Maternal Micronutrient Status and Intake: Effects on Human Milk Composition

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Issues

• Human milk is definitely best source of nutrients for young infants!

• But questions remain:
  – Poor data on micronutrient content:
    • Many nutrients, uncertain how/when to collect, milk matrix, effects of maternal status.
  – Does it supply enough nutrients for first 6 months?
  – What if mother has poor diet?
  – Are supplements needed for lactating women?
  – For their infants?
# Micronutrient groups in lactation

(Allen 1994, 2018)

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk MN $\propto$ to maternal status, infant depleted. Supplements can ↑ MN in milk.</td>
<td>Milk MN independent of maternal status, mother depleted. Supplements no effect on milk.</td>
</tr>
<tr>
<td>B-1, B-2, B-6, B-12, A, D, K, E, Choline, Iodine, Selenium</td>
<td>Folate, Calcium, Iron, copper, zinc</td>
</tr>
</tbody>
</table>
Few data available for setting Adequate Intakes for infants and lactation (Allen et al., 2018)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Value used by IOM, /L</th>
<th>Data</th>
<th>Range/other studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1 (mg)</td>
<td>0.21±0.4</td>
<td>Only study, source unknown</td>
<td></td>
</tr>
<tr>
<td>B2 (mg)</td>
<td>0.35 (0.31-0.51)</td>
<td>n=5, USA</td>
<td>Only 1 study with valid method</td>
</tr>
<tr>
<td>Niacin (mg)</td>
<td>1.8 (1.2-2.8)</td>
<td>n=23 (UK, 16-244 d)</td>
<td>Only 1 study</td>
</tr>
<tr>
<td>Pantoth.</td>
<td>1.7 mg/d</td>
<td>2 studies (UK, USA)</td>
<td>Range: 2.2-2.5mg/L, but higher values includes women consuming supplements</td>
</tr>
<tr>
<td>B6 (mg)</td>
<td>0.13 (0.07-0.18)</td>
<td>n=6 (USA, 3 wk to 30 mo)</td>
<td>Intakes were &lt;RDA (0.24, 0.31 if intake &gt;RDA)</td>
</tr>
<tr>
<td>Biotin</td>
<td>5 µg/d</td>
<td>3 studies</td>
<td>Range: 3.8-7ug/L (different methods)</td>
</tr>
<tr>
<td>B12 (ug)</td>
<td>0.42 (0.01-1.47)</td>
<td>n=9 (Brazil, 4 d to 3 mo)</td>
<td>0.31 (vegan), 0.34, 0.91 (suppl)</td>
</tr>
<tr>
<td>Choline (mg)</td>
<td>125mg/d</td>
<td>2 studies</td>
<td>160-200 mg/L</td>
</tr>
<tr>
<td>C (mg)</td>
<td>50mg</td>
<td>8 studies, n=12-200 /study</td>
<td>Range 34-83mg/L if no supplement</td>
</tr>
</tbody>
</table>
Development of analytical methods

- **Free thiamin, riboflavin, FAD, nicotinamide, pyridoxal, pyridoxine, biotin, pantothenic acid via UPLC-MS/MS**
- **B12 via CPBA**
- **Iron, copper, zinc, calcium, potassium, magnesium, phosphorus, sodium via ICP-AES**
- **Carbohydrates, fat, protein via NIRS**
- **Vitamin A and E via HPLC-DAD**
- **Total thiamin via HPLC-FLD**

**5 platforms**

**6 methodological approaches**

- ≈1 mL of milk
- + omics on 20 uL
Many recent measurements of milk vitamins globally show median levels below current values used to set AIs for infants.
Milk thiamin in a High Income Country

All values well below the AI (median 125 ug/L vs AI 210 ug/L. Recommended intake for infants is higher than needed.

Note AI was set based on 1 study (source unknown).

Supplementation trials (fortified fish sauce) in Cambodia increased milk content from 66% up to 100% of the IOM AI concentration.

However our results suggest 66% below may actually be close to normal!
Vitamin B-6

- Neither global nor US deficiency prevalence known.
- NHANES: low serum PLP in 11% supplement users, 24% non-users.
- Serum PLP correlates and maternal intake rapidly increases milk B6.
- AI value milk 0.13 mg/L; <60% AI most LIC.
- 40% Egyptian mothers had milk B-6 <0.1 mg/L, abnormal infant behavior.
- Davis, 0.3 mg/L. High in prenatal supplements?

≈60% prenatal suppl. USA >RDA for B6.
ACOG: 10-25 mg B6, 3-4x/d, ± doxylamine, to treat nausea.
(RDA pregnancy 1.9 mg/d).
Iodine in Human Milk: A Systematic Review

- Rapid fall in first weeks.
- Varies 100-fold across studies.
- Very sensitive to maternal intake and supplements.
- Values can be low even with USI.
- Older analytical methods unreliable.
- Current debate about infant requirements and need for maternal supplementation in lactation.
Longitudinal studies on milk iodine: mixed exposure to USI (Dror & Allen, 2018)

***Hannan (2009): 31 Mexican-American women in Texas
Iodine deficiency

- Breast milk iodine parallels maternal U iodine.
- Review of 57 studies: iodine in milk =
  - 13-18 ug/L in women with goiter
  - 9-32 ug/L where prevalence of goiter high
  - >90 ug/L where effective salt iodization
- Low iodine in breast milk very common.
- WHO: give 250 ug/d to lactating women in areas of moderate/severe iodine deficiency if iodized salt reaches <50% households.
- APA and ATA (2014) recommend 150 ug/d supplemental iodine in lactation.
Assessing iodine status in lactation

• Current cutpoint is maternal UIC <100 ug/L lactation (vs. <150 ug/L pregnancy) (WHO 2007).
• Requirements similar in lactation vs pregnancy but in lactation UI is diverted to milk.
• “WHO’s ≥100 ug/L UIC for lactation is inappropriate”;
• Iodine preferentially partitioned into milk when maternal intake/status is low (Dold et al. 2017).
• Low intakes, ≈70% total excreted milk, 30% urine.
• Higher intakes, ≈40% total excreted milk, 60% urine.
• BMIC best measure of iodine status lactation.
Iodine requirements lower than currently?

• IOM’s Al for infants based on 1984 study, n=37, 14d to 3.5 y lactation.

• Assumes BMIC 146 ug/L so infant obtains 114 ug/d from milk.

• **EAR lactation 209 ug/d** (BM 114 + NPNL 95 ug/d).

• New: infant requires 72 ug/d for balance (= BMIC ≥92 ug/L).

• So EAR should be 95 + 72 = **167 ug/d**.
Infant is in iodine balance at intake 70 ug/d = 92 ug/L BMIC, but use BMIC 171 (60-465) ug/L to evaluate population status.
Wean infants risk ID because iodized salt and milk contribute little dietary iodine; in Switzerland infants sufficient (UIC >100) only if fortified complementary foods

- BM iodine (40-140 µg/L) from maternal dietary iodine
- Home-prepared complementary foods very low in iodine
- No added salt or cow’s milk in the 1st year
Systematic review: vitamin B12
Dror & Allen, 2018

- 26 studies, but half in LIC, MIC or deficiency.
- 7/26 used invalid analytical method – uncertain removal of binding to haptocorrin.
- Wide range of values across studies.
- Large decrease early lactation.
- Milk B12 correlates with maternal intake and maternal and infant status.
Longitudinal data on milk B12: valid methods, unsupplemented women

- Bangladesh [Siddiqua 2016 (28)]
- Denmark [Greibe 2013 (25)]
- India [Duggan 2014 (23)]
- Malawi [Allen 2015 (19)]
- Norway [Varsi 2018]
Breastmilk B12 across lactation in a high income country 5 Nov 2019

Concentrations appear to be stable across 9 months. Disagrees with some previous Scandinavian reports showing marked fall around 4 to 6 months.
Global values for milk B12: analyses from the Allen lab
Median values as % of Adequate Intake value (310 pmol/L)
% Infants with symptoms, in case studies of B-12 deficiency (Dror & Allen)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mother pern. anemia (n=18)</th>
<th>Mother vegan (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt &lt;10 pcle</td>
<td>93</td>
<td>89</td>
</tr>
<tr>
<td>L &lt;10 pcle</td>
<td>83</td>
<td>60</td>
</tr>
<tr>
<td>Head &lt;10 pcle</td>
<td>91</td>
<td>77</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>56</td>
<td>60</td>
</tr>
<tr>
<td>Lethargy</td>
<td>50</td>
<td>63</td>
</tr>
<tr>
<td>Slow/abnl EEG</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>Not able to sit alone</td>
<td>33</td>
<td>43</td>
</tr>
<tr>
<td>Convulsions/tremors</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Cerebral atrophy</td>
<td>28</td>
<td>37</td>
</tr>
<tr>
<td>Irritable</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Not smiling</td>
<td>11</td>
<td>23</td>
</tr>
</tbody>
</table>
Virtually no data on B12 (or other nutrient) status in vegetarians/vegans in US.
Likely more conscious of need for supplements, fortified foods.

74 women N. Carolina
Prevalence low sB12
15-19% all groups
No differences BMIC
Supplement use:
46% vegans
27% vegetarians
3% non-vegetarians

Vitamin B-12 content in breast milk of vegan, vegetarian, and nonvegetarian lactating women in the United States

Roman Pawlak, Paul Vos, Setareh Shahab-Ferdows, Daniela Hampel, Lindsay H. Allen, and Maryanne Tichelaar Perrin
Effects of B12 interventions on milk B12, 3-6 months

- Sig. ↑ milk B12 only in Ghana & Bangladesh (P+L), Malawi (L)
- Overall, ↑ only 33 (15 to 154) pmol/L (AI value 310 pmol/L)
- Dose not important
- Fortification most effective.
Continuum of mother-child B12 depletion in Guatemala

(3 studies)

Maternal depletion in pregnancy

↓

Low B12 stores in infant at birth?
& in breast milk

↓

Infant depletion by 3 months

↓

Depletion at 7 and 12 months (r=0.49)

Breastfed freq (-)
Cows milk (+)

Depletion at 21 months (and still correlated with 12 month maternal B12)

↓ weight, length, motor development

(r=0.54)
Conclusions: B12 interventions

• Important to ensure good maternal status throughout pregnancy, but one-a-day supplements may not be very effective.

• **Dose unimportant** for maternal, milk and infant response (2 – 250 ug/d).

• Early pregnancy sB12 predicts infant B12 at 4-6 mo postpartum regardless of supplement dose in pregnancy + lactation.

• In lactation, single dose or one-a-day supplement little effect on milk or infant status.

• **Current maternal intake is not main influence on milk B12.**

• **Complementary foods** do increase infant B12 status.

• More effective approach may be small repeated maternal doses to mother (e.g. **fortified flour** causes a 300% greater increase in milk vs. supplements).
Vitamin D

- Human milk is very poor source of vitamin D (<50 IU/L).
- Infants born with low stores. Depend on milk and sun.
- AAP recommends **direct supplementation of infants** starting in early days of life;
  - 400 IU/day if breastfed
  - None if weaned to D-fortified formula, or to D-fortified milk after age 12 mo., or
  - 2 h sun/week with only face and hands exposed, or
  - 30 minutes/week wearing only a diaper
- New: If mother supplemented 6400 IU/d (UL is 4000 IU) will supply infant enough VD in her milk so no need for infant drops; adherence to drops is poor. Risks?
- Higher risk of maternal deficiency and low milk D if low sunlight exposure, darker skin, urban, air pollution.
High dose vitamin D to lactating mother increases plasma vitamin D in infant

4 months

7 months

No data on many micronutrients e.g. riboflavin

- 25-60% depletion in adults in UK, Canada, Europe, Irish National Survey. NO DATA FOR USA.
- Low dairy product and egg intake.
- In severe deficiency infant has poor growth & development.
- Milk levels affected by maternal deficiency and supplements – faster and to greater extent than other nutrients.

Our data:
10-20% AI in most LICs
How much does maternal supplementation affect infant intake?

Malawi, EBF infants. Daily LNS from ≈ birth to 6 months.

Increased infant intake by:

5-23% of AI after 2 weeks

but only 0-5% at 6 weeks.

(ARVs eliminated increase).
MILQ study

- To establish Reference Values for concentration of each milk nutrient across first 9 months lactation.
- Well-nourished (but not supplemented) mothers.
- 4 countries, same methods and selection criteria
- Supported by data on diets, maternal and infant status, milk volume, plasma and milk infants, microbiome...

![Graph showing concentration over months of lactation with 5th, 50th (estimated median), and 95th percentiles marked.](image)
Summary

• Very poor data on micronutrient status in lactating women, infants and milk concentrations in US.
• Maternal and infant requirements and cut-points uncertain.
• Milk MN greatly affected by maternal status.
• Ongoing MILQ study will provide Reference Values for milk micronutrients and relationship to maternal and infant status in unsupplemented, well-nourished women (in 2022?) using efficient, valid methods.
• National study being considered (Casavale et al., 2019), but who to sample? When in lactation? Effects supplements/ and fortification?
• Maternal status pre-pregnancy may be critical for milk micronutrients; not much of daily supplements appears in milk?
Collaborators in milk research

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Juliana Haber
Janet Peerson

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