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EXPERT OPINION

Current issues and perspectives in prenatal nutrition

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John C Morrison[1]
John Elliott[2]
Robert A Knuppel[3]
Baha Sibai[4]
Michael W Pill[5]

[1]Department of Obstetrics and Gynecology, University of Mississippi Medical Center, Jackson, MS, USA; [2]Saddleback Memorial Medical Center, Women's Hospital, Laguna Hills, CA, USA; [3]DuBois Regional Medical Center, DuBois, PA, USA; [4]University of Cincinnati College of Medicine, Cincinnati, OH, USA; [5]Gemini Healthcare, Westbrook, CT, USA

Abstract: The typical American diet, characterized by energy-dense foods rich in starches, sugars, and saturated fats, and low in fruits and vegetables, is relatively unhealthy and is associated with nutritional deficiencies. Suboptimal diets for pregnant women have been associated with serious maternal medical complications (eg, iron deficiency anemia, high blood pressure, gestational diabetes, and morning sickness), as well as an increased risk of intrauterine growth restriction, birth defects, developmental delays after birth, and future chronic health problems, (eg, heart disease, type 2 diabetes, high blood pressure, and high cholesterol) during childhood, as well as later in life. Folic acid deficiency is one of the most common problems among pregnant women, and supplementation with folic acid during pregnancy has been reported to decrease the occurrence and recurrence of fetal neural tube defects. Folate supplementation beginning preconception, along with a multivitamin, at least 12 weeks prior to conception is recommended to achieve maximal risk reduction. The reported benefits of supplementing docosahexaenoic acid, an unsaturated omega-3 essential fatty acid, during pregnancy include promoting proper neurodevelopment in fetuses and infants that extends into childhood. Pregnancy is also associated with an increased susceptibility to oxidative stress, resulting from the imbalance between oxygen free radicals and the essential antioxidants that maintain homeostasis. Associated complications include preeclampsia, preterm labor, and intrauterine growth restriction. There is not enough evidence to support routine use of antioxidants, such as vitamins C and E during pregnancy, but coenzyme Q10 and lycopene are additional antioxidants under study and are yielding promising results by decreasing the occurrence of maternal complications.

Keywords: prenatal nutrition, oxidative stress, coenzyme Q10, lycopene

Introduction

The typical American diet, characterized by energy-dense foods rich in starches, sugars, and saturated fats and low in fruits and vegetables, is relatively unhealthy and associated with multiple nutritional deficiencies.[1,2] Good nutrition is particularly important for pregnant women, because pregnancy places extra nutritional demands on the mother to satisfy the needs of the growing fetus.[1,3] The ability of many pregnant women to consume an optimal diet throughout pregnancy is also limited by factors such as fatigue, nausea, food cravings, busy lifestyles and, for some, lack of knowledge in this area.[2]

Suboptimal prenatal diets have been associated with serious maternal medical complications, such as iron deficiency anemia, high blood pressure, gestational diabetes, and morning sickness.[2] Moreover, deficient prenatal diets have been reported to lead to an increased risk of intrauterine growth restriction, birth defects,

Correspondence: John C Morrison
Professor of Obstetrics, Gynecology, and Pediatrics, Department of Obstetrics and Gynecology, University of Mississippi Medical Center, Jackson, MS 39216, USA
Tel +1 601 668 2024
Email jmorrison@umc.edu

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and developmental delays after birth, as well as future chronic health problems (ie, subsequent heart disease, type 2 diabetes, high blood pressure, and high cholesterol during childhood, as well as later in life).[2,4] While the risk of complications is higher among women whose diets are deficient in micronutrients, even a healthy and carefully planned diet may not be sufficient to meet the increased demands of pregnancy.[2] It has been estimated that up to 30% of pregnant women suffer from a vitamin deficiency.[4] Therefore, many experts in pregnancy nutrition recommend prenatal nutritional supplements to ensure optimal infant and maternal outcomes.[2–5]

To help prevent pregnancy-related complications associated with diets low in nutritional value, the American College of Obstetricians and Gynecologists has recommended that pregnant women have appropriate weight gain, consume a variety of foods in accordance with the Food Guide Pyramid during pregnancy, have appropriate and timely vitamin and mineral supplementation added to the diet, and that alcohol, tobacco, and other harmful substances be avoided.[3] Because approximately 50% of pregnancies are unplanned, and women's health status may not be optimal when they conceive, women in the reproductive age group should be advised about the benefits of folic acid in addition to a multivitamin supplement during wellness visits, especially if pregnancy is contemplated.[6]

Based on our review of the literature and clinical practice experience, we provide our perspective on two key nutrients that contribute to maternal and fetal health (folate and docosahexaenoic acid [DHA] supplementation), as well as discuss the importance of oxidative stress in pregnancy and current research with antioxidants that may have a role in reducing its sequelae. To the extent that there are some relevant differences in diet and nutritional guidance among countries, the perspective for the current discussion is prenatal diet and nutritional supplementation in the US.

Current prenatal nutrition supplements

Prenatal nutrition supplements are formulated with a wide variety of micronutrients; most include vitamins, essential fatty acids, and minerals. Actual combinations of micronutrients may vary from one supplement to another, depending upon the intended nutritional focus, eg, a higher amount of iron for women who are prone to iron deficiency anemia. Many commercially available formulations of prenatal nutrition supplements include vitamins C, B1, B2, B12, E, D3, folic acid, copper, zinc, iron, magnesium, docusate, DHA, linolenic acid, eicosapentaenoic acid, calcium, and pantothenic acid (Table 1).

Importance of folic acid: Metafolin® versus folic acid

Adequate intake of folic acid is necessary during pregnancy and confers benefits for both mother and fetus. Folic acid is a water-soluble B vitamin that is needed for efficient red blood cell production and metabolism of homocysteine.[4] This is an essential vitamin during pregnancy and also plays a vital role in DNA synthesis and methylation (gene silencing), contributing to regulation of gene expression.[4] Folic acid deficiency is one of the most common problems amongst pregnant women. Supplementation with folic acid during pregnancy has been reported to decrease the occurrence and recurrence of fetal neural tube defects; a preventive role for folic acid has also been suggested for other congenital anomalies, such as oral clefts and congenital heart disease, although the clinical evidence for this role remains somewhat equivocal.[7–9] Currently available prenatal nutrition supplements generally contain 1 mg of folic acid. Supplemental folic acid in excess of 1 mg can prevent some of the signs and symptoms of vitamin B12 deficiency from being expressed, including megaloblastic anemia, but it will not halt the progression of associated severe neuropathies.[10] Thus, supplements that contain folic acid at levels of 1 mg or greater are dispensed via prescription in the US. In addition, concerns were raised in the late 1960s, suggesting that folic acid in large amounts might counteract the antiseizure effects of antiepileptic drugs and increase the seizure frequency in some children.[11] We are unaware of published reports of pregnant women consuming too much folic acid leading to toxicities.

A recent question has been raised as to what is the best formulation of folic acid for pregnant women? Some suggest that the combination of L-methylfolate (as Metafolin® 600 μg, folic acid USP 400 μg) is better than the standard 1 mg of folic acid. Theoretically, Metafolin results in higher folate levels and, in the rare case where the fetus is deficient (homozygous) in methylenetetrahydrofolate reductase, it seems better incorporated into fetal tissue. Lamers et al measured red cell folate concentrations in 136 nonpregnant women who received either 400 μg folic acid, 416 μg Metafolin, 208 μg Metafolin, or placebo daily for 24 weeks (Table 2). During the first four weeks of treatment, folic acid was more rapidly absorbed than Metafolin.[12] At eight weeks, both compounds yielded red cell folate levels above the threshold level (906 nmol/L as determined by Daly et al[13]) for open neural tube defects (at levels of 906 nmol/L or greater,

no neural tube defects should occur). At 16 weeks, Metafolin yielded a red cell folate concentration that was 8% higher than folic acid. However, since all subjects were above the 906 nmol/L cutoff, the 8% increase would not be clinically important in our opinion. The upper limit of red cell folate levels achieved at 24 weeks was approximately 1400 nmol/L with Metafolin 416 µg/day, 1300 nmol/L with folic acid 400 µg/day, and 1100 nmol/L with Metafolin 208 µg/day. Similarly, Venn et al studied red blood cell folate concentrations every four weeks over a 24-week period in 104 nonpregnant women (Table 2).[14] The folic acid preparations in this study used lower doses of both Metafolin and folic acid, and both products resulted in levels >900 nmol/L by four weeks. The upper limit of red cell folate levels achieved at 24 weeks was approximately 1050 nmol/L with Metafolin 113 µg/day and 1150 nmol/L with folic acid 100 µg/day.

Based on our review of the literature, there does not appear to be a clinically compelling reason to use the more expensive Metafolin product. We acknowledge the theoretical concern regarding the high serum folate levels that might occur with the additional 1 mg of folic acid in prenatal vitamins in areas where folate fortification of food is common. However, to our knowledge, there have been no human data or animal data published to suggest that high serum folate levels have been associated with adverse effects, and, as noted in the American Academy of Pediatrics statement on the use of folic acid for the prevention of neural tube defects, approximately a quarter of all women have consumed folic acid for many years and extensively during later pregnancy without apparent adverse effects.[15] Regarding the potential for higher doses of folic acid to mask megaloblastic anemia, but not neuropathies associated with vitamin B12 deficiency, pernicious anemia rarely occurs before 50 years of age, so is likely to be rare among women consuming folic acid during the reproductive years.[15] In view of these data, the health care provider should prescribe the folate product with which he or she is most comfortable.

As it may take up to 12 weeks for plasma folate and red blood cell folate concentrations to reach the threshold level needed to minimize the risk for neural tube defects, folate supplementation preconception, along with a multivitamin, at least 12 weeks prior to conception is recommended to achieve maximal risk reduction.[6,12]

How much DHA is needed?

DHA is an unsaturated omega-3 essential fatty acid found mainly in fish and marine plants. The benefits of DHA supplementation during pregnancy have been reported in randomized clinical trials, and several observational studies have reported a correlation between higher intrauterine DHA exposure and a number of positive developmental outcomes, including promoting proper neurodevelopment in fetuses and infants that extends into childhood.[16–18] However, the results are far from conclusive because other studies have reported no effects on neurodevelopment.[19,20] A number of studies have reported positive effects on fetal growth that continues after birth.[19,21,22] Results from the DOMINO trial[19] (DHA to Optimize Mother Infant Outcome) indicated that women who had supplemental DHA administered from week 21 onwards had a statistically significant reduction in preterm births ($P = 0.03$) and birth of low weight infants ($P = 0.03$) when compared with the control group administered matched vegetable oil capsules (Table 2). The trial further reported an overall decrease in neonatal intensive care admissions ($P = 0.04$). A study by Stein et al reported that maternal DHA supplementation during the second half of gestation may enhance growth through 18 months for children born to primigravid women (Table 2).[21]

While there is no standard recommendation for daily intake of DHA across the various professional agencies, organizations and societies, a general range does exist. A consensus statement from a workshop sponsored by the National Institutes of Health and the International Society for the Study of Fatty Acids and Lipids recommends a DHA intake of 300 mg/day for pregnant and nursing women.[23] Other consensus groups have recommended at least 200 mg/day as the optimal dose.[24,25]

A variety of DHA supplements are available, but there has been some debate about the equivalence of supplement-derived sources and natural food sources.[26] This was examined in a study that compared the nutritional availability of DHA from algal oil capsules with that from assayed cooked salmon in 32 healthy men and women. Participants consumed either 600 mg DHA from the algal oil capsules or cooked salmon for 14 days. Both interventions resulted in equivalent amounts of DHA delivered to plasma phospholipids and erythrocytes. However, in a study using DHA derived from fish oil capsules, daily intake of cooked salmon resulted in considerably higher levels of DHA than the supplement.[27] The Institute of Medicine guidance for daily intake of fish during pregnancy results in consumption of about 200–300 mg/day of DHA.[16] However, the availability of bioequivalent supplements is important because it is highly unlikely that all women will consume the recommended amount of fish during pregnancy, particularly in view of the guidance that only

Table 1 Prenatal micronutrient supplement comparison[89–101]

	RDA (FNB 2009)	PreQue 10[1]	OB complete 400[2]	PreNexa[3]	Prenate DHA[4]	Vitafol OB-DHA[5]
Administration	–	2 tablets once daily or 1 tablet twice daily	Once daily	Once daily	Once daily	2 pills once daily
Antioxidants						
Coenzyme Q10	0	100 mg	0	0	0	0
Lycopene	0	10 mg	0	0	0	0
Vitamins						
Vitamin A (beta-carotene)	0.75–0.77 mg[a]	2500 IU	0	0	0	2700 IU
Vitamin B_1 (thiamine mononitrate)	1.4 mg	2 mg	2 mg	0	0	1.6 mg
Vitamin B_2 (riboflavin)	1.4 mg	3.4 mg	3.4 mg	0	0	1.8 mg
Vitamin B_6 (pyridoxine HCl)	1.9 mg	0	25 mg	25 mg	25 mg	2.5 mg
Vitamin B_{12} (cyanocobalamin)	26 μg	2 μg	26 μg	0	12 μg	12 μg
Folate/folic acid	0.6 mg	1 mg	1.2 mg	1.2 mg	1.0 mg	1.0 mg
Vitamin D_3 (cholecalciferol)	200 IU[b]	240 IU	800 IU	170 IU	200 IU	400 IU
Vitamin C	80–85 mg[c]	60 mg	100 mg (as ascorbic acid with calcium ascorbate and calcium threonate)	25 mg	85 mg	70 mg
Vitamin E (d-alpha tocopherol)	22.35 IU	30 IU	30 IU (as hypersorb vitamin E)	30 IU	10 IU	30 IU
Niacin (niacinamide)	18 mg	0	10 mg	0	0	18 mg
Minerals						
Copper	1 mg	2 mg	1 mg	0	0	2 mg
Zinc (zinc oxide)	11–12 mg[d]	25 mg	25 mg	0	0	25 mg
Iron	27 mg	30 mg	40 mg (as Ferronyl and Ferrochel®)	30 mg	27 mg	65 mg
Calcium	1000–1300 mg[e]	0	0	160 mg	140 mg	100 mg
Magnesium (magnesium oxide)	350–400 mg[f]	20 mg	0	0	45 mg	25 mg
Selenium (as sodium selenate)	0	15 μg	0	0	0	0
Purified fish oil						
Docosahexaenoic acid	NA	100 mg	≥320 mg	265 mg	300 mg	250 mg
Other omegas						
Other micronutrients						
Iodine (potassium iodide)	0.22 mg	0	0	0	0	0
Choline (choline bitartrate)	450 mg	0	0	0	0	0

Citranatal Assure[6]	Gesticare DHA[7]	OB Complete One[8]	Prenate Essentia[9]	Citranatal Harmony[10]	Prefera OB One[11]	Neevo DHA[12]	Concept DHA[13]
2 pills once daily	2 pills once daily	Once daily	Once daily	Once daily	Once daily	Once daily	Once daily
0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0
3 mg	3 mg	2 mg	0	0	0	0	2 mg
3.4 mg	3 mg	4 mg	0	0	0	0	3 mg
25 mg	50 mg	30 mg	25 mg	25 mg	50 mg	25 mg	25 mg
0	8 µg	50 µg	12 µg	0	12 µg	50 µg	12.5 µg
1.0 mg	1.0 mg	1.0 mg	1.0 mg[l]	1.0 mg	1.0 mg	1.0 mg[m]	1.0
400 IU	410 IU	1200 IU	200 IU	400 IU	400 IU	400 IU	0
120 mg	120 mg	70 mg	85 mg	0	25 mg	40 mg	25 mg
30 IU	30 IU	30 IU	10 IU	30 IU	10 IU	30 IU	0
20 mg	20 mg	10 mg	0	0	17 mg	0	1.8 mg
2 mg	0	1 mg	0	0	0	0	2 mg
25 mg	15 mg	15 mg	0	0	15 mg	0	10 mg
35 mg	27 mg	40 mg (Ferronyl) 10 mg sumalate (elemental iron)	28 mg (ferrous fumarate)	27 mg (carbonyl iron)	22 mg polysaccharide iron complex 6 mg as (heme iron polypeptide)	27 mg (ferrous fumarate)	17.5 mg (ferrous fumarate) 17.5 mg polysaccharide iron complex
125 mg	200 mg	25 mg (DimaCal®) and 25 mg calcium carbonate	140 mg	100 mg	0	75 mg	0
0	0	25 mg	45 mg	0	0	0	5 mg
0	0	0	0	0	0	0	0
300 mg	250 mg	≥300 mg ≥40 mg	300 mg 40 mg	250 mg	200 mg	250 mg	156 mg 39 mg
150 µg	150 µg	150 µg	150 µg	0	175 µg	0	0
0	55 mg	0	0	0	0	0	0

Notes: [a]0.75 mg/day for women 14–18 years and 0.77 mg/day for women 19–50 years; [b]AI, daily adequate intake for pregnant women; [c]80 mg/day for women 14–18 years and 85 mg/day for women 19–50 years; [d]11 mg/day for women 19–50 years and 12 mg/day for women 14–18 years; [e]AI, daily adequate intake for pregnant women; 1000 for women 19–50 years and 1300 mg for women 14–18 years; [f]350 mg/day for women 19–30 years, 360 mg/day for women 31–50 years, and 400 mg/day for women 14–18 years.

Abbreviations: FNB, Food and Nutrition Board; RDA, recommended dietary allowance per day for pregnant women.

Table 2 Selected clinical outcome studies of prenatal supplements

Study	Subjects (n)/duration/design	Intervention	Outcome
Lamers et al[12]	Nonpregnant women 18–35 years (n = 136) 24 weeks DB, R, PC	FA 400 μg or [6S]-5-MTHF* 416 μg or [6S]-5-MTHF 416 μg or placebo	Red cell folate levels: • 4 weeks – FA more rapidly absorbed • 8 weeks – both compounds yield levels above "safe" threshold • 16 weeks – [6S]-5-MTHF yields concentration 8% higher than FA
Venn et al[14]	Nonpregnant women 18–49 years (n = 104) 24 weeks DB, R, PC	FA 100 μg or [6S]-5-MTHF* 113 μg or placebo	• No difference in slopes between active treatment groups in either plasma folate or red cell folate levels • At 24 weeks, estimated mean increase in red cell folate levels: FA: 275 nmol/L [6S]-5-MTHF: 251 nmol/L
Makrides et al[19]	Pregnant women less than 21 weeks gestation (n = 2399) Follow-up of children (n = 726) Treatment received from study entry until delivery DB, R, PC	DHA fish oil 800 mg/day or placebo	• No difference between groups in mean cognitive scores or mean language scores[102] • Very preterm births (<34 weeks): 1.09% DHA vs 2.25% placebo (adjusted RR, 0.49; 95% CI 0.25–0.94, $P = 0.03$) • Post-term births requiring induction or cesarean delivery: 17.6% DHA vs 13.7% placebo (adjusted RR, 1.28; CI 1.06–1.54, $P = 0.01$) • Low birth weight infants: 3.41% DHA vs 5.27% placebo (adjusted RR 0.65, CI 0.44–0.96; $P = 0.03$)
Stein et al[21]	Pregnant women at gestational week 18–22 Follow-up of children (n = 739) Treatment received from study entry until delivery DB, R, PC	Algal DHA 400 mg/day or placebo	• At 18 months, differences in length, weight, and head circumference were not significantly different between groups in total population • Among offspring of primigravid women: length at 18 months increased by 0.72 cm vs placebo (95% CI 0.11–1.33)
Roberts et al[59]	Nulliparous pregnant women at gestational week 9–16 (n = 10,154) Treatment received from study entry until delivery DB, R, PC	Vitamin C 1000 mg and vitamin E 400 IU or placebo	• No significant difference between treatment group and placebo in rates of pre-eclampsia (7.2% vs 6.7%, respectively; RR 1.07, CI 0.93–1.24) or in rates of other complications (eg, severe pregnancy-related hypertension, elevated liver enzymes, thrombocytopenia, elevated serum creatinine, eclamptic seizure, fetal growth restriction, perinatal death)
Spinnato et al[60]	Pregnant women at gestational week 12–19 with chronic hypertension or prior history of pre-eclampsia (n = 739) Treatment from study entry until delivery or diagnosis of pre-eclampsia DB, R, PC	Vitamin C 1000 mg and vitamin E 400 IU or placebo	• No significant difference between treatment group and placebo in rate of pre-eclampsia (13.8% vs 15.6%, adjusted RR 0.87, CI 0.61–1.25), or in mean gestational age at delivery, rates of perinatal mortality, preterm delivery, low birth weight, or other complications
Poston et al[61]	Pregnant women at increased risk for pre-eclampsia and at gestational week 14–21 (n = 2410) Treatment from study entry until delivery DB, R, PC	Vitamin C 1000 mg and vitamin E 400 IU or placebo	• No significant difference between treatment group and placebo in rate of pre-eclampsia (15% vs 16%, adjusted RR 0.97, CI 0.80–1.17) • More low birth weight infants born in antioxidant treatment group vs placebo (28% vs 24%, RR 1.15, CI 1.02–1.30) • No difference between groups in small size for gestational age

(*Continued*)

Table 2 (*Continued*)

Study	Subjects (n)/duration/design	Intervention	Outcome
Teran et al[67]	Primigravid pregnant women at increased risk for pre-eclampsia, 20 years old or younger, and at gestational week 16–20 (n = 235) Treatment from study entry until delivery DB, R, PC	Coenzyme Q10 200 mg/day or placebo	• Pre-eclampsia 14.4% vs 25.5% in coenzyme Q10 and placebo groups, respectively (RR 0.56, CI 0.33–0.96; $P = 0.035$) • Incidence of low birth weight similar between groups (10% vs 12.3% for coenzyme Q10 and placebo groups, respectively) • No perinatal mortality
Sharma et al[74]	Primigravid women at gestational week 16–20 (n = 251) Treatment from study entry until delivery DB, R, PC	Lycopene 2 mg twice daily or placebo	• Pre-eclampsia 8.6% vs 17.7% in lycopene and placebo groups, respectively ($P = 0.043$) • Mean DBP 86.7 mmHg vs 92.2 mmHg in lycopene and placebo groups, respectively ($P = 0.012$) • Mean fetal weight 2751 g vs 2657 g in lycopene and placebo groups, respectively ($P = 0.049$) • Incidence of intrauterine growth retardation 12% vs 23.7% in lycopene and placebo groups, respectively ($P = 0.033$)
Kramer et al[75]	Frozen plasma samples from pregnant women taken at 24–26 weeks' gestation: spontaneous preterm births (n = 207) and term delivery controls (n = 443) Case-control nested study	No treatment	• High (above median) plasma concentrations of lycopene were associated with reduced risk of spontaneous preterm birth: • Median-based: adjusted OR 0.6 (95% CI 0.4–0.9) • Dose-response effects across quartiles
Banerjee et al[86]	Primigravid women at gestational week 12–20 weeks (n = 159) Treatment from study entry until delivery R, DB, PC	Lycopene 2 mg/day or placebo	• No difference between treatment groups in pre-eclampsia • Preterm labor: 10.39% vs 1.22% in lycopene and placebo groups, respectively ($P = 0.02$) • Low birthweight (<2.5 kg) infants: 22.08% vs 9.76% in lycopene and placebo groups, respectively ($P = 0.05$)

Note: *Metafolin®.
Abbreviations: DB, double-blind; R, randomized; PC, placebo-controlled; DBP, diastolic blood pressure; FA, folic acid; DHA, docosahexaenoic acid; RR, relative risk; OR, odds ratio; CI, confidence interval.

certain types of fish be consumed due to concerns about mercury contamination.

In addition, discussions have centered on the best source of DHA. The most common supplements are derived either from fish oil or microalgae.[28] While both types of supplements have reported good safety and efficacy profiles, the microalgae-derived products have several advantages over the fish-derived products. First, supplements derived from microalgae are acceptable to vegetarians who do not consume fish. Second, mercury or polychlorinated biphenyl contamination of microalgae supplements has not been reported in the scientific literature, which is in contrast with what has been found in fish oil supplements.[29] Third, overfishing is recognized as a prevalent problem around the globe, but products derived from microalgae do not contribute to this environmental burden. Furthermore, although algae is an important component of the marine life cycle, the algae used to produce supplements is generally grown in fermenters, so there is no impact on the environment. Fourth, no allergic reactions to microalgae supplements have been reported in the scientific literature, which is in contrast with fish oil supplements, which have been associated with adverse allergic reactions and the risk may be higher in those with fish allergies.[30,31] Lastly, patients have reported a problem with a fishy taste significantly more often with fish oil than microalgae supplements.[32]

Pregnancy-induced oxidative stress

Pregnancy is undoubtedly associated with an increased susceptibility to oxidative stress.[33] Oxidative stress results from the imbalance between oxygen free radicals and the essential antioxidants that maintain homeostasis. Free radicals are unstable and highly reactive, causing cell damage during the process of becoming stable through the

acquisition of electrons from nucleic acids, lipids, proteins, and carbohydrates.[34] While oxygen free radicals serve as key signaling molecules and lead to necessary pathological processes, an abundance of these free radicals in excess of available antioxidant-buffering capacity can cause adverse outcomes for the mother, the developing fetus, and the child after birth.[33] The increased physiologic demands of pregnancy are associated with increased basal oxygen consumption, changes in energy substrate used by different organs, and production of free radicals that damage the endothelial lining cells of the maternal vasculature.[33] Transitional metals, especially iron and cadmium, which are abundant in the placenta, are also involved in the production of free radicals.[33,35] The transfer of iron to the placenta and fetus is enhanced by incremental increases in placental blood flow and transferrin receptors as pregnancy progresses.[33] Cadmium is a common pollutant from a variety of sources, including tobacco smoke, and is easily detectable in meat, fish, and fruits due to high concentration in the soil and water supply. It accumulates over time in the blood and several organs, including the placenta.[35] Pregnancy complications, such as preeclampsia, preterm labor, and intrauterine growth restriction, are all examples of conditions that can result from free radical damage.[36] Antioxidants function by converting reactive oxygen species to water, thereby alleviating maternal and early fetal damage, allowing endothelial cells to heal.[33,34] Therefore, it can be hypothesized that prenatal nutritional supplements that promote oxidative homeostasis may aid in preventing several maternal-fetal complications. However, to date, not all micronutrients contained within current prenatal supplements with antioxidant properties have been reported to be beneficial in reducing complications of pregnancy associated with oxidative stress.

Prenatal obstetric complications correlated with oxidative stress

Among the 875,000 women who experience one or more pregnancy complications every year, between 30% and 40% (about 4%–6% of total yearly pregnancies) are affected by preeclampsia, preterm labor, or preterm rupture, all complications that have the potential to affect both the mother and the fetus adversely.[37–39]

Preeclampsia

Preeclampsia is the second leading cause of maternal morbidity and mortality in the US, and is also associated with a significant increase in perinatal mortality. Infants born to affected mothers face a five-fold increase in mortality.[40] Preeclampsia usually occurs after 20 weeks of gestation, and is characterized by hypertension and proteinuria.[40] In addition, it is associated with diffuse endothelial activation and dysfunction as well as oxidative stress which occurs over several weeks or months, and is characterized by focal or segmental vasospasm, a proinflammatory state, and prothrombic properties.[42] Subcellular mechanisms that participate in vasoconstriction, resulting from endothelial cell dysfunction, include decreased nitric oxide generation and excess free radicals.[43] The severity of vascular endothelial dysfunction has been reported to have prognostic value for maternal hypertension, strokes, intrauterine growth restriction, and placental abruption.[43,44] Clinically, there is no cure for preeclampsia, and it is usually treated by placental delivery following vaginal birth, cesarean section, or after abortion.[45,46] If preeclampsia is not properly diagnosed, monitored, and treated, the condition can quickly progress to eclampsia, an acute and life-threatening complication characterized by the appearance of tonic-clonic seizures and/or coma. The clinical manifestations of this condition can appear any time from the second trimester through the postpartum period.[47]

While the pathogenesis of preeclampsia has not been completely elucidated, it is believed to be mediated by a generalized maternal inflammatory response that originates in the placenta, and is characterized by activation of vascular endothelial cells and maternal leukocytes. The pathogenesis of preeclampsia has been described as a two-stage process involving reduced placental perfusion, followed by the release of placental factors that trigger maternal vascular endothelial cell dysfunction.[48] Presence of specific mediators of oxidative stress in the intervillus space, and subsequent transfer of those mediators to the maternal systemic circulation has been hypothesized as the link between the two stages, triggering the endothelial dysfunction.[43,49] The increased rate of lipid peroxidation and decrease in antioxidants such as selenium, beta-carotene, and alpha-tocopherol observed in women with preeclampsia seem to support this hypothesis, although decreased antioxidants could be evidence of either an antioxidant deficiency or of excess free radical generation.[44,50] Based on this evidence, antioxidants have been proposed for prevention and treatment of this condition.[50]

Preterm labor and preterm rupture of membranes

Spontaneous preterm birth is commonly defined as any delivery before 37 weeks' gestation. Infants are born preterm

following spontaneous labor with intact membranes (about 45% of cases), preterm membrane rupture (about 30%), and after labor induction or cesarean delivery for maternal or fetal indications (about 25%).[51,52] While these events are distinctively defined, the evidence indicates that the risk factors for their occurrence are similar.[53] Since most fetal organs are not fully developed, the earlier the delivery prior to 37 weeks, the greater the risk for long-term newborn health complications. Premature infants born after 34 weeks of pregnancy tend to have less chance of complications than those born earlier. Infants born between 22 and 34 weeks of pregnancy have increased mortality and morbidity rates.[51,52] Two thirds of the perinatal mortality and half of long-term neurologic disabilities, including cerebral palsy, are associated with preterm birth.[52] Obstetric triggers for preterm labor include premature rupture of membranes, uterine infections, multifetal pregnancy, or disorders that include preeclampsia, placental abnormalities, such as previa and abruption, and pyelonephritis, leading to an increase in medically indicated deliveries before 37 weeks' gestation. Preterm birth is very common in women who experience preterm premature rupture of membranes, but with intact membranes, pregnancy can be extended significantly in up to 50% of the cases.[52]

Several lines of evidence implicate oxidative stress in preterm labor. In a case-control study in 265 Korean women, oxidative stress-related gene interactions were associated with preterm delivery.[54] Several studies utilizing urinary or plasma biomarkers for oxidative stress have yielded associations between oxidative stress, decreased serum antioxidant status, and shortened gestation duration.[55–57] Oxidative stress has also been implicated in preterm rupture of membranes, in which increased generation of reactive oxygen species may arise from infection and inflammation, cigarette smoking, or vaginal bleeding and release of free iron.[58] As with preeclampsia, the role of oxidative stress in preterm labor and preterm rupture of membranes suggests antioxidants may help to prevent these events.[33,48]

Preeclampsia, preterm labor, and preterm rupture of membranes have been associated with oxidative stress and increased levels of lipid peroxidation. Imbalances between lipid peroxides and antioxidants have been reported in preeclampsia, and may contribute to vascular endothelial cell damage.[50] Reduced perfusion of the placental tissue, in turn, may lead to the production of large amounts of oxygen-free radicals responsible for lipid peroxidation. Oxidative stress in high risk or preeclamptic patients is likely to be worsened by high levels of free radicals and low nutritional status.

Previous studies of plasma antioxidants in preeclampsia have primarily focused on single supplements, such as vitamin E, vitamin C, carotenoids, and thiols. Three large studies of combinations of vitamin C and vitamin E are summarized in Table 2. In a large study of 10,154 women, the combination of vitamin C 1000 mg and vitamin E 400 IU was started at 9–16 weeks' gestation and continued throughout pregnancy, and showed lack of efficacy in preventing the condition, despite consistent evidence for a state of oxidative stress.[59] A second study conducted in Brazil treated 355 women at 12–19 weeks' gestation with vitamin C 1000 mg and vitamin E 400 IU or placebo (n = 352).[60] This study also failed to demonstrate any beneficial effect on reducing the rate of preeclampsia.[60] The placebo-controlled VIP (Vitamin C and vitamin E In pregnant women at risk for Preeclampsia) trial of vitamin C 1000 mg and vitamin E 400 IU administered daily from the second trimester of pregnancy until delivery in 2410 women yielded similar incidences of preeclampsia in the treatment and placebo groups, but a higher incidence of low birth weight babies among women who took antioxidants compared with controls.[61] While a recent meta-analysis concluded that there is not enough evidence to support routine use of these antioxidants during pregnancy to reduce the risk of preeclampsia,[62] the potential importance of oxidative stress in preeclampsia has led investigators to consider the use of other antioxidants, such as coenzyme Q10 and lycopene.

Next generation antioxidants for prenatal nutrition

Coenzyme Q10

Coenzyme Q10 is an essential component of oxidative phosphorylation at the mitochondrial level. It also has potent antioxidant and membrane-stabilizing properties,[62] and is postulated to be a modulator of gene expression and cell growth.[63,64] As shown in Table 3,[65] coenzyme Q10 is found in a variety of food sources.

Given its antioxidant benefits, coenzyme Q10 has also been used as a dietary supplement in a number of countries, such as Japan and the US, as well as all across Europe, for more than 30 years.[66] Data from both clinical and preclinical studies indicate that coenzyme Q10 has a safety profile appropriate for use as a dietary supplement, does not interfere with the biosynthesis of endogenous coenzyme Q9/coenzyme Q10, nor does it accumulate in plasma or tissues.[66] Three preclinical studies examined the genotoxicity of coenzyme Q10, with no genotoxic or mutagenic potential reported.[66] A preclinical trial in mice and rats to examine the potential effects of coenzyme Q10 on fetal and neonatal

Table 3 Coenzyme Q_{10} levels in food[65]

Food	Concentration (mg/kg)	Food	Concentration (mg/kg)	Food	Concentration (mg/kg)
Beef		**Fish**		**Oils**	
Beef heart	113	Sardines	5–64	Soybean	54–282
Beef liver	39–50	Red flesh	43–67	Olive	4–160
Beef	16–40	White flesh	11–16	Rapeseed	64–73
Pork	13–45	Salmon	4–8	Sunflower	4–15
Chicken	8–25	Tuna	5		
Nuts		**Vegetables**		**Fruit**	
Peanuts	27	Parsley	8–26	Avocado	10
Walnuts	19	Broccoli	6–9	Blackcurrant	3
Pistachio	20	Spinach	1–10	Orange	1–2
Hazelnuts	17	Cauliflower	2–7	Strawberry	1
Almond	5–14	Cabbage	2–5	Apple	1
Sesame seed	18–23			Grapefruit	1

development found no deleterious effects on the dams, the progress of pregnancy, or incidence of abnormalities, and no findings of postnatal toxicity.[66] No teratogenic studies of coenzyme Q10 in human pregnancy have been reported to our knowledge. In studies performed in healthy humans and those with chronic illnesses such as heart failure, Huntington's disease, and Parkinson's disease, no serious adverse effects associated with coenzyme Q10 were observed.[66] Doses employed in these studies were as high as 3000 mg/day administered for as long as eight months. A study by Teran et al in 2009 used coenzyme Q10 supplementation at 200 mg/day in pregnant women for 20 weeks and reported no differences in birth weight between those who received coenzyme Q10 or placebo (2981 g versus 2938 g, respectively). There was no perinatal mortality, and the duration of pregnancy was equivalent for both groups.[67] However, the dosage used in that study was lower than the acceptable daily intake of coenzyme Q10, which has been calculated at 12 mg/kg/day, which for a 60 kg person is 720 mg/day.[58] The Council for Responsible Nutrition has determined that 1200 mg/day is the "observed safe level" of coenzyme Q10. Although no studies of the effects of nutritional supplements on coenzyme Q10 concentrations in breast milk have been performed, coenzyme Q10, as a naturally occurring compound, has been found in human breast milk.[68] However, in one study, higher concentrations of coenzyme Q10 were found in the bloodstream of nursing mothers than in breast milk.[68] The implications of these findings are unknown. There are no studies evaluating the safety of coenzyme Q10 in nursing infants.

Evidence of the cellular role of coenzyme Q10 suggests that this molecule may have a role in preventing preeclampsia in pregnant women. For example, one study showed that levels of coenzyme Q10 in preeclamptic women were half those in women without preeclampsia, which has been confirmed by cohort studies.[64,69,70] The effect of coenzyme Q10 supplementation in pregnant women at increased risk of preeclampsia was recently assessed in a randomized, double-blind, placebo-controlled trial. Two hundred and thirty-five women were assigned to receive 200 mg of coenzyme Q10 or placebo daily from 20 weeks of pregnancy until delivery (Table 2). The rate of preeclampsia in the placebo group was significantly higher than that in the coenzyme Q10 group (25.6% versus 14.4%, $P = 0.035$), indicating that supplementation with coenzyme Q10 reduces the risk of developing preeclampsia in women at risk for this condition. Mild gastrointestinal symptoms were the most common adverse effects, but the difference was not significant between the groups (1.3% in the coenzyme Q10 group experienced gastrointestinal symptoms versus 1.5% for the placebo group, $P = 0.84$).[67]

A recent longitudinal study to assess the relationship between maternal serum coenzyme Q10 levels and maternal body weight gain, fat mass gain, and infant birth weight was conducted in 50 healthy pregnant women. Maternal serum coenzyme Q10 levels were positively correlated with maternal weight gain ($P < 0.05$) and fat mass gain ($P < 0.05$), as well as positively correlated with fetal growth ($P < 0.05$).[71] This study did not investigate differences in dietary intake between the groups.

Coenzyme Q10 was found to increase levels of extracellular superoxide dismutase, a major antioxidant enzyme system of the vessel wall that has been reported to lead to endothelium-dependent dilation of conduit arteries.[72,73] The ability of oral coenzyme Q10 supplementation (100 mg three times daily) to improve extracellular superoxide dismutase

activity and endothelium-dependent vasodilation in patients with coronary artery disease was investigated in a recent randomized trial. Both extracellular superoxide dismutase and endothelium-dependent relaxation, as well as peak VO_2 and O_2 pulse increases in the coenzyme Q10-treated group, were statistically greater versus the variations in the placebo group. Improvements induced by coenzyme Q10 supplementation were particularly remarkable in patients with low initial endothelium-bound extracellular superoxide dismutase and thus more prone to oxidative stress. Together, these results suggest that the improvements in endothelium-dependent relaxation and endothelium-bound extracellular superoxide dismutase activity might be related to the ability of coenzyme Q10 to enhance endothelial functionality by counteracting nitric oxide oxidation.[73]

Lycopene

Deficiency of lycopene, a carotenoid, has been associated with preterm labor and intrauterine growth restriction.[74,75] Lycopene is a carotenoid present in human serum and skin as well as in the liver, adrenal glands, lungs, prostate, and colon. This micronutrient is believed to possess antioxidant and antiproliferative properties.[76,77] The evidence suggests that lack of lycopene is associated with cancers of the digestive tract, cervical intraepithelial neoplasms, breast cancer, skin cancer, bladder cancer, prostate cancer, and cardiovascular disease.[78–85] A prospective, randomized, controlled study showed that, in primigravid women in the second trimester, administration of oral lycopene 2 mg twice daily reduced the rate of preeclampsia compared with placebo (8.6% in the lycopene group versus 17.7% in the placebo group, $P = 0.043$, Table 2).[74] The incidence of intrauterine growth restriction was also found to be significantly lower in the lycopene group (12% in the lycopene group versus 23.7% in the placebo group, $P = 0.033$). A prospective, multicenter cohort study of 5337 women examined frozen plasma samples from spontaneous preterm births (n = 207) and term controls (n = 443) for carotenoids, retinol, tocopherols, and long-chain fatty acids (Table 2).[75] High plasma concentrations of lycopene were associated with a reduced risk of spontaneous preterm birth, with evidence of dose-response effects across quartiles. Together, these results suggest a potential role for lycopene in reducing the incidence of preeclampsia, preterm birth, and subsequent intrauterine growth restriction in pregnant women.[75] However, a recent study conducted by Banerjee et al, utilizing a lycopene dose of 2 mg daily in primigravidas beginning on average at week 15.7, showed no difference in the rate of preeclampsia between the lycopene and placebo groups.[86] Furthermore, this study reported a significantly higher incidence of adverse events, such as preterm labor and low birthweight, with lycopene supplementation. The investigators noted that a dose of 2 mg daily may not be an optimal dose to show a statistical difference compared with placebo, and that the study population may have been too low-risk for discerning complication rates between the groups. Additional studies of lycopene are warranted in this area.

Lycopene is a naturally occurring compound, which is found in high concentrations in a variety of foods, including tomatoes. However, little data are available on the teratogenicity of lycopene or its safety during breastfeeding. In a study of rats and rabbits administered high doses of lycopene during gestation, no effects on body weight, necropsy findings, fetal development, or skeletal morphology were observed in the offspring.[87] Another study has reported that tomato consumption increases lycopene isomer concentrations in both the breast milk and plasma of lactating women without complications.[88] In this study, the concentration of lycopene in breast milk was one tenth that of the serum concentration. Lycopene is designated "Generally Recognized as Safe" by the US Food and Drug Administration. However, no specific studies are available to address its safety or lack thereof in breastfeeding, and there are no studies evaluating the safety of lycopene in nursing infants.

While the overall number of published clinical trials using either coenzyme Q10 or lycopene in pregnant women is currently limited, the results to date, combined with the Generally Recognized as Safe designation of these ingredients by the Food and Drug Administration, provide a foundation for future research into their utility for preventing pregnancy-related complications reported to result from oxidative stress.

Despite their potential role in minimizing preeclampsia, rupture of membranes, and preterm labor, to our knowledge, coenzyme Q10 and lycopene are only included in one commercial prescription prenatal nutritional supplement.

Conclusion

Considerable clinical and therapeutic evidence exists to support the need for nutritional supplementation during pregnancy for the benefits conferred to both mother and fetus. Therapeutic knowledge, clinical research, and technological advancements have had a significant impact on the prenatal nutrition market, from the initial focus on high calcium loads and iron and folic acid supplementation in the 1980s and 1990s, to the inclusion of DHA, smaller tablet

size, and improved taste in this century. As the 21st century progresses, we should continue to focus on the importance of precise amounts of micronutrient supplementation and perhaps consider the next stage of antioxidant therapy aimed at minimizing oxidative stress in the expectant mother.

Disclosure

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