Maternal Nutrition & Supplementation - Effects on Pregnancy Outcome

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Introduction
• Review increased micronutrient needs in pregnancy
• Highlight health risks of micronutrient deficiency in pregnancy
• Review the rationale for the new SOGC-MOTHERISK Vitamin/Folic Acid Clinical Practice Guideline

Maternal Nutrition and Supplementation

Vitamin A
• Essential for normal reproduction, embryonic development and growth
• 57% of Native Canadian women have low daily vitamin A intake
• Pregnancy RDI: 0.4 - 0.8 mg/day
• Mega dose of vitamin A (> 10,000 IU): association with NTD
• SOGC: beta-carotene as source; not retinol since potentially teratogenic
Vitamin D & Calcium
- Critical for bone development and integrity
- Low consumption of milk products and lack of sunlight exposure are risk factors for lack of vitamin D
- In Canadian climate: lack of vitamin D production
- Native Canadians: 46% have low vitamin D and calcium intake

Iron
- In 1st-2nd trimesters: placenta accumulates iron to release to fetus later
- Between 28-38 wks – fetus grows from 1 to 3.4 kg
- Iron requirement throughout pregnancy: 27 mg/day
- Average iron intake by Canadian women: 12 mg/day
- CDC: start iron supplementation in 1st prenatal visit
- Calcium inhibits iron absorption

Maternal Iron Status
- Evidence that maternal anemia linked to neonatal anemia
- Strong emerging evidence: neonatal hemoglobin linked to child development
- Severe maternal anemia may be a human teratogen
Iodine
- Critical for fetal brain development
- <8 weeks – fetus has no thyroid function
- 8-16 weeks – fetus still dependent on mother’s thyroid hormone
- Endemic low iodine – low IQ in babies
- Maternal hypothyroidism, even subclinical (high TSH) – lower IQ
- 15% of US women of childbearing age have low urine iodine
- Pregnancy RDI: 160 IU/day
- RDI should be increased to 240 IU/day

Omega-3
- Polyunsaturated fatty acids, mostly:
  - Alpha linolenic acid (plants)
  - Eicosapentaenoic acid (fish oil)
- Essential for a healthy diet and normal development

Omega-3 Supplementation
- Potential effects?
  - Prevention of pre-eclampsia – not proven in interventional studies
- Brain function of offspring?
  - Maternal omega-3 supplementation associated with higher cognitive function (IQ)
- Existing evidence too sparse and conflicting to recommend omega-3 maternal supplementation
Folic Acid
Numerous observational studies since 1966 showed an increase in NTDs with low folate:
- **Wald:** RCT of 4 mg folate vs. placebo in mothers with previous NTD: 85% protection
- **Czeizel:** RCT of 0.4 mg folate in women with no previous NTD: potential eradication of 75% of NTD (i.e. folate-dependent)
- **Dublin:** Case control study: 900 nM RBC folate - needed for optimal protection against NTD

Folic Acid Fortification
- **1997-98**
  - USA and Canada fortified flour with folic acid (140 mcg / 100 g)
  - Population levels of folic acid doubled
  - Rates of NTD halved

Folic Acid
- **Wald:**
  Using the Dublin study (protective levels against NTD):
  - 0.4 mg/day: risk reduction of only 36%
  - 5 mg/day: risk reduction of 85%
- **Kapur:**
  - 40% of women of reproductive age in Ontario: RBC levels below 900nM
Prenatal Vitamins Containing Folic Acid and Prevention of Other Malformations

Recently:
• Associated with decreased risk of neural tube defects and other congenital malformations

Meta-analysis:
Prenatal Vitamins Containing Folic Acid and Prevention of Other Malformations

Cardiac: > 20,000 patients
OR: 0.72 (0.62-0.84); protective effect: 28%

Limb: 15,000 patients
OR: 0.23 (0.06-0.79); protective effect: 77%

Cleft palate: > 22,000 patients
OR: 0.68 (0.45-0.96); protective effect: 32%

Meta-analysis:
Prenatal Vitamins Containing Folic Acid and Neonatal Cancers

• Neuroblastoma: 585 patients
  OR: 0.53 (0.42-0.68); protective effect: 47%

• Leukemia: 1995 patients
  OR: 0.60 (0.50-0.74); protective effect: 40%

• Brain cancer: 931 patients
  OR: 0.73 (0.60-0.88); protective effect: 27%
Folic Acid Fortification and Neuroblastoma

- Since 1997-98: an apparent decrease of 50% of neuroblastoma in Ontario
  - Time related to folic acid fortification
  - Based on POGO data (Paediatric Oncology Group)

Recommendations

- Prenatal MV containing FA for all women of childbearing age
- Prenatal MV containing FA as opposed to FA alone
- Diet alone is unlikely to provide adequate RBC folate levels
- Many more women would benefit from 5 mg FA
- 1 dose/day of prenatal MV
- 5 mg FA will not mask B12 deficiency
- Preconception use (2-3 months) of prenatal MV containing folic acid and throughout pregnancy and postpartum (4-6 weeks)
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**FA Dose for Women at Low Risks of NTD**
- Good diet & good prenatal MV compliance (15-20%)
- Use prenatal MV containing 0.4 - 1.0 mg FA

MNU-10, 12

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**FA Dose for Women at Increased Risks of NTD**
- Poor lifestyle or poor prenatal MV compliance (80-85%)
- Use prenatal MV containing 5 mg FA – 3 months preconception until 10-12 weeks postconception
- Then switch to a prenatal MV containing 0.4-1.0 mg FA for remaining of pregnancy and postpartum period

MNU-12, 15, 32-33

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**Who is at Increased NTD Risk?**
- Previous NTD or family history of NTD
- Use of anti-epileptic drugs
- Malabsorption disorders (e.g. IBD)
- Use of folate antagonists (e.g. MTX, sulfas)
- Obese (BMI > 35)
- Smokers
- Ethnicity (e.g. Sikh, Celtic, Northern China)
- Diabetic
- Poor compliance and lifestyle issues

MNU-12, 15, 32-33
**Commonly Asked Questions (1)**

If 40% of Ontario women did not attain the recommended 900 nM RBC folate level due to poor compliance with their prenatal MV containing 1 mg of FA, why assume they would, by using 5 mg?

- Mean compliance in taking prenatal vitamins: 54-59% (range 0-100%)
- Partial compliance with 5 mg/day will increase levels to the protective range in many more women

**Commonly Asked Questions (2)**

Would high dose of folic acid mask B₁₂ deficiency?

- Not according to existing studies
- Prenatal vitamins contain B₁₂
- Measurement of B₁₂ levels are not required prior to initiating supplementation

**Commonly Asked Questions (3)**

FA and Cancer?

Several suggestions of high folate associated with “increased risk of cancer”

- 13 published case control studies
- Overall: a 30-35% reduction in the risk of breast cancer
  - Theoretical increased risk of worsening precancerous progress
  - The “dual effect theory”, may protect against cancer in the general population, but facilitates growth of pre-neoplastic cells
Commonly Asked Questions (4)

FA and Cancer?
- Decrease in breast cancer incidence in USA despite doubling of folate levels
- Ovarian cancer: Prospective cohort study: "...suggests that relatively high dietary folate intake may be associated with reduction of ovarian cancer..."
- Reduction in cancers of: head & neck, pancreas, esophageal, gastric

Commonly Asked Questions (5)

FA and Twinning?
- Association between folate status and risk of twinning
- Systematic review: "possible", but not significant overall evidence

Commonly Asked Questions (6)

What about the long-term use of FA?
- Guideline recommends the use of FA in the perinatal period
- Use of FA is therefore limited to usually recurrent 6- to 12-month time periods
- Other long-term uses (non perinatal context) of FA in the clinical context (alcoholism, anemia, liver and kidney diseases...) are not discussed
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Take Home
- Diet alone is unlikely to provide adequate folate levels
- Use of prenatal MV containing FA as opposed to FA alone
- Use of prenatal MV containing FA for all women of childbearing age
- Planned pregnancy: start prenatal MV 2-3 months before conception

MAT-10, 57, 12, 15

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Take Home
- 5 mg FA will not mask B<sub>12</sub> deficiency
- Many more women will need 5 mg FA within a prenatal multivitamin
- Take beta-carotene, not retinol, as source of vitamin A
- Calcium and iron should be taken separately

MAT-10, 57, 12, 15, 39, 3

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Case Study 1
- A 24 y.o. woman with celiac disease comes for first visit due to unplanned pregnancy which she wants to keep
- She is now 8 weeks pregnant (10 weeks gestation)
- She did not supplement with prenatal vitamins

Issues to discuss?
Case Study 1

- She has not supplemented with folic acid, thus not preventing NTD
- Having celiac, she is not eating cereals, hence not benefiting from flour fortification with folate

How should you manage her?

Case Study 1

- AFP in serum: 4SD higher than the mean
- Detailed Level 2 ultrasound: Lumbo-sacral Spina Bifida

Case Study 2

- A 32 y.o. woman is coming to see you planning pregnancy
- Her nutrition is based mostly on meat and cereals. She hardly touches green vegetables and she tries to avoid bread due to overweight
- She is not very keen of medication. In the past, she became pregnant failing her oral contraceptives

How much folic acid would you recommend she take?
Case Study 2
• Consider 5 mg folic acid, as the typical 1 mg in most prenatal vitamins may not be sufficient to prevent NTDs in this non compliant patient