Nutritional Antioxidants during Pregnancy and Lactation

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I have no conflict of interest to disclose

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Oxidative stress

What is it?

An imbalance between the production of various reactive species and the ability of the organisms' natural protective mechanisms to cope with these reactive compounds and prevent adverse events[1]

What does it do?

Reactive oxygen species and reactive nitrogen species react in the body and generate radical intermediates of lipids, protein, and nucleic acids that ultimately form the chemical end products of oxidative stress[1]

Dietary antioxidants

Food and Nutrition Board, Institute of Medicine
Dietary Reference Intakes[1]

Definition: A dietary antioxidant is a substance in foods that significantly decreases the adverse effects of reactive oxygen species, reactive nitrogen species, or both on normal physiological function in humans

Criteria:

- The substance must be found in human diets
- The content of the substance has been measured in foods commonly consumed
- The substance decreases the adverse effects of reactive species in vivo in humans

Substances meeting the criteria:

- Vitamin C
- Vitamin E (as α-tocopherol)
- Selenium

Influencers of biochemical reactions involving the oxidative process:

- β-carotene and other carotenoids
    - α-carotene
    - β-cryptoxanthin
    - Lutein
    - Lycopene
    - Zeaxanthin

Dietary Reference Intake Levels for Dietary Antioxidants

Nutrient	Pregnancy	Lactation	Relationship to serum concentrations
Vitamin C	≤18 years: 80 mg/day 18-50 years: 85 mg/day	≤18 years: 80 mg/day 18-50 years: 85 mg/day	Intakes of 90 mg/day = plasma levels of 50 µmol/L, which has been shown to inhibit LDL oxidation
Vitamin E	15 mg/day	19 mg/day	Adequate intake is defined as intakes that increase serum levels to at or above 12 µmol/L, (based on prevention of hemolysis)
Selenium	60 µg/day	70 µg/day	Levels of intake expected to maximize glutathione peroxidase production
Carotenoids	No recommendations made, current state of research is not of sufficient strength and consistency to support recommendations at this time		Serum carotenoid levels are a biomarker of fruit/vegetable intakes

Correlations of maternal and cord serum carotenoids concentrations in a Midwestern cohort

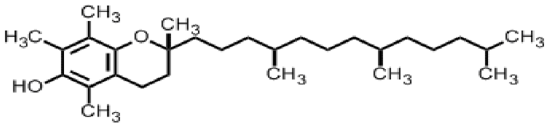
Serum Level	Correlation Coefficient (r)	p-value
Lutein+zeaxanthin	0.45	<0.0001
β-cryptoxanthin	0.64	<0.0001
Lycopene	0.30	<0.0001
α-carotene	0.70	<0.0001
β-carotene	0.65	<0.0001

Carotenoid status of infants as a proportion of maternal concentrations in a Midwestern cohort

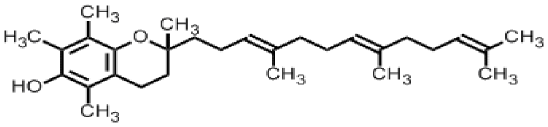
Measure (ug/L)	Maternal Level	Infant Level	Infant % of Mother
Lutein	196.5	30.6	16%
Lycopene	469.0	21.9	5%
α-carotene	53.8	4.7	8%
β-carotene	214.9	13.5	6%
β-cryptoxanthin	104.9	11.1	10%

Pro-oxidants

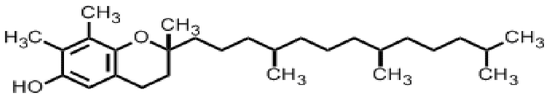
No dietary compounds are defined as pro-oxidants, however nutrients may have opposing actions



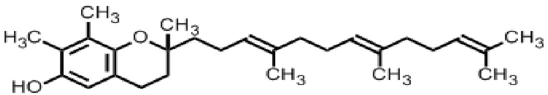
alpha-Tocopherol
"Vitamin E"



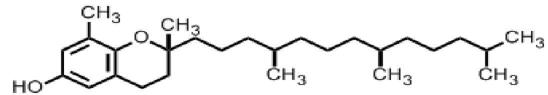
alpha-Tocotrienol



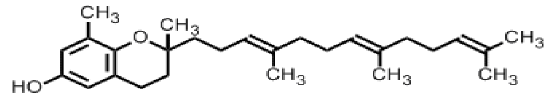
gamma-Tocopherol



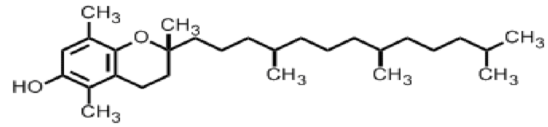
gamma-Tocotrienol



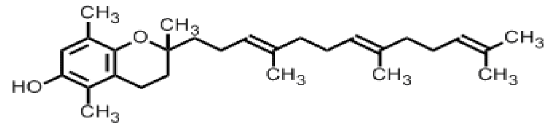
delta-Tocopherol



delta-Tocotrienol



beta-Tocopherol



beta-Tocotrienol

Predictors of Antioxidant Status in Pregnant Women in the US

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Socioeconomic factors affecting antioxidant status in a Midwestern cohort

Food deserts

Living in a food desert is associated with lower serum concentrations of:

- **Lycopene** (399.1 v. 475.8, p=0.04)
- **β-carotene** (143.5 v. 228.5, p=0.005)
- **β-cryptoxanthin** (100.7 v. 107.4, p=0.02)

Socioeconomic factors affecting antioxidant status in a Midwestern cohort

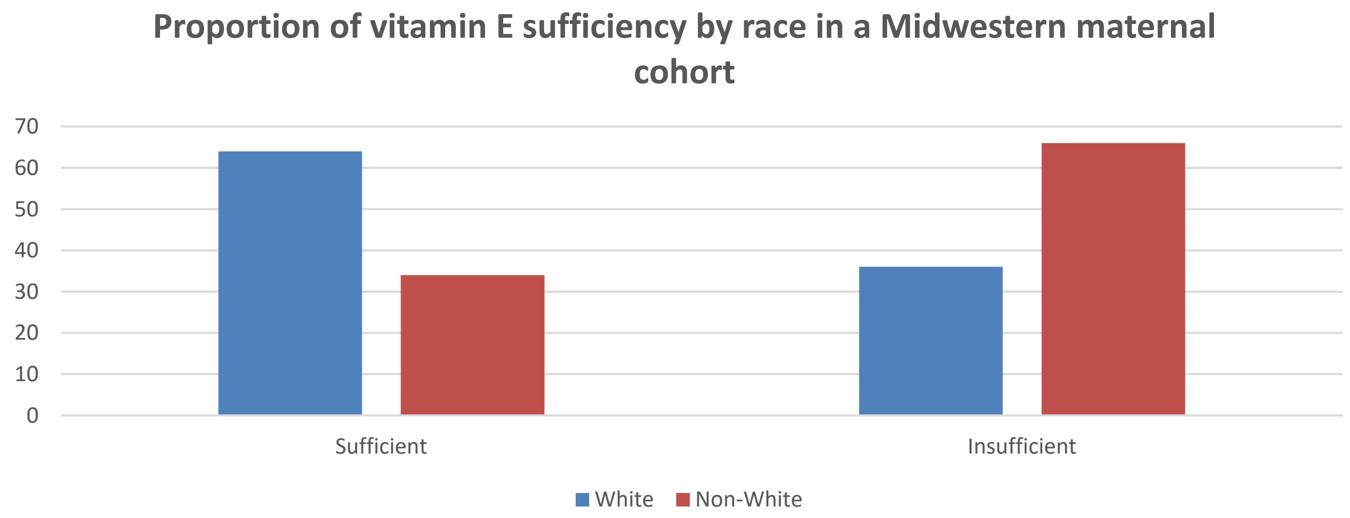
Payor Source:

Compared to those with public insurance, those with private insurance have higher serum concentrations of:

- **Lutein** (184.3 v. 220.6, p=0.003)
- **β-carotene** (171.4 v. 282.7, p=0.01)

Socioeconomic factors affecting antioxidant status in a Midwestern cohort

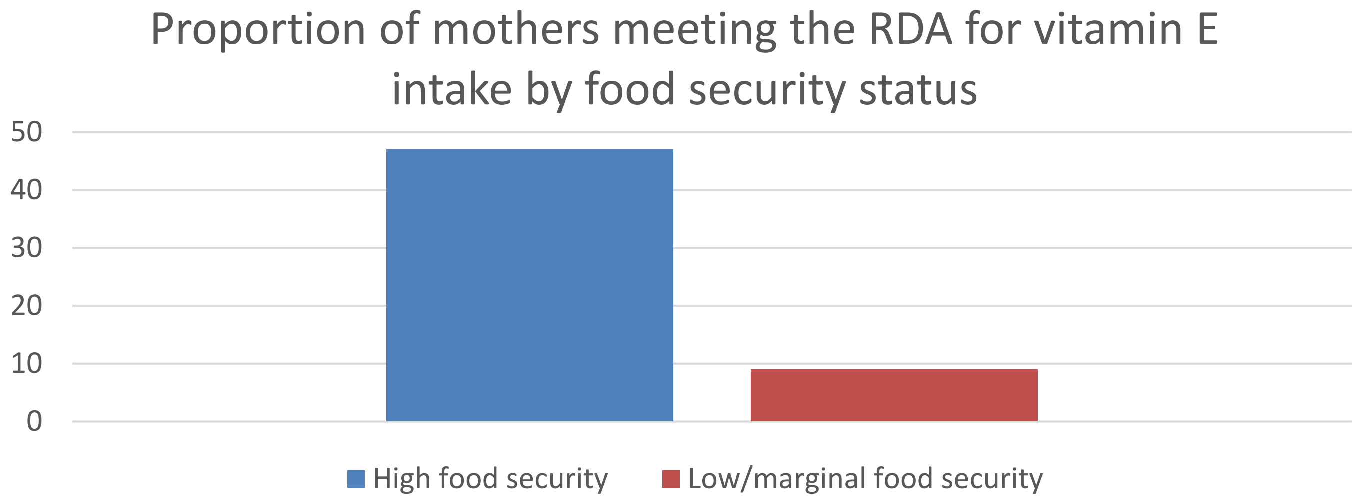
Race



Odds of being vitamin E deficient were 3.52 times higher for non-Whites when compared to Whites (95% CI: 1.51, 8.10; p=0.003)

Socioeconomic factors affecting carotenoid status in a Midwestern cohort

Food Security



- Marginal or low food security had 5.4 times higher odds of intakes below the RDA for vitamin E when compared to those with high food security (95% CI: 1.73. 17.0, p=0.003).

Pregnancy outcomes studied in relation to antioxidant status

Premature delivery/premature rupture of membranes

Observational Evidence

Author	Design	Year	Nutrients evaluated	Significant findings
Kramer[3]	Case-control	2009	Plasma carotenoids, retinols, tocopherols	Higher plasma α-and β-carotene, β-cryptoxanthin, and lycopene associated with reduced risk of preterm birth Higher plasma γ-tocopherol associated with increase risk of preterm birth
Carmichael[4]	Observational cohort	2013	Intakes of multiple nutrients and 2 diet patterns	OR were above 1.5 for α-carotene, β-carotene, and vitamin E
Siega-Riz[5]	Observational cohort	2002	Intakes of vitamin C	Intakes less than the 10th percentile were associated with twice the risk of PTD

Premature delivery/premature rupture of membranes

Supplementation Trials

- Supplementation with 1000 mg vitamin C/400 mg vitamin E: delayed latency period after PROM compared to controls (11.2 vs. 6.2 days; $p < 0.001$) (in a Turkish population)[6]
- No impact on preterm birth[7]
  - However, preterm PROM occurring before 32 weeks gestation was less frequent in the women supplemented with vitamins (0.36% vs. 0.64%, $p=0.046$)

Preeclampsia

Observational evidence

Author	Year	Results
Azar[8]	2011	Serum B-carotene lower in cases
Mikhail[9]	1994	Serum vitamin C, β-carotene and α-tocopherol lower in cases
Chappell[10]	2002	Serum vitamin C lower in cases Serum vitamin E not different between cases and controls
Schiff[11]	1996	Serum vitamin E intakes and serum levels higher in cases
Rajasingam[12]	2009	Vitamin C not different between cases and controls Vitamin E not different between cases and controls
Palan [13]	2004	Serum β-carotene, α- carotene and lycopene lower in cases
Roland[14]	2010	Serum vitamin E higher in cases

Preeclampsia

Supplementation trials

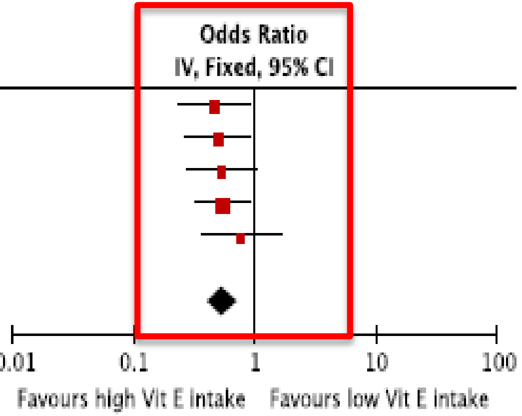
- Combined 400 mg vitamin C/1000 mg vitamin E had no impact on rates of preeclampsia in women at risk[15,16]
    - Increase the rate of babies born LBW seen in the supplemented group
    - Secondary analysis: indicated supplementation improved rates of placental abruption and preterm birth in smokers[17]
- Selenium supplementation decreased biomarkers of pre-eclampsia (sFlt-1) in women in the lowest tertile of selenium status[18]

Respiratory outcomes

Observational evidence for Vitamin E

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Devereux 2006	−0.7765	0.3405	17.5%	0.46 [0.24, 0.90]
Litonjua 2006	−0.7133	0.3102	21.1%	0.49 [0.27, 0.90]
Martindale 2005	−0.6404	0.3338	18.2%	0.53 [0.27, 1.01]
Miyake 2010b	−0.6162	0.2606	29.9%	0.54 [0.32, 0.90]
West 2012	−0.2614	0.3919	13.2%	0.77 [0.36, 1.66]
Total (95% CI)			**100.0%**	**0.54 [0.41, 0.71]**

Heterogeneity: $Chi^2 = 1.14$, df = 4 ($P = 0.89$); $I^2 = 0\%$
Test for overall effect: $Z = 4.37$ ($P < 0.0001$)



Pooled difference for maternal dietary vitamin E intake during pregnancy and childhood wheeze.

- 4/5 studies above showed no significant relationship with vitamin C (one significant association found)[19]

Respiratory outcomes

Supplementation Trials

- Supplementation with 1000 mg vit C and 400 mg vitamin E during pregnancy
  - Did not impact respiratory outcomes in the offspring
  - Associated with increased health care utilization (Secondary analysis of the VIP trial)[20]

Infant growth outcomes

Results of multivariate analysis for maternal serum concentrations of total lycopene and infant growth outcomes at birth

Growth Variable (at Birth)	Maternal Total Lycopene		Maternal *Cis*-Lycopene		Maternal *Trans*-Lycopene	
	β	*p*-Value	β	*p*-Value	β	*p*-Value
Birth Weight *	0.29	0.03	0.59	0.03	0.53	0.04
Birth Weight percentile **	0.02	0.008	0.05	0.006	0.04	0.01
Head Circumference (cm) *	0.001	0.009	0.003	0.01	0.003	0.007
Head Circumference ** percentile	-	-	0.04	0.05	-	-
Length *	0.001	0.20	0.002	0.18	0.002	0.24
Length percentile **	0.02	0.01	0.05	0.01	0.04	0.02
	Cord Total Lycopene		**Cord *Cis*-Lycopene**		**Cord *Trans*-Lycopene**	
Birth Weight *	-	-	-	-	−10.3	0.04
Birth Weight percentile **	-	-			-	-
Head Circumference (cm) *	-	-	-	-	-	-
Head Circumference percentile **	-	-	-	-	-	-
Length *	-	-	-	-	-	-
Length percentile **	-	-	-	-	-	-

* Models adjusted for gestational age and smoking; ** Models adjusted for smoking (percentile rankings are gestational age adjusted measures).

Infant growth outcomes

Maternal vitamin E isoform concentration and newborn weight, length, head circumference and percentile rakings at birth.

	Weight[a]		Weight %ile[b]		Length[a]		Length %ile[b]		Head circumference[a]		Head circumference %ile[b]	
Vitamin E isoform (μg/L)	β	p	β	p	β	p	β	p	β	p	β	p
α	–	–	0.0001	0.04	0.0001	0.03	0.0005	0.03	0.00007	0.03	0.001	0.03
γ	0.10	0.04	–	–	–	–	–	–	–	–	–	–
δ	0.47	0.02	0.02	0.05	–	–	–	–	–	–	–	–

[a] Models adjusted for gestational age and smoking.

[b] Models adjusted for smoking (percentile rankings are gestational age adjusted measures).

Supplementation trials

Supplementation with 400 mg vitamin C/1000 mg vitamin did not reduce the risk of intrauterine growth restriction[16]

Congenital heart defects

Observational evidence

- Dietary vitamin E intake was higher in cases than in controls, 13.3 (8.1–20.4) vs 12.6 (8.5–19.8) mg/day ($p=0.05$).

- Periconception use of vitamin E supplements in addition to a high dietary vitamin E intake above 14.9 mg/day up to nine-fold increased CHD risk[21]

Diet Patterns

Author	Diet Pattern	Year	Results
Hanson	Dietary Inflammatory Index (DII)	2019	Maternal pro-inflammatory diet associated with decreased lung function outcomes in the offspring
Sen	DII	2018	Maternal pro-inflammatory diet associated with later adiposity measures in boys
Sen	DII	2016	Maternal pro-inflammatory diet associated with impaired fetal growth and breastfeeding failure
Rifas-Shiman	Alternate Healthy Eating Index	2009	Better diet quality associated with lower screening blood glucose levels and lower risk of preeclampsia
Lange	Mediterranean diet, Alternate Healthy Eating Index	2010	Diet pattern not associated with wheeze in the offspring
Nguyen	Dutch dietary guidelines	2017	No association between diet pattern during pregnancy and atopic or allergic outcomes in childhood
Knudsen	“Western” vs “Health conscious”	2008	Health conscious diet associated with lower odds of SGA infants
Shaheen	“Processed” vs “Health conscious”	2009	No association between diet patterns and asthma or related outcomes

Summary and Conclusions

- Observational evidence shows potential associations between dietary antioxidant status and PROM, respiratory outcomes
- Supplementation trials are often conducted in replete individuals and do not show consistent benefit
- Nutrients may work synergistically, with food sources being more impactful than supplementation of individual nutrients
- Socioeconomic disparities in antioxidant status in pregnant women exist in the US

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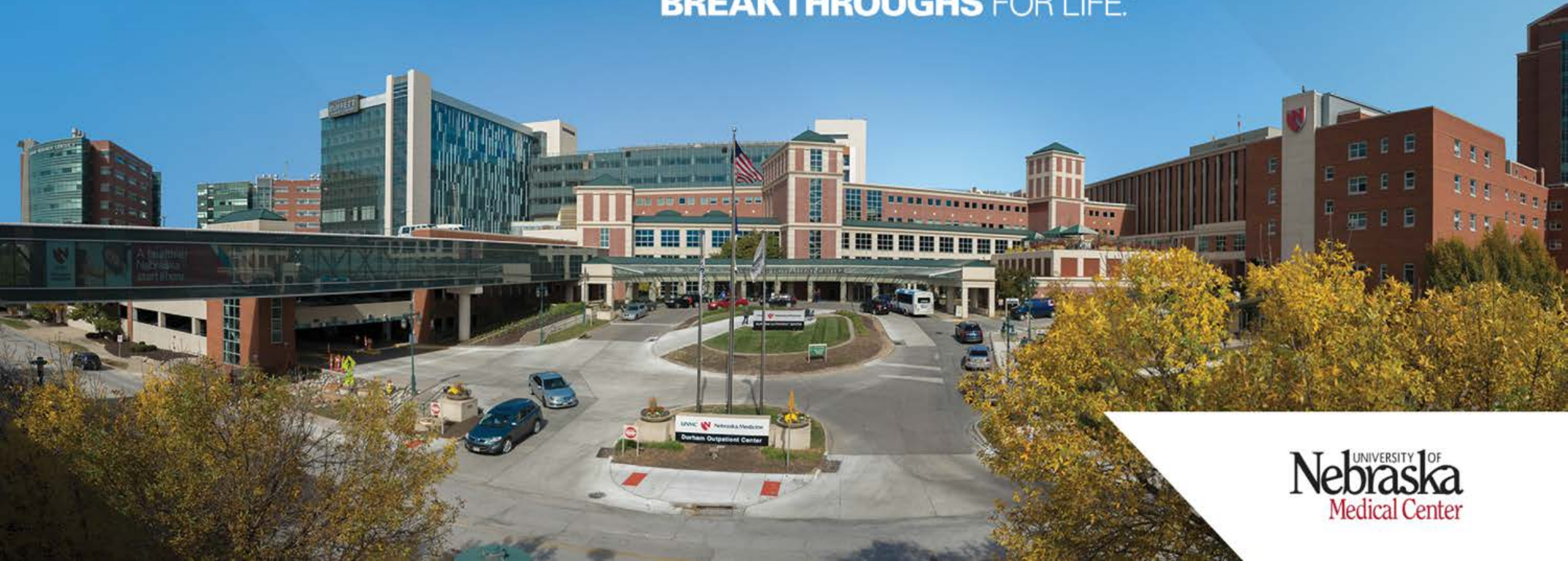

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