NUTRITION RECOMMENDATIONS FOR PREGNANT WOMEN

J. Seiler, E. Jackson, T. Libby, J. Lingappa
September 10, 2020

START CENTER

STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER

Department of Global Health | University of Washington

Photo: World Bank

AGENDA

- START team introductions
- START overview
- Review of project timeline
- Hierarchy of proposed research priorities
- Key takeaways for each micronutrient
- Key themes across micronutrients

START CENTER

Photo: Princeton

PROJECT TEAM

Jessie Seiler, MPH

PhD Student in Epidemiology

Project Manager

Emahlea Jackson, NDTR

MPH Student in Nutrition, MS Student in Epidemiology

Research Assistant

Tanya Libby, MPH

PhD Student in Epidemiology

Research Assistant

Jai Lingappa, MD PhD

Professor of Global Health, Medicine

Faculty Lead

START OVERVIEW

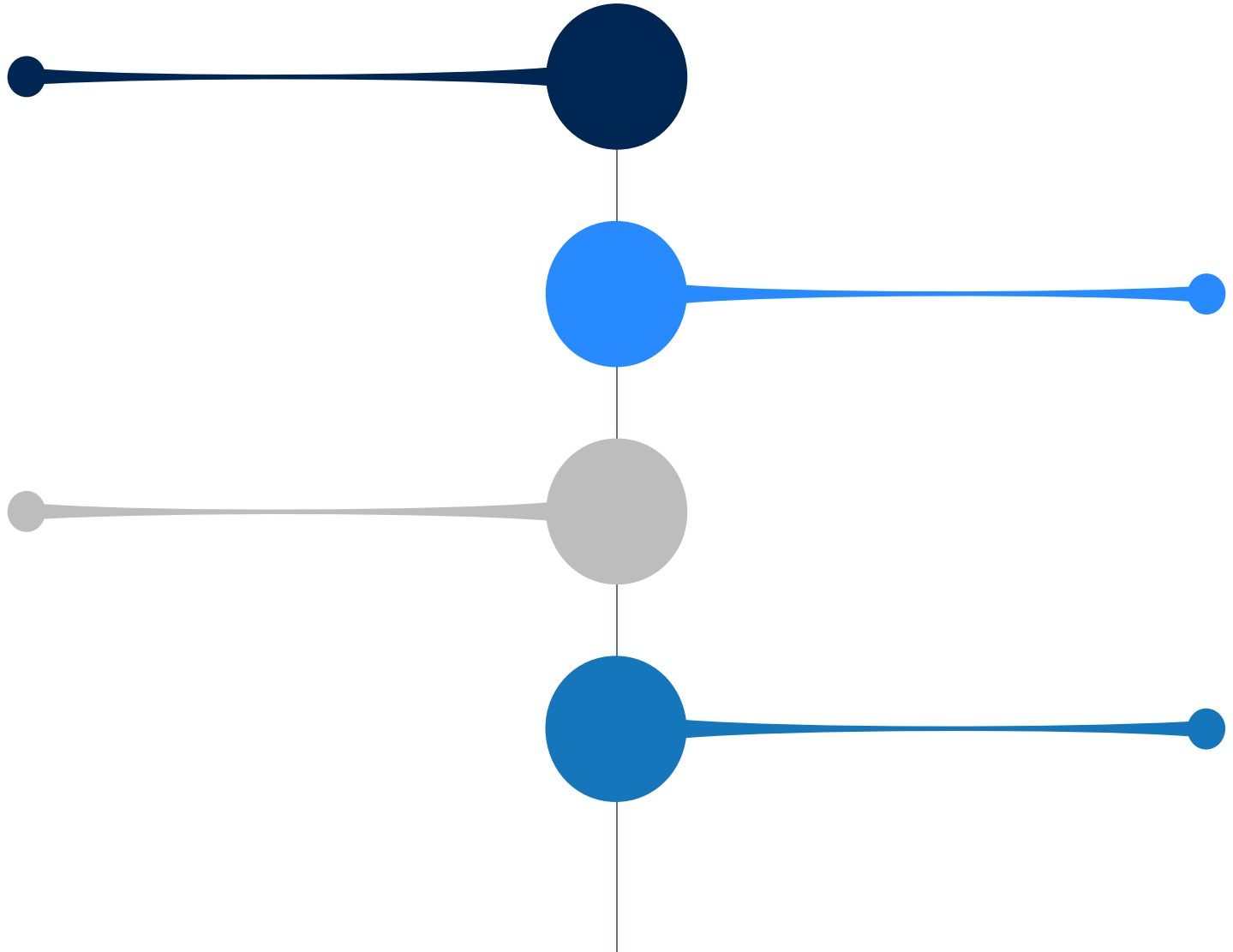
Leverages leading content expertise from across the University of Washington

Provides high quality research and analytic support to the Bill & Melinda Gates Foundation and global and public health decision-makers

Provides structured mentorship and training to University of Washington graduate research assistants

NUTRITION RECOMMENDATION REVIEW

PROCESS TIMELINE



Deep dive into iron

The team summarized IOM- and WHO-cited evidence for iron recommendations during pregnancy.

Omics review

The team produced an annotated bibliography with a special focus on recent works in metabolomics and proteomics.

Micronutrient review

The team investigated IOM- and WHO-cited evidence for a variety of micronutrient recommenations during pregnancy and lactation.

Summary

The team prioritzed micronutrients for further research and review.

MICRONUTRIENT REVIEW

- What is the evidence associated with IOM and WHO guidelines?
- Where are the evidence gaps and which micronutrients are high-priority?

START CENTER

Photo: UW DGH

PROPOSED HIGHER PRIORITIES

HIGH

Iron

Vitamin D

Choline

B12

Copper

MEDIUM

B6

B7

Zinc

B1

Iodine

PROPOSED LOWER PRIORITIES

Vitamin A
B2
B3
B5
Vitamin E

Phosphorus
Folate
Selenium
Calcium
Vitamin C

PRIORITIZATION

Designation of priority was based on the preponderance of evidence (rather than a hierarchical evaluation) of the following criteria:

Strength of evidence
- Presence of multiple types of evidence, including *in vivo* studies, demonstration of mechanisms, etc.
- Study cohorts included pregnant and lactating women
- Study cohorts included people from ethnically and racially diverse backgrounds
- Studies conducted in low- and middle-income settings
- Studies were epidemiologically sound, without major issues of internal or external validity, bias or other methodological issues

Significance (severity, prevalence) of disease burden associated with micronutrient deficiency

Whether indicators used for evaluating deficiency have been associated with clinical or physiological outcomes

Whether clinical manifestations of deficiency have been seen in the absence of severe malnutrition (i.e. independent of other nutritional deficiencies)

Existence of current interventions and recommendations

Pregnancy

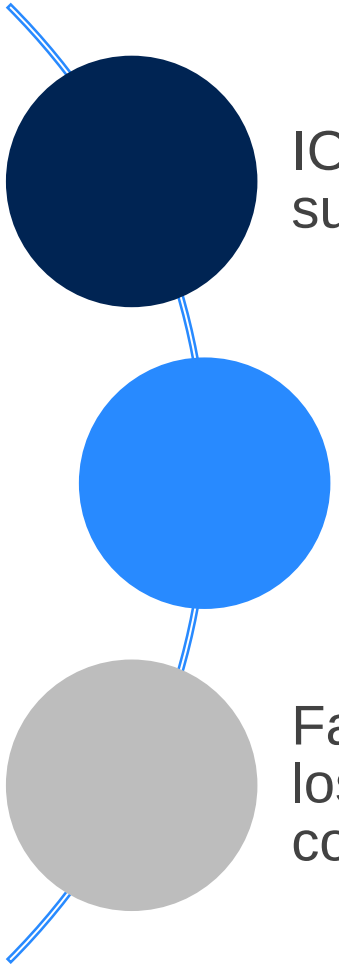
IOM

- Calculating recommendations
  - Need for choline is likely higher for pregnant than for nonpregnant women (Zeisel, 1995)
    - Pregnancy renders female rats vulnerable to deficiency (Zeisel, 1995)
  - During pregnancy in humans (Welsch, 1978; Welsch, 1981), guinea pigs (Swiery, 1985; Swiery, 1986; Yudilevich, 1985), and rats (Jorswieck, 1974), large amounts of choline are delivered to the fetus through the placenta
    - Depletes maternal stores of choline
  - Choline availability during embryogenesis & perinatal development may be important during embryonic days 12-17 and postnatal days 16-30 (Loy, 1991; Meck, 1988, 1989).
    - Choline concentration is 10x greater in amniotic fluid than in maternal blood (Zeisel, 1997)
  - Unknown whether de novo synthesis of choline increases during pregnancy
- Recommendations
  - Ages 14-50 yrs
    - AI: 450 mg/day
      - Based on the fetal and placental accumulation of choline
      - Published values for choline concentration of various adult rat tissues (Pomfret, 1989) and assumption of body organ weight percentage (Widdowson, 1963) for human fetus, fetal choline content is ~5 mmol/kg (520 mg/kg) fetal weight
      - Human placental tissue is ~1.26 ± 0.24 mmol/kg (mean ± standard error) in a small sample (n = 7) (Welsch, 1976)
      - 2 mmol of choline per kg of placental tissue should be adequate for most pregnant women → average choline content of fetal and placental tissue combined is approximately 3 mmol/kg (312 mg/kg)
        - Assuming no extra synthesis during pregnancy, no contribution of choline by placental or fetal synthesis

INSTITUTE OF MEDICINE
DIETARY REFERENCE INTAKES (DRI)

- Estimated Average Requirement (**EAR**): amount estimated to meet the nutritional adequacy requirement of 50% of healthy individuals in a given group.
- Recommended Daily Allowance (**RDA**): amount estimated to meet the nutritional adequacy requirement of 97-98% of healthy individuals in a given group.
- Adequate Intake (**AI**): used instead of RDA when EAR is not calculable; can be used as a goal of individual nutrient intake but is not marker for assessment.

IRON: IOM RECOMMENDATIONS

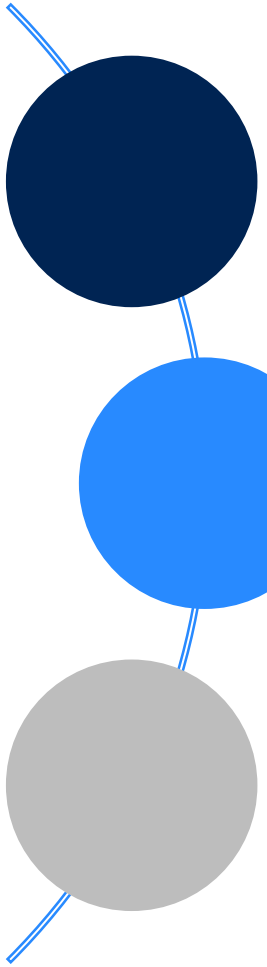


IOM recommendations are based on functional, biochemical, and/or surrogate indicators of iron deficiency anemia.

Direct correlation between iron intake and iron status is low.

Factorial model components for requirements include basal iron losses, menstrual losses, fetal development, and/or maternal bodily composition shifts during pregnancy.

IRON: IOM CRITIQUES

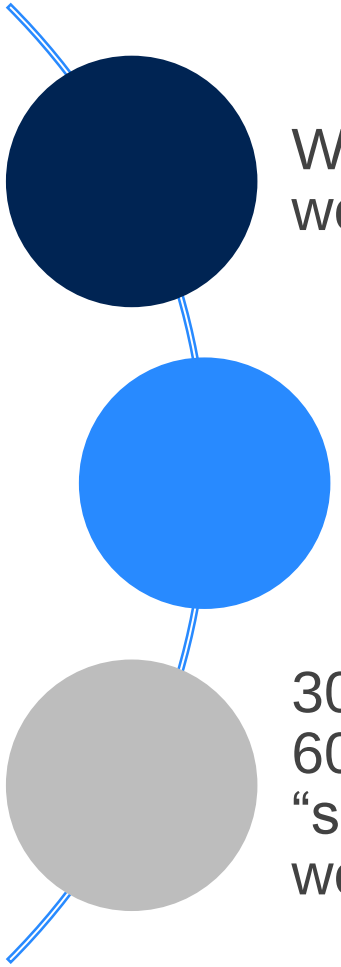


Literature base for IOM recommendations lacks graded feeding studies, compromising the reliability of functional indicators of iron status.

Body weight, heme/non-heme iron, bioavailability, diet composition contribute to variation in iron absorption across all populations (in addition to factorial modeling components).

Evidence relies on many assumptions that fail to account for differences in menstrual and/or basal iron losses.

IRON: WHO RECOMMENDATIONS

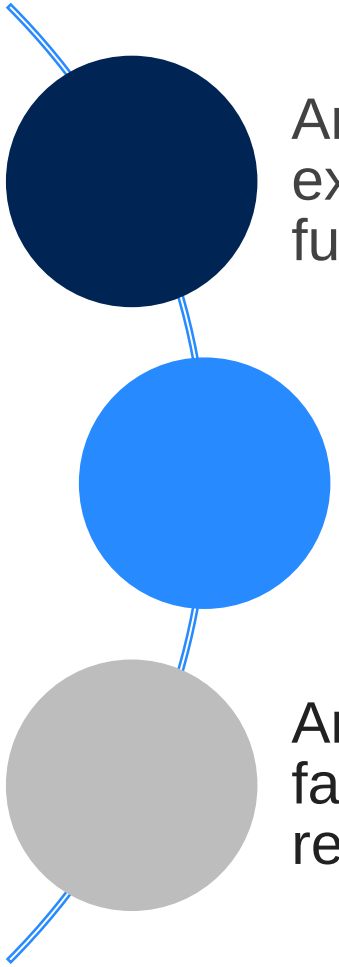


WHO estimates that anemia affects ~38% of pregnant women world-wide; about half are amenable to iron supplementation.

Severe anemia is associated with increased risk of maternal and infant mortality.

30-60 mg/day of elemental iron recommended during pregnancy; 60 mg preferred in settings where anemia in pregnant women is a “severe public health problem” (defined as >40% of pregnant women w/ blood hemoglobin concentration < 110 g/L).

IRON: WHO CRITIQUES



Anemia diagnosis cutpoints were initially proposed by a panel of experts in 1959; still based on statistical calculations rather than functional consequences of hemoglobin concentrations.

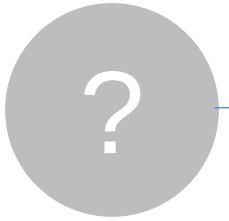
Iron supplementation found to reduce maternal anemia, but the impact on other maternal and infant outcomes is less clear. Low quality evidence.

An understanding of the etiology of anemia (e.g. malaria) and risk factors at the country level is essential for context-specific recommendations.

VITAMIN D

Vitamin D deficiency varies greatly across differing latitudes.

Co-supplementation with calcium during pregnancy may increase risk of preterm birth.

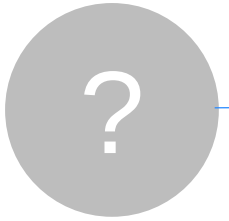


What is the role of vitamin D during pregnancy and lactation above and beyond offspring skeletal outcomes?

CHOLINE

Unknown whether choline is an essential nutrient.

IOM produced Adequate Intake value based largely on animal studies.

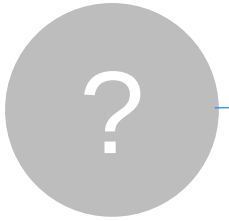


What is choline's role in pregnancy, lactation, and fetal brain development?

VITAMIN B12 (COBALAMIN)

High prevalence of deficiency in LMIC, associated with adverse pregnancy outcomes and infant neurodevelopmental morbidity.

Meta-analysis (2017) found association with preterm birth and LBW. Due to inadequate evidence, supplementation is not recommended during pregnancy or lactation.

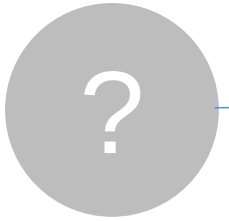


Need for RCTs and unified guidelines. What are the functional outcomes of supplementation, the reference range, and the optimal dose during pregnancy?

COPPER

Deficiency is rare in isolation of absence of malnutrition, but has measurable impacts on antioxidant status.

There is no data available for establishing an EAR during pregnancy, and lactation recommendations are informed only by animal studies.

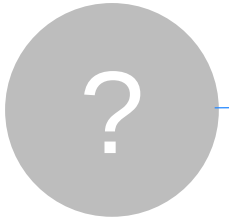


Is the evidence available sufficient enough to reasonably set an EAR and RDA?

VITAMIN B6 (PYRIDOXINE)

Deficiency usually occurs in combination with other B vitamins. True prevalence unknown, in part due to lack of single, reliable indicator.

RDAs derived from biochemical indicators, which decrease throughout pregnancy; cutoff values not linked to clinical insufficiency. WHO does not recommend supplementation.



Need for trials evaluating clinical impacts of supplementation to bolster evidence regarding prevention of preeclampsia and preterm birth.

VITAMIN B7 (BIOTIN)

Marginal deficiency is common in normal pregnancy, though concern of teratogenicity.

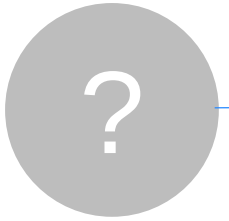
Adult AI extrapolated from infants, based on intake from breast milk. Sparse data on dietary requirements.

Markers of metabolism indicate intakes exceeding current recommendations are needed. Need for longitudinal studies evaluating birth defects.

ZINC

Deficiency is rare in isolation or absence of malnutrition.

Supplementation is not recommended during any life stage for women.

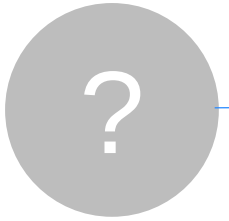


Potential relationship between supplementation and reduced risk of preterm birth in low-income settings.

VITAMIN B1 (THIAMIN)

Deficiency in pregnant and lactating women and small children may be common in some areas with diets heavy on unfortified white rice.

The difference in RDAs for men and women was estimated based on mean differences in body sizes and energy utilization.

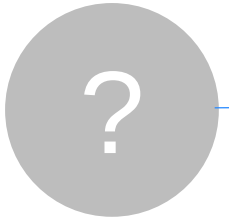


What is the best clinically-relevant cut-off for measuring thiamin status?

IODINE

Most countries in the world still have some degree of iodine deficiency.

Nutritional needs are well-characterized, but there is still a lack of clarity around clinical outcomes on fetal and early childhood health outcomes.



Can we leverage current knowledge on thyroid hormones to learn more about iodine nutrition? Is there an important difference between mild to moderate iodine deficiency and severe deficiency?

COMMON LIMITATIONS

- Lack of biomarkers and other clinical indicators of adequacy
- Poor-quality studies, including potential sources of bias
- Outdated, limited evidence-gathering practices constraining generalizability and external validity
- Few studies on optimal dose and duration in pregnant or lactating women
- Difficulty in studying importance of some micronutrients in isolation due to physiological and ethical constraints

Thank you!

START CENTER

STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER

Department of Global Health | University of Washington

APPENDIX

The following slides contain key takeaways from low-priority micronutrients.

VITAMIN B2 (RIBOFLAVIN)

- The recommendations for riboflavin put forth by the IOM and WHO are congruent for all life stages. Recommendations are based on the occurrence of clinical signs of riboflavin deficiency and increases in urinary excretion of riboflavin.
- There is evidence from an observational study conducted in 1972 that indicates that adolescent girls of color may have less sufficient intake when compared to white adolescent girls.
- Ariboflavinosis is rare across all life stages. In the United States, refined grains and cereals are fortified with riboflavin.

VITAMIN B3 (NIACIN)

- The WHO does not have official guidelines regarding niacin consumption or requirements during any stage of the life cycle.
- Overall, evidence regarding niacin requirements is insufficient. The requirements appear to be based on lower-quality studies that have been subject to lower validity, coexisting deficiencies in the populations studied, poor dietary intake measures, and a limited understanding of the bioavailability of niacin.
- The IOM's Estimated Average Requirements (EAR) and Recommended Dietary Allowances (RDA) for adolescents, pregnant women, and lactating women appear to be largely extrapolated without supporting evidence.
- Despite the apparent lack of cited evidence surrounding an increase in intake needs during pregnancy and lactation (from the IOM guidelines), niacin deficiency is rare in most regions across the globe, lending to its low-priority status.

VITAMIN B5 (PANTOTHENIC ACID)

- The recommendations for pantothenic acid put forth by the IOM and WHO are congruent for all life stages.
- The IOM notes that there is a great deal of uncertainty in the accuracy of both published values of pantothenic acid content of foods as well as the reliability of original research (primarily due to inconsistency between written values and graphed values in a key paper).
- Literature available regarding pantothenic acid requirements during pregnancy and lactation are sparse. Despite the limited evidence, deficiency of pantothenic acid in the absence of severe malnutrition has not been reported, lending to its lower-priority status.

VITAMIN A

- Evidence suggests adequate vitamin A is critical for the health of pregnant women and their fetuses, however, high intakes can be teratogenic.
- The WHO only recommends supplementation for the prevention of night blindness, in countries with a high prevalence of deficiency, supported by high quality evidence.
- While the RDA during lactation is 400 mcg more than during pregnancy, the WHO does not recommend routine supplementation due to insufficient evidence that it improves maternal outcomes.
- Further research is needed to determine the optimal dose and duration of supplementation during pregnancy and lactation.

CALCIUM

- The WHO recommends supplementation with 1.5-2.0g/day for pregnant women in populations with low dietary calcium intake for the prevention of preeclampsia.
  - Evidence is deemed low-quality due to heterogeneity and small study effects.
  - This exceeds the IOM RDA of 1g/day (1.3g/day for adolescents)
- Evidence suggests that dietary calcium requirements are not increased during pregnancy and lactation.
- Further research is warranted to determine the optimal dose and timing of supplementation during pregnancy and lactation, and to evaluate any adverse effects of higher doses.

VITAMIN B9 (FOLATE)

- IOM recommendations for folate are based on relatively few but methodologically diverse older studies; WHO makes used of a much more recent evidence base, including at least four systematic reviews.
- The IOM suggests an RDA of 400 mcg for women and girls of reproductive age, 600mcg for pregnant women, and 500 for lactating women. The WHO suggests an RDA of 400 mcg for women beginning when they plan to get pregnant and continuing through week 12 of gestation. However, the recommendations do not extend to lactation or women and girls before planning to conceive.

PHOSPHORUS

- The WHO does not have official guidelines regarding phosphorus consumption or requirements during any stage of the life cycle.
- Phosphorus deficiency appears to be rare, occurring only in situations of severe malnutrition rather than as a result of a lack of any particular type of food.
- In spite of an apparent lack of evidence, phosphorus may be a low-priority nutrient, given the lack of evidence to suggest clinical ramifications or even prevalence of deficiency.

SELENIUM

- The WHO does not have official guidelines regarding selenium consumption or requirements during any stage of the life cycle.
- The selenium content of foods is highly dependent upon the selenium content of the soil from which the food originated; however, selenium is highly bioavailable. As such, selenium deficiency appears to be rare across a variety of populations, save for in the presence of severe malnutrition.
- Intakes as low as 25% of the RDA for both pregnancy and lactation have not been associated with adverse effects to either the mother or offspring.

VITAMIN E

- Functions as an antioxidant, but no known role in required metabolic processes; overt deficiency is very rare.
- Current evidence does not support routine supplementation.
  - Appears to reduce risk of placental abruption, but increased the risk of term pre-labor rupture of membranes
  - No effect on neonatal death, preterm birth, preeclampsia.
  - Few studies examined women with inadequate intakes.
- What are the long-term effects of vitamin E supplementation during pregnancy?