Hypozincemia in Premature Infant

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Objectives

- Explain basic zinc physiology
- Outline the role and importance of zinc in pregnancy
- Describe the limitation of serum zinc concentration & reference ranges in ELBW
- Delineate the clinical signs and treatment of zinc deficiency
- Review the process that has determined recommended zinc intakes for ELBW / preterm infants
Introduction

• low-birthweight/preterm infants survival ↑ → micronutrient needs important

• Zinc fetal accretion → the 3rd trimester
  • Preterm → risk of clinical zinc deficiency ↑

• Recommendations on the amount of zinc should be provided, by the parenteral / enteral route, in human / formula milk to the smallest baby.

Clinical deficiency is uncommon → increasing evidence suggested problems associated with subclinical zinc deficiency

Monitoring serum zinc concentrations is problematic:
A. No accepted data on normal values
B. Variation in preterm infants hardly interpreted
Zinc Function & Basic Physiology

- Involved in protein structure & function
  - enzymes, transcription factors, hormonal receptor sites, & biological membranes
  
- Important in gene expression, neurotransmission, apoptosis & inflammatory response.

- Vital for optimal metabolism of protein, carbohydrate, and lipid

Agett O. Springer Verlag. 1998:909-942
• Absorbed → small intestine, the large intestine,
  • proximal gut ↑↑
• Protein, lipid, lactose → zinc absorption ↑
• Phytate (soy milk), Cu, Fe, Mg → zinc absorption ↓

• Normal serum zinc concentration
  • 70 mcg/dL (10.7 mcmol/L)

• Zinc is stored
  • Bone (40%) & liver (15-25%) .

• Hepatic zinc:
  a. Mobilized early in life
  b. Protect the infant from zinc deficiency when dietary intake is limited

• Rickets & bone turnover → plasma zinc concentration ↑

• Preterm infants with rickets and/or fractures increased plasma Zn & alkaline phosphatase concentration → explained by mobilization of bone Zn

Koo WW, Succop P, Hambridge KM. Am j dis child. 1989;143:1342-1345
Placental transfer of zinc

Active process

Fetal zinc concentration > maternal zinc concentration

Premature

Inadequate hepatic stores of zinc

Zinc deficiency: serum zinc concentration < 55 mcg/dL (8.4 mcmol/L)
Decline in maternal serum zinc concentration over the last trimester

Mothers with acrodermatitis enteropathica

Maternal zinc deficiency

Fertility ↓
Fetal malformation
IUGR

Achondroplasia & neural tube defects ↑
## Zinc concentration

Normal ranges of serum zinc concentrations over the first postnatal year

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean Serum Zinc Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>103 ± 16 mcg/dl (15,8 ± 2,5 mcmol/L)</td>
</tr>
<tr>
<td>9 week</td>
<td>71 ± 11 mcg/dl (10,9 ± 1,7 mcmol/L)</td>
</tr>
<tr>
<td>24 week</td>
<td>102 ± 20 mcg/dl (15,6 ± 3,1 mcmol/L)</td>
</tr>
<tr>
<td>52 week</td>
<td>119 ± 34 mcg/dl (18,2 ± 5,2 mcmol/L)</td>
</tr>
</tbody>
</table>

Currently, it is reasonable to diagnose zinc deficiency when serum concentration are less than 55 mcg/dL (8.4 mcmol/L) because normal concentration are greater than 70 mcg/dL (10.7 mcmol/L).

Extra supplements could be considered in infant who have these values.

No guidance when to monitor serum zinc concentration.

Giles E, Doyle LW, Neo Review 2007
Pre term infant

Skin changes in the anterior neck fold, with poorly marginated erythema in the depth of the fold

Well demarcated & scaling within 5 days

Therapy: zinc supplementation 1-2 mg/kg per day (1 mg zinc ion is equivalent to 4.5 mg zinc sulfate)
Acrodermatitis enteropathica: 2-4 mg/kg per day
Not to exceed 20 to 30 mg/kg per day

Hambridge K, Cooper. United Kingdom: Cambridge University Press. 2006: 281-283
Zinc Supplementation in Parenteral Nutrition

- Early preterm zinc-deficiency babies → unsupplemented parenteral nutrition.
  - Low serum zinc concentration
  - Poorer growth in preterm infants
  - Parenteral nutrition must include micronutrient
- Fecal zinc losses → 25 to 61 mcg/kg per day
- 60 % of parenteral → retained.

Michie D, Wirth F., J Pediatr. 1978;92:798-800
Mean gestational age was 29 weeks
- serum zinc concentration were considerably higher in zinc-supplemented parenteral nutrition (350 mcg/kg per day vs standard enteral feeding)

Targets for zinc intakes: 350-400 mcg/kg per day → zinc retention in the first postnatal weeks for ELBW infants
Zinc Supplementation

- In poor socioeconomic group, low maternal zinc concentration → zinc supplementation 5 mg daily in breastfeed infant improve growth outcome.

- Infant born with small gestational age → zinc supplementation with 3 mg/day also improve growth.

- Unsupplemented human milk with zinc was insufficient to meet the need of zinc of preterm infant.
Zinc is better absorbed from human milk than cow milk bound to casein in cow milk.

Comparison of zinc content:
- Cow milk 1.9 to 6 mg/L
- Formula 1.8 to 3.5 mg/L
- Soy based formula 2.2 to 3.8 mg/L

Zink in soy milk is poorly absorbed, but can be improved by removing the phytate in the formula.

Agett O. Springer Verlag. 1998:909-942
• Absorption preterm human milk >> preterm formula milk in premature infants

• Comparison of preterm infants fed either preterm formula / fortified human milk was no substantial difference in zinc homeostasis

• Zinc supplementation of 4.4 mg/L added to formula & fed to a preterm infants → improved growth & motor development at 12 months

• The AAP committee on nutrition recommendation Zn intake for the premature infants of 9.2 µmol/kg/day

• The European Society of Paediatric Gastroenterology and Nutrition recommended a Zn intake of 10.7-13.3 µmol/kg/day

• Recommendation of enteral Zn intake (premature infant) absorption rate is 15.3 µmol/kg/day

• Intake of Zn ↑ in infant formulas didn’t interfere with iron absorption in premature infant

ESPGAN Committe on nutrition of the preterm infant. Acta paediatr scand. 1987;78(336):2-14
Reifen RM, Zlotkin S. Williams & wilkins. 1993:119-133
Incidence and predicting factors of hypozincemia in very low birth weight infants at near term postmenstrual age

K. Itabashi, T. Saito, Y. Ogawa, Y. Uetani

- 19 nurseries in Japan: 118 infants with a gestational age of 29.5 ± (SD) 2.5 weeks, a birth weight of 1,094 ± 254 g
- Mean serum zinc concentration = 54 ± 14.4 mcg/dl (8.3 ± 2.2 mcmol/L)
- 5th percentiles being 35 mcg/dL (5.3 mcmol/L)
- Subclinical zinc deficiency ≤ 46 mcg/dl (7 mcmol/L), 25th percentiles
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95 % CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain/1 g/kg/day</td>
<td>1,1762</td>
<td>1,0414-1,3286</td>
<td>0,009</td>
</tr>
<tr>
<td>Serum albumin/1 g/dl</td>
<td>0,0816</td>
<td>0,0152-0,4372</td>
<td>0,0034</td>
</tr>
</tbody>
</table>

• Conclusion:
  1. Hypozincemia VLBW at near-term postmenstrual age → greater weight gain & lower serum concentration
  2. Nutritional supply of Zn by human milk fortifier & preterm formula does not appear to meet the demands of rapidly growing VLBW
Prevalens dan Faktor Risiko Terjadinya Hipozincemia Bayi Berat Lahir Rendah pada Usia Koreksi Mendekati Cukup Bulan atau Cukup Bulan (RSCM, HARKIT, BUDIKEMULIAAN)

Risma Kerina Kaban, Nani Dharmasetiawani, Johanes Edy Siswanto

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proportion</th>
</tr>
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<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>* Male</td>
<td>34 (54)</td>
</tr>
<tr>
<td>* Woman</td>
<td>29 (46)</td>
</tr>
<tr>
<td><strong>Gestational age, weeks</strong></td>
<td>30,76 ± 2,33</td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td>1318,29 ± 301,05</td>
</tr>
<tr>
<td><strong>Postnatal age at the time of study</strong></td>
<td>40,95 ± 18,02</td>
</tr>
<tr>
<td><strong>Postmenstrual age at the time of study</strong></td>
<td>36,78 ± 1,04</td>
</tr>
<tr>
<td><strong>Body weight at the time of study</strong></td>
<td>1875,48 ± 304,09</td>
</tr>
<tr>
<td><strong>Weight gain</strong></td>
<td>8,48 ± 3,31</td>
</tr>
<tr>
<td><strong>Milk intake during 1 week prior to the study</strong></td>
<td>155,46 ± 24,27</td>
</tr>
<tr>
<td><strong>Types of milk feeding</strong></td>
<td></td>
</tr>
<tr>
<td>* human milk</td>
<td>3 (4,8)</td>
</tr>
<tr>
<td>* Preterm formula</td>
<td>46 (73)</td>
</tr>
<tr>
<td>* mixed</td>
<td>14 (22,2)</td>
</tr>
<tr>
<td><strong>Iron administration</strong></td>
<td>33 (52,4)</td>
</tr>
</tbody>
</table>

Kaban RK, Dharmasetiawani N, Siswanto JE, Sari pediatri, 2011
<table>
<thead>
<tr>
<th>Clinical features</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis</td>
<td>1</td>
</tr>
<tr>
<td>Irritability</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95 % CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>0,622</td>
<td>0,42-0,91</td>
<td>0,015</td>
</tr>
<tr>
<td>calcium</td>
<td>0,376</td>
<td>0,16-0,88</td>
<td>0,024</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>4,764</td>
<td>1,06-21,4</td>
<td>0,042</td>
</tr>
<tr>
<td>Iron administration</td>
<td>0,062</td>
<td>0,008-0,46</td>
<td>0,007</td>
</tr>
</tbody>
</table>

Kaban RK, Dharmasetiawani N, Siswanto JE, Sari pediatri, 2011
Mean serum zinc concentration 9.65 umol/L
Hypozincemia < 55 mg/dL (< 8.4 umol/L)

- Prevalence hypozincemia for baby gestational age ≤ 34 weeks, BW ≤ 2000 g, at near term postmenstrual age 28%
- 67% symptomatic hypozincemia
- We consider that Zn supplementation may be necessary for preterm ≤ 34 weeks

Kaban RK, Dharmasetiawani N, Siswanto JE, Sari pediatri, 2011
Conclusion

- Zinc deficiency → significant cause of morbidity & mortality in developing countries → SUBOPTIMAL GROWTH, INCREASED RISK OF INFECTION AND WORSE DEVELOPMENT OUTCOME,

- Benefit of zinc supplementation outweigh the risks

- Usefulness of routine serum zinc concentration monitoring: uncertain

- The concentration to treat asymptomatic zinc deficiency is not known
Take Home Messages

- Zinc deficiency is reasonable to diagnosed when serum concentration < 55 mcg / dL (8.4 mcmol/L)

- Concentration greater than 70 mcg/L (10.7 mcmol/L) appropriate for all preterm infant

- Prevalence hypozincemia in jakarta 28%

- Screening hypozincemia for VLBW infant should be considered at near term postmenstrual ages

- Therapy: Zinc supplementation 1-2 mg /kg/day