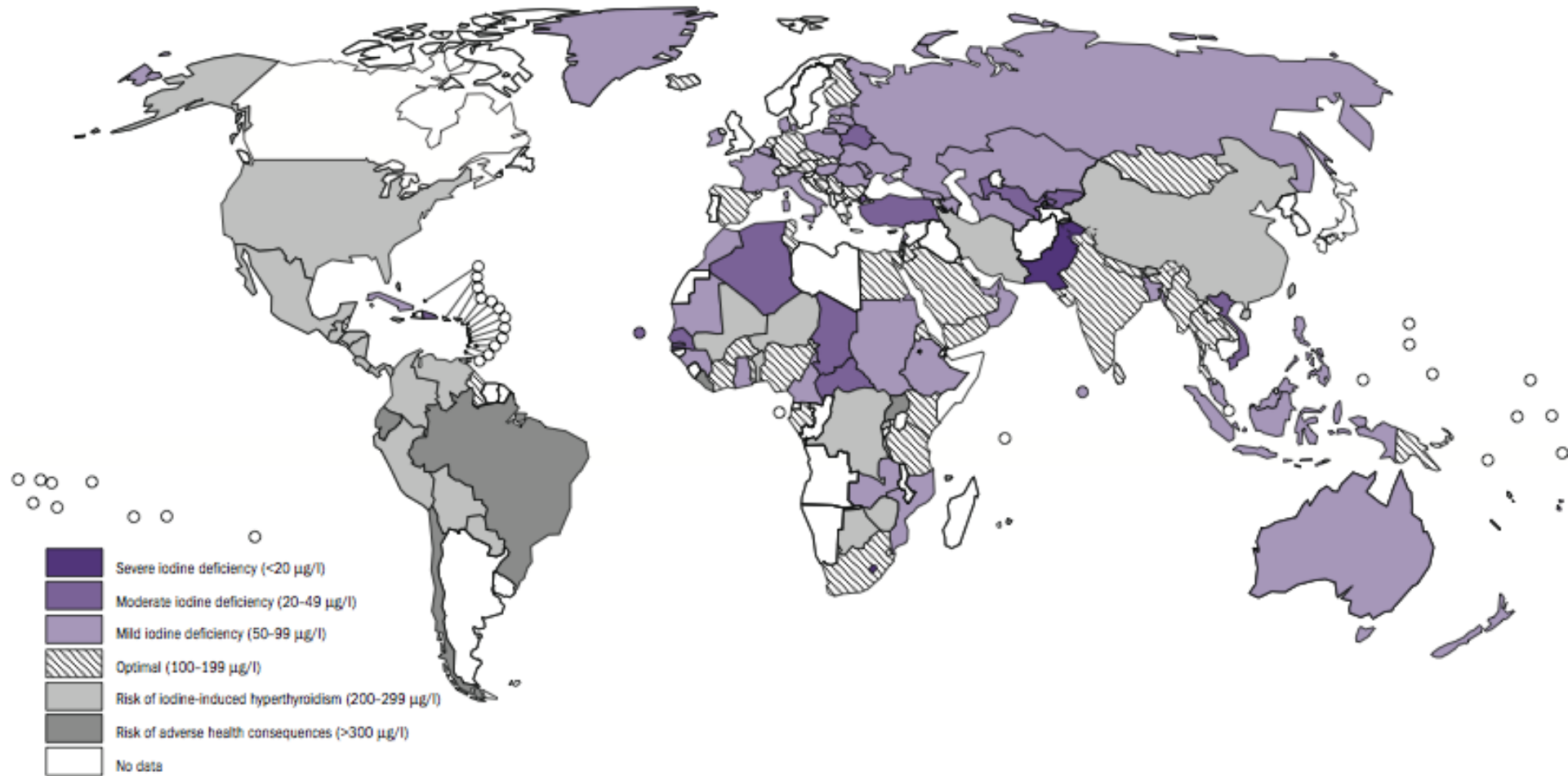
Pearce EN et al. *Clin Endocrinol (Oxf)* 2012

Sullivan S et al. *Ob Gyn* 2012

Katz PM et al. *Endo Pract* 2013

Charatcharoenwitthaya N. et al. *ATA* 2013

# Iodine Deficiency Worldwide (WHO report)





# Effects of mild-moderate I deficiency in pregnancy

## Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC)

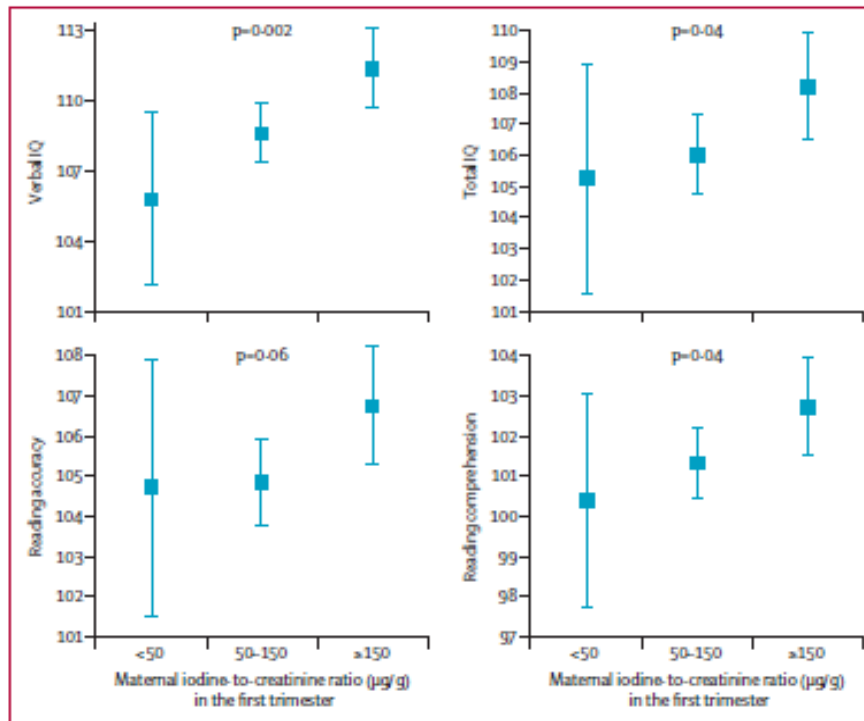


Figure: Means (95% CIs) for child cognitive outcomes according to maternal iodine status in the first trimester. Values are adjusted for the effect of confounders (model three). Child verbal and total IQ were assessed at age 8 years and reading accuracy and comprehension at age 9 years. IQ=intelligence quotient.

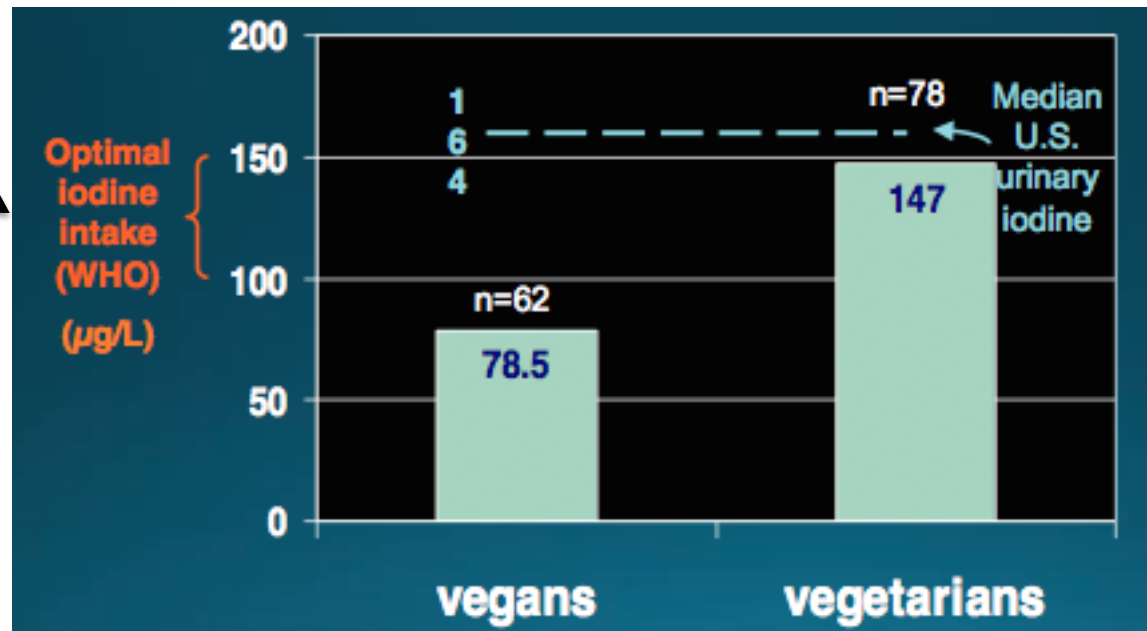
Offspring of women with  
UI between 50-150 µg/l  
**in 1<sup>st</sup> trimester**

studied at 8-9 yrs

↓ IQ  
↓ Reading accuracy  
↓ Reading comprehension

# Iodine Deficiency

- **Mild-to-moderate iodine deficiency** → *first cause of preventable mental retardation worldwide*
- Higher risk for inadequate iodine intake
  - ✓ Pregnancy
  - ✓ Lactation
  - ✓ Fetus and neonate
  - ✓ Dietary habits



# Iodine: recommendation in pregnancy

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- WHO/UNICEF/ICCIDD (2007): 250 µg/die
- IOM (2001): 220 µg/die → upper intake level: 1100 µg/die
- EFSA 2014: 200 µg/die → upper intake level: 600 µg/die

## Programme

- Universal **salt iodization** since 1993
- **Iodine supplementation** (WHO/UNICEF)
  - **Supplementation for pregnant and lactating women with 150-200 µg/die in countries with iodine deficiency**

## *outline*

- ✓ nutritional facts
- ✓ omega 3 - DHA
- ✓ iodine
- ✓ **magnesium**
- ✓ key points



# Health Outcomes potentially related to Mg deficiency

***Mechanisms for preterm births***

***Block Voltage Dependent Ca<sup>++</sup>***

***Channel → increased calcium effects***

muscle contractions

PREMATURITY

↓ nutrient availability  
to the fetus

PREECLAMPSIA

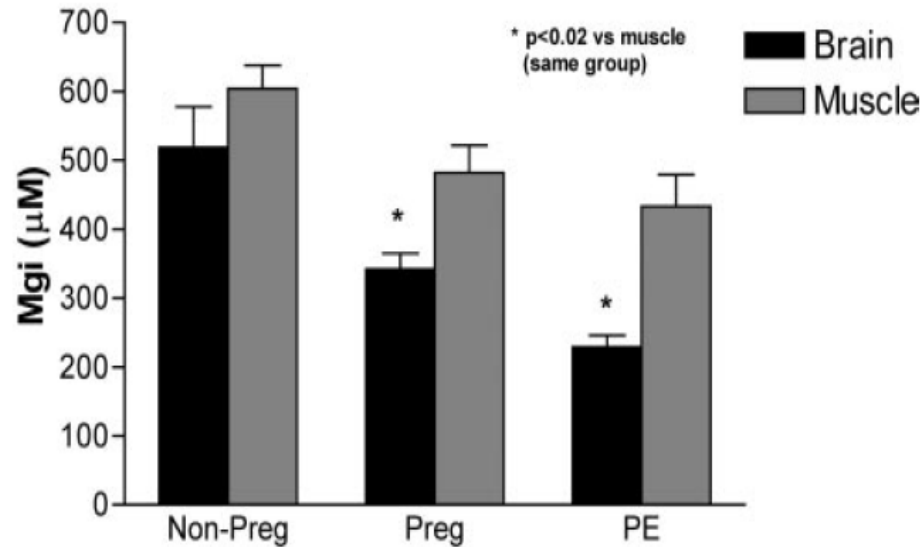
↓ perfusion of  
placental vasculature

IUGR  
worse brain dvlpn

Mg deficiency and mechanisms of preeclampsia:

- **mitochondrial oxidative phosphorylation → increased release of oxidative products**
- **vasomotor tone → increased calcium effects**
- ↓ perfusion of placental vasculature

# Magnesium and Preeclampsia

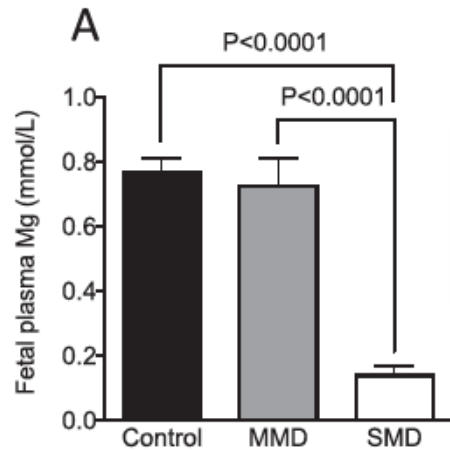


**Figure 4.** Brain versus muscle Mg<sub>i</sub> levels in nonpregnant, pregnant, and preeclamptic women.

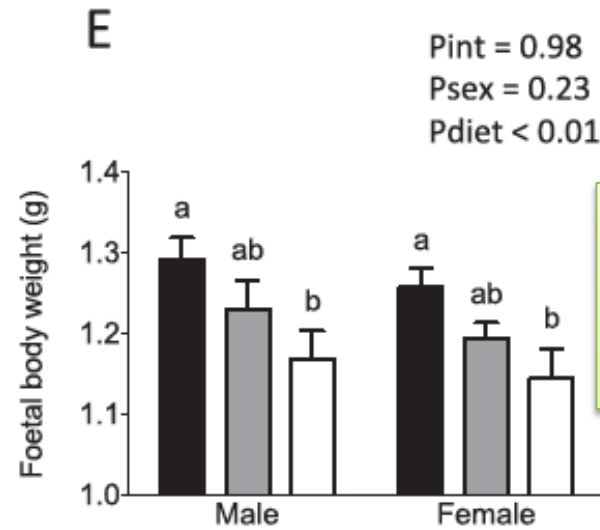
1. **Pregnancy itself is characterized by lower Mg<sub>i</sub> values** both in brain and muscle tissue
2. **Brain Mg<sub>i</sub> levels are further suppressed in preeclamptic compared with normal pregnant and non-pregnant women**
3. Both systolic and diastolic blood pressures are quantitatively and inversely related to brain Mg<sub>i</sub> values
4. Mg depletion in pregnancy appears to be differentially expressed in brain and muscle, Mg<sub>i</sub> concentrations being equivalent in the non-pregnant state, but, with pregnancy, decreasing in brain to a greater extent than in muscle



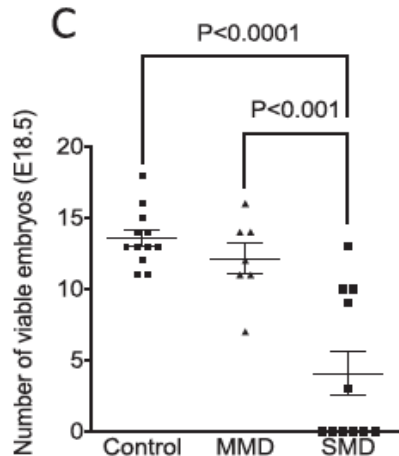
# Placental dysfunction caused by Mg deficiency



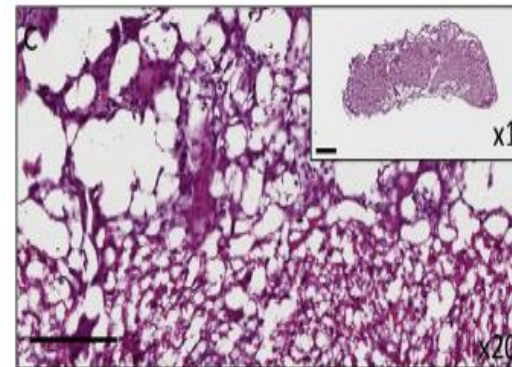
SMD decreased fetal plasma Mg



HypoMg is associated with fetal growth restriction



HypoMg is associated with fetal loss



Gross abnormalities, increased glycogen cells

# Magnesium and Preterm Delivery

## Magnesium sulphate for preventing preterm birth in threatened preterm labour (Review)

Crowther CA, Brown J, McKinlay CJD, Middleton P



- **37 included trials** (total of 3571 women and over 3600 babies)
- **Trials of moderate to high risk of bias**
- **Antenatal magnesium sulphate was compared with either placebo, no treatment, or a range of alternative tocolytic agents.**

Magnesium sulphate is **ineffective at delaying birth or preventing preterm birth** and has no apparent advantages for a range of neonatal and maternal outcomes as a tocolytic agent

Its use could be appropriate in specific groups of women for maternal, fetal, neonatal and **infant neuroprotection** where **beneficial effects have been demonstrated**

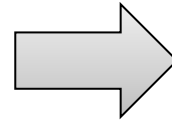
# Are we meeting nutrients needs in pregnancy?

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Diets high in fat and sugar  
and low in whole grains,  
vegetables and fruit

→ low Mg content

***Most Western diets are  
magnesium deficient  
EURRECA guidelines***



**nutritional status  
of females of  
reproductive age**



**Nutrient needs of  
pregnancy**

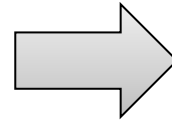
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↓ **nutritional status  
of females of  
reproductive age**

↑ **Nutrient needs of  
pregnancy**

pregnancy  
s

	400 mg/day	
19-30 years		350 mg/day
31-50 years		360 mg/day
		<i>IOM 1997</i>

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- ✓ **key points**



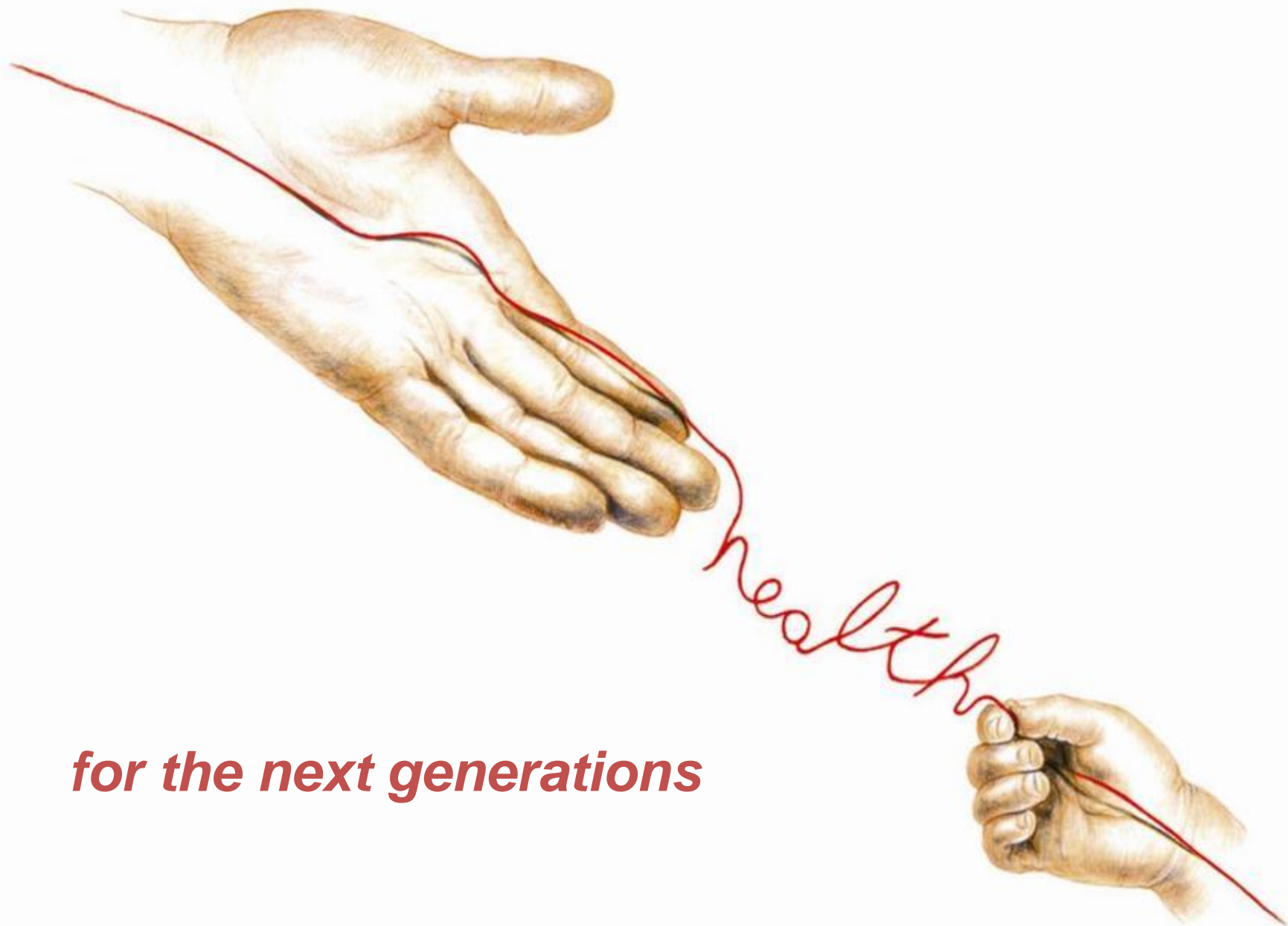
# KEY POINTS

- ✓ Encourage women to establish healthy dietary practice before conception
- ✓ Nutritional inadequacies are very likely to occur in the pre-conceptual period as well as in pregnancy

	AI	SUPPLEMENTATION
<b>magnesium</b>	350-400 mg/die	240 mg/die in women at risk for preterm delivery, preeclampsia,
<b>DHA</b>	200 mg/die up to 1 g	<b>all women that do not eat fish at least 2 times per week; all women at risk for preterm delivery</b>
<b>IODINE</b>	220 µg/die	<b>200 µg/die</b> – from 3 months before conception - in iodine deficient areas

- ✓ supplementation for: twin pregnancies, obesity, adolescents, low BMI, celiac disease, risk for preterm delivery and preeclampsia





***for the next generations***