MeritCare Medical Center's


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Aunt Cathy's Guide to:

A Top Ten Nutrition Plan for Optimizing Pregnancy Outcome

(Subject to Change at Any Moment ☺)

An important note to the reader:

This is a quick summary of my main conclusions on nutrition in pregnancy based on the current medical literature (as of date shown). My workshops include considerable detail describing the research leading to these conclusions, and the complete bibliography is far too large to include here. Some pertinent references are cited, however. This "Top Ten" list was designed at the request of health professionals in practice who have attended a workshop at which the supporting literature was presented because they felt a quick "bottom line" summary would assist in applying the research to patient care. Readers who have not attended the workshops will be viewing this list of suggestions out of context. References regarding a particular suggestion can be provided if you send an e-mail requesting it to the address above.

And now, the current "Top Ten":

1. **The physician or other primary health care person should emphasize the importance of eating a good variety of foods and taking appropriate supplements.**

This is in addition to the support of other health care professionals (nurses, dietitians, etc.) who may be encouraging good nutrition. Reason: many patients believe that if the doctor does not mention diet and nutrition, it must not be very important. Patients are more likely to take the issue seriously when the point is reinforced by all the team members, including the team leader especially.

2. **Establish a simple nutrition screening protocol and refer women for appropriate nutrition counseling.**

Utilize settings other than pregnancy visits to optimize effectiveness in birth defects prevention. For example, evaluate nutrition at other OB visits for birth control or for annual exams, and provide advice to help correct nutrition problems before a pregnancy is established

3. **Start supplementation with a multivitamin with minerals and begin providing nutrition advice preconceptionally.**

It used to be standard practice to postpone nutrition discussions and/or nutrient supplementation until the first pregnancy visit, which was often scheduled at the end of the first trimester. It is now well documented that nutritional status in the preconceptional period and throughout the entire pregnancy is truly critical for

optimizing outcome. Similarly, the old practice of discontinuing vitamin/mineral supplements because of nausea in early pregnancy is no longer recommended because (in addition to concerns about nutrient inadequacy during critical construction periods) research shows that the supplements (minus the high-dose iron) can actually decrease nausea, vomiting and vertigo in pregnancy. The discomfort associated with taking prenatal vitamins appears to be more related to the extremely high iron content of some prenatal products. Such a high amount of extra iron is contributory to GI distress and it is not needed in early pregnancy. Additionally, the form of iron in supplements (i.e, inorganic ferrous and ferric iron) is clearly not the most efficient or biologically absorbable form at any time. Most are far less than 2% absorbed, which is substantially less than the 20% iron absorption from "heme" iron forms in meat, for example. [Please see my "Nutrition Support of Iron Deficiency" handout for more on this topic.]

[J Obstet Gynaecol Can. 2007 Dec;29(12):1003-26. Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can. 2007 Dec;29(12):1003-26. J Obstet Gynaecol Can. 2006 Aug;28(8):680-9. Prenatal multivitamin supplementation and rates of congenital anomalies: a meta-analysis. J Obstet Gynaecol Can. 2006 Aug;28(8):680-9. Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. Acta Obstet Gynecol Scand. 2003 Oct;82(10):916-20. Prevalence and severity of nausea and vomiting of pregnancy and effect of vitamin supplementation. Clin Invest Med. 1999 Jun;22(3):106-10. Periconceptional folic acid containing multivitamin supplementation. Eur J Obstet Gynecol Reprod Biol. 1998 Jun;78(2):151-61.]

The EXTRA folic acid in prenatal products (800 mcg instead of 400 mcg) is also generally not needed in EARLY pregnancy. In preconception and early pregnancy, 400 mcg of folic acid in supplement form appears to be is sufficient to prevent neural tube defects in most situations, and the fetus has priority for this nutrient over the mother's needs. A fetus sequesters folic acid for its own use and then "leaves town" with it, potentially leaving the mother folate deficient after delivery unless intake is sufficient to meet both of their needs. The EXTRA 400 mcg in the prenatal vitamin is to prevent the mother from becoming depleted as the pregnancy progresses, both for her own health and to prevent birth defects should a pregnancy occur within a few months of delivery of the present infant.

Toward this end, a STANDARD vitamin/mineral product can be very helpful, especially for women who eat poorly at this time due to nausea (or general poor diet) and are therefore obtaining suboptimal amounts of vitamins and minerals. A standard product (which generally provides about 18 mg iron) is also less constipating than the very high iron products. Most research now suggests that the very high iron products are more problematic than they are helpful – other interventions improve iron status more effectively without the unpleasant side effects. If providing 800 mcg of folic acid is preferred, simply add a small and inexpensive OTC 400 mcg folic acid tablet. Folic acid adequacy is also now recognized to be a factor in decreasing risk of miscarriage, depression, stroke and cancer of the colon and breast, so our advice to women to take a multivitamin during childbearing years should be expanded to all of a woman's life. The use of this kind of product is now generally regarded as "prudent for most adults."

Recently a large epidemiologic study suggested that use of a general multivitamin in the periconceptional period may actually decrease risk of developing pre-eclampsia. Because the report is quite new at the time of this update, and the topic is so important, I am including the abstract below.

Periconceptional Multivitamin Use Reduces the Risk of Preeclampsia. Am J Epidemiol. 2006 Jun 13; The objective was to assess the independent effect of regular periconceptional multivitamin use on the risk of preeclampsia. Pregnant women (n = 1,835) enrolled in the Pregnancy Exposures and Preeclampsia Prevention Study (Pittsburgh, Pennsylvania, 1997-2001) at less than 16 weeks' gestation were asked whether they regularly used multivitamins or prenatal vitamins in the past 6 months. Women were classified as users or nonusers. The unadjusted prevalence of preeclampsia was 4.4% in nonusers and 3.8% in users. After adjustment for race/ethnicity, marital status, parity, prepregnancy physical activity, and income in a multiple logistic regression model, regular use of multivitamins was associated with a 45% reduction in preeclampsia risk compared with nonuse (odds ratio (OR) = 0.55, 95% confidence interval (CI): 0.32, 0.95). Prepregnancy overweight modified this effect. After confounder adjustment, **lean multivitamin**

users had a 71% reduction in preeclampsia risk compared with lean nonusers (OR = 0.29, 95% CI: 0.12, 0.65). In contrast, there was no relation between multivitamin use and preeclampsia among overweight women (OR = 1.08, 95% CI: 0.52, 2.25). A sensitivity analysis for unmeasured confounding by fruit and vegetable intake supported these conclusions. **If confirmed by others, these results suggest that regular use of a multivitamin supplement in the periconceptional period may help to prevent preeclampsia, particularly among lean women.**

Similarly interesting in regard to nutrition and pre-eclampsia prevention (and deserving of the "box-of-its-own") is a new report from the Cochrane Database: **Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. [**Cochrane Database Syst Rev. 2006 Jul 19;3:CD001059.]

The authors concluded: "Calcium supplementation appears to almost halve the risk of pre-eclampsia, and to reduce the rare occurrence of the composite outcome 'death or serious morbidity'. There were no other clear benefits, or harms." This observation is particularly noteworthy because the Cochrane Database group has a mandate to be very picky and skeptical; it takes quite a lot of consistency among reports of what they regard as quality studies for this organization to conclude something other than "there is not enough evidence" to come to any conclusions.

[Multivitamin use and the risk of preterm birth. Am J Epidemiol. 2004 Nov 1;160(9):886-92. A role for supplements in optimizing health: the metabolic tune-up. Arch Biochem Biophys. 2004 Mar 1;423(1):227-34. Vitamins for chronic disease prevention in adults: clinical applications. JAMA. 2002 Jun 19;287(23):3127-9. Eat Right *and* Take a Multivitamin NEJM 338 (15):1060-1061 1998], and particularly so for any who may become pregnant. [Vitamin supplements and the risk for congenital anomalies other than neural tube defects. Am J Med Genet. 2004 Feb 15;125C(1): 12-21. Impact of folic Acid fortification in the United States: markedly diminished high maternal serum alpha-fetoprotein values. Obstet Gynecol. 2004 Mar;103(3):474-9. The use of folic acid for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can. 2003 Nov;25(11):959-73. Folic acid deficiency during late gestation decreases progenitor cell proliferation and increases apoptosis in fetal mouse brain. J Nutr. 2004 Jan;134(1):162-6.]

Assume that at least some nutrients are NOT adequate unless you have actually checked that they are. Just as one example, the most recent National Health and Nutrition Examination Survey of the CDC found that the majority of Americans obtain less than 2/3 of the RDA for magnesium. As magnesium is known to be a critical cofactor in over 300 metabolic pathways, it is a very key nutrient in perinatal health and suboptimal intake of this nutrient is a very serious problem. [More on magnesium will be discussed later.] In general, choose a multivitamin/mineral supplement product that is as complete as possible but inexpensive. Generics are fine. A complete-type "prenatal" product that is not of the very high-iron type can also be helpful.

It seems prudent during pregnancy in particular to choose a vitamin/mineral supplement product with no more than the RDA for vitamin A. Preferably one should be selected which provides some (at least 25-50%) of the vitamin A in the precursor form "as ß-carotene" instead of providing it all as retinyl palmitate or retinyl acetate, since the retinol (hormonal) form in high amounts is a risk factor for birth defects.

A closer look at vitamin A: Vitamin A has important functions in cell differentiation, and similar types of birth defects are associated with both vitamin A deficiency and vitamin A excess. This is an area of considerable interest at present. Opinions differ regarding the teratogenicity of various forms of vitamin A. For example, one group of researchers concluded "the available human data suggest that threshold concentrations of these retinoids resulting in teratogenesis were unlikely to be exceeded following vitamin A supplements of 25,000 IU/day." Another study found no association between periconceptional vitamin A exposure at doses >8000 IU or >10,000 IU per day and malformations in general, cranial neural crest defects, or neural tube defects. They concluded that if vitamin A is a teratogen, the minimum teratogenic dose appeared to be well above the level consumed by most women during organogenesis.

[Model predicting the teratogenic potential of retinyl palmitate, using a combined in vivo/in vitro approach. Teratology 1998 Sep-Oct;58(3-4): 113-23. Vitamin A and birth defects. Am J Obstet Gynecol 1997 Jul;177(1):31-6.]

However, other maternal factors may result in increased risk of teratogenicity**.** For example, **hyperglycemia** increases embryonic susceptibility to the teratogenic effects of vitamin A in diabetic mice, and normalization of blood sugar completely the erased increased susceptibility. The damaging effects of **high dose retinol can also be affected by folate and methionine** status, and genetic predisposition.

[Hyperglycaemia potentiates the teratogenicity of retinoic acid in diabetic pregnancy in mice. Diabetologia. 2004 Feb 14. Antagonism of hypervitaminosis A-induced anterior neural tube closure defects with a methyl-donor deficiency in murine whole-embryo culture. J Nutr. 2003 Nov;133(11):3561-70. Combination therapy with folic acid and methionine in the prevention of retinoic acid-induced cleft palate in mice. Birth Defects Res Part A Clin Mol Teratol. 2003 Mar;67(3):168-73. Increased susceptibility to retinoid-induced teratogenesis in TGF-beta2 knockout mice. Reprod Toxicol. 2002 Nov-Dec;16(6):741-7. Maternal diabetes increases the risk of caudal regression caused by retinoic acid. Diabetes. 2002 Sep;51(9):2811-6. Retinoids and cardiovascular developmental defects. Cardiovasc Toxicol. 2002;2(1):25-39. Vitamin A during pregnancy. Nutr Health. 2001;15(3-4):237-43. All-trans-retinoic acid-mediated modulation of p53 during neural differentiation in murine embryonic stem cells. Cell Biol Toxicol. 2002;18(4):243-57. Teratogenic effects of chronic ingestion of high levels of vitamin A in cats. J Anim Physiol Anim Nutr (Berl). 2003 Feb;87(1-2):42-51.Effects of excess vitamin A on development of cranial neural crest-derived structures: a neonatal and embryologic study. Teratology 2000 Oct;62(4):214-26. Vitamin A teratogenicity and risk assessment in the macaque retinoid model. Reprod Toxicol 2000 Jul-Aug;14(4):311-23. Dietary vitamin A and teratogenic risk: European Teratology Society discussion paper. Eur J Obstet Gynecol Reprod Biol 1999 Mar;83(1):31-6. Prevention of congenital abnormalities by vitamin A. Int J Vitam Nutr Res 1998;68(4):219-31. Safety of vitamin A: recent results. Int J Vitam Nutr Res 1998;68(6):411-6. Periconceptional vitamin A use: how much is teratogenic? Reprod Toxicol 1998 Jan-Feb;12(1):75-88. Teratogenic effects of vitamin A and its derivates Arch Pediatr 1997 Sep;4(9):867-74.]

It also appears that the **FORM of vitamin A used can greatly alter the toxicity of supplements** in addition to the dichotomy between beta-carotene (the vitamin A precursor) and a variety of the hormonal forms of vitamin A in foods and supplements (retinol, retinoic acid and retinyl esters.) It was shown that **the degree of toxicity of vitamin A also depends greatly on whether it is provided in a oil-based preparation, or as water-miscible, emulsified, or solid preparation.** The results of a recent important animal study were as follows: "Chronic hypervitaminosis A is induced after daily doses of 2 mg retinol/kg in oil-based preparations for many months or years. In contrast, doses as low as 0.2 mg retinol. kg(-1). d(-1) in water-miscible, emulsified, and solid preparations for only a few weeks caused chronic hypervitaminosis A. Thus, water-miscible, emulsified, and solid preparations of retinol are approximately 10 times as toxic as are oil-based retinol preparations. The safe upper single dose of retinol in oil or liver seems to be approximately 4-6 mg/kg body wt. These thresholds do not vary considerably with age." Another form of vitamin A (a metabolite called **isotretinoin – the drug Accutane**) is well recognized as causing birth defects. And as a rule, because it is a very rich source of the hormonal forms of vitamin A, some researchers have raised concerns about frequent consumption of liver during pregnancy. Positions taken on "the liver question" vary greatly in the official recommendations of experts in various nations, ranging from alarm to unconcern.

[Water-miscible, emulsified, and solid forms of retinol supplements are more toxic than oil-based preparations. Am J Clin Nutr. 2003 Dec;78(6):1152-9. A call for action--prevention of fetal exposure to isotretinoin. A position paper by The Organization of Teratology Information Services Public Affairs Committee.Reprod Toxicol. 2001 Nov-Dec;15(6):729. Teratogenicity of isotretinoin revisited: species variation and the role of all-trans-retinoic acid. J Am Acad Dermatol. 2001 Nov;45(5):S183-7. The problem of a high content of vitamin A in the liver of calves, cattle, sheep and swine for the consumer. Amount of accumulation and mechanism of teratogenic effect (review article). Berl Munch Tierarztl Wochenschr. 1994 Oct;107(10):342-7. Survey of animal livers for vitamin A content. Food Addit Contam. 1992 May-Jun;9(3):237-42. A survey of vitamin A concentrations in the liver of food-producing animals. Food Addit Contam. 1998 Jan;15(1):10-8. Health risks related to high content of vitamin A in liver Nord Med. 1990;105(5):149-50, 153. Evaluation of vitamin A toxicity. Am J Clin Nutr. 1990 Aug;52(2):183-202.]

Use a children's chewable version (one daily) if needed or desired for people who have trouble with pills or for those with nausea. **Use the regular dosage of one tablet per day,** (the standard dose for people ages 4-to-adult). Do <u>not</u> suggest taking two tablets ("because the product is designed for children") because the vitamin A (retinol) content would then be higher than is desirable during pregnancy, and as noted above, in early pregnancy this could increase the risk of birth defects. If most of the vitamin A is provided in the form

of beta carotene, the risk of contributing to birth defects is much less. In general, children's products are quite similar to those formulated for adults.

Choose a product with at least 400-800 mcg folic acid. If the mother previously had a child with a neural tube defect (NTD), providing the usually recommended amount of folic acid preconceptionally may be adequate. However, for some women it may not be adequate for genetic reasons (e.g. some women who have high homocysteine levels that are unresponsive to the usual intake levels of folic acid) or those who are chronic users of antibiotics, certain epilepsy medications or alcohol (all of which impair folic acid absorption or metabolism.) In some unusual cases, up to 4000 mcg/day (4 mg) may be needed to normalize folic acid-dependent metabolism.

If a genetic or other medical condition that greatly increases requirements for folic acid is suspected, the physician can order a one-time "methionine-load homocysteine" level in the mother when not pregnant to determine if her folic acid needs are higher than usual. This test is unnecessary in the vast majority of situations, however, as even for those with the MTHFR gene (known to affect folic acid metabolism), provision of the RDA level in a vitamin pill form (i.e. the crystalline well-absorbed form) almost always corrects the problem. Identifying those with higher than average requirements will both protect her future babies from birth defects and it will also significantly reduce her own risk of stroke, DVT, depression and cancer. High-dose folic acid can also help those with a family history of cleft lip or palate (one study used 10 mg/day), NTD-affected previous pregnancy or family history, insulin-dependent diabetes, epilepsy treatment with valproic acid, phenytoin or carbamazepine.

A recent summary of recommendations of the major association of obstetricians in Canada was that for these women "high-dose folic acid (4.0 mg-5.0 mg daily) supplementation is recommended. This should be taken as folic acid alone, not in a multivitamin format, due to risk of excessive intake of other vitamins such as vitamin A." Other seizure medications can increase folic acid requirements as well, such as phenytoin (Dilantin), which when taken during pregnancy has been associated with cleft lip/palate and heart and uro-genital defects. Norwegian experts make the following recommendations: "Valproate and carbamazepine have been associated with neural tube defects and phenytoin with cleft lip/palate and heart and urogenital defects. All women taking valproate and carbamazepine are advised to take 4 mg/day of folic acid at least one month before pregnancy and during the first trimester. Other women with epilepsy in fertile age are recommended to take 0.4 mg/day. Vitamin K 10 mg/day should be given the last 4 weeks to women on liver enzyme-inducing AEDs."[Anti-Epilepsy Drugs] Ideally, women taking phenytoin would already be receiving folic acid supplementation since the time that she began to use the drug "because of the hypothesized cofactor mechanism, decreased adverse effects associated with folate deficiency, and better seizure control with no perturbation of phenytoin pharmacokinetics." However, if this has not been done (and it may not have been) it is important to increase folic acid intake gradually and under the physician's supervision, as a sudden increase in intake could have a negative effect on seizure control in this situation.

[**A sample of some references on this very large topic:** The use of folic acid for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can. 2003 Nov;25 (11):959-73. Folic acid and homocysteine affect neural crest and neuro-epithelial cell outgrowth and differentiation in vitro. Dev Dyn. 2003 Jun;227(2):301-8. Vitamin and homocysteine status of mothers and infants and the risk of nonsyndromic oro-facial clefts. Am J Obstet Gynecol. 2003 Oct;189(4):1155-60. Is there more to folates than neural-tube defects? Proc Nutr Soc. 2003 Aug;62(3): 591-8. The use of folic acid for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can. 2003 Nov;25(11): 959-73. Pregnancy and birth in women with epilepsy. Tidsskr Nor Laegeforen. 2003 Jun 12;123(12):1695-7. Management issues for women with epilepsy: neural tube defects and folic acid supplementation. Neurology. 2003 Sep 1;61(6 Suppl 2):S23-6. The effects of folic acid in the prevention of neural tube development defects caused by phenytoin in early chick embryos. Spine. 2003 Mar 1;28(5):442-5. Primary prevention of neural-tube defects and some other major congenital abnormalities: recommendations for the appropriate use of folic acid during pregnancy. Paediatr Drugs. 2000 Nov-Dec;2 (6):437-49. Nonsyndromic orofacial clefts: association with maternal hyperhomocysteinemia. Teratology. 1999 Nov;60(5):253-7. Folic acid for the prevention of congenital anomalies. Eur J Pediatr. 1998 Jun;157(6):445-50. Neural tube and craniofacial defects with special emphasis on folate pathway genes. Crit Rev Oral Biol Med. 1998;9(1):38-53. Reduced recurrence of orofacial clefts after periconceptional supplementation with high-dose folic acid and multivitamins. Teratology. 1995 Feb;51(2):71-8. Phenytoin-folic acid interaction. Ann Pharmacother. 1995 Jul;29 (7-8):726-35.

Regarding dietary sources of folate, it is often not recognized that many popular fruits and vegetables do not even contain folate (e.g. apples and grapes have none), and that not all food sources of folate are equally

well absorbed or utilized. The form in vitamin pills, fortified grains and cereals ("folic acid") IS well absorbed. In view of the importance of assuring folic acid adequacy at this critical phase of fetal development and the studies showing that the most **reliable** way to assure an adequate intake of a bioavailable form of folic acid is via supplementation, it is prudent to simply provide a multivitamin. Interestingly, several countries have attempted to improve women's preconceptional folic acid intake via ad campaigns urging supplement use. In several cases it has been quite unsuccessful, not because the supplements did not prevent birth defects, but because women simply have still not adopted the practice of reliably taking the supplements. As a result, there is considerable pressure in several countries at present to establish a folic acid food-fortification program such as that initiated in 1998 in the US.

Since January 1998, folic acid (in a well-absorbed form) has been added to grains in the U.S. The results of this large public health undertaking were recently reported. Compared with the incidence before fortification, the supplementation of grains has decreased the incidence of neural tube defects by an astounding 70%. During the same period, stroke and stroke deaths have declined by an impressive 15%. [Improvement in stroke mortality in Canada and the United States, 1990 to 2002. Circulation. 2006 Mar 14;113(10):1335-43.] No problems were identified as a result of the fortification.

In several studies throughout Europe, it has been found that although there is clear evidence for NTD prevention by assuring adequacy of periconceptional folic acid, it continues to be found that public health messages urging women to take folic acid supplements have been ineffective in bringing about the kind of changes observed with food fortification with folic acid. The reason is that with supplementation of food, one does not need awareness of the issue nor the motivation to plan ahead. Further, there are no limitations of willingness/ablilty to purchase supplements limits. [Example: Promotion of folate for the prevention of neural tube defects: who benefits? Paediatr Perinat Epidemiol. 2005 Nov;19(6):435-44.]

Studies continue to show that the simple use of a multivitamin can decrease risk of quite a number of birth defects besides the well-documented neural tube defects of spina bifida and anencephaly. For example, periconceptional intake of thiamine, niacin and pyridoxine seems to contribute to the prevention of oral-facial clefts**.** A multivitamin will also decrease risk of birth defects associated with vitamin B12 deficiency, which has been shown to occur in unsupplemented vegans and also (surprisingly) among people with gastro-esophageal reflux problems (GERD) who use medications that decrease stomach acid production (such as Prilosec®, Prevacid ®, Nexium®, Protonix® and others.) Low stomach acid production impairs absorption of vitamin B12 from food, but it is easily corrected by providing the crystalline form of vitamin B12 found in vitamin supplements. Glucophage® (Metformin) is a medication for diabetes that has been shown to negatively affect absorption of vitamin B12.[For more information on these issues, please see "Aunt Cathy's Guide to Nutrition: New Discoveries about Folic Acid and Health." And "Aunt Cathy's Guide to Nutrition: a Vitamin B12 Update."]

Folic acid supplementation, fortification and/or multivitamin supplementation has been associated with significant reduction of risk for many anomalies besides neural tube defects.

1) incidence of all birth defects overall;
2) cardiovascular anomalies,
3) orofacial clefts;
4) limb deficiencies ;
5) urinary tract defects;
6) nonsyndromic omphalocele;
7) imperforate anus; and
8) incidence of pediatric cancers.

[Prenatal supplementation with multivitamins and the incidence of pediatric cancers: clinical and methodological considerations. Pediatr Blood Cancer. 2008 Feb;50(2 Suppl):487-9. Prenatal multivitamin supplementation and rates of pediatric cancers: a meta-analysis. Clin Pharmacol Ther. 2007 May;81(5):685-91. Periconceptional folates and the prevention of orofacial clefts: role of dietary intakes in France Rev Epidemiol Sante Publique. 2005 Sep;53(4):351-60. Vitamin supplements and the risk for congenital anomalies other than neural tube defects. Am J Med Genet. 2004;125C(1): 12-

21. Maternal dietary B vitamin intake, other than folate, and the association with orofacial cleft in the offspring. Eur J Nutr. 2004;43(1):7-14. Maternal myo-inositol, glucose, and zinc status is associated with the risk of offspring with spina bifida. Am J Obstet Gynecol. 2003;189(6): 1713-9. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. J Intern Med. 2003;254(5):455-63. The syndrome of food-cobalamin malabsorption revisited in a department of internal medicine. A monocentric cohort study of 80 patients. Eur J Intern Med. 2003;14(4):221-226. Should we screen diabetic patients using biguanides for megaloblastic anemia? Aust Fam Physician. 2003;32(5):383-4. Metformin-associated vitamin B12 deficiency. Arch Intern Med. 2002 28;162(19):2251-2. Side effects: Calcium supplements help metformin users absorb vitamin B12. Treatment update. 2000;12(7):6-7. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes Care. 2000;23(9): 1227-31. Ambulatory care increased vitamin B12 requirement associated with chronic acid suppression therapy. Ann Pharmacother. 2003;37(4): 490-3. Changes in gastric mucosa and luminal environment during acid-suppressive therapy: a review in depth. Dig Liver Dis. 2001;33(8):707-19. Maternal periconceptional vitamins: interactions with selected factors and con-genital anomalies? Epidemiology. 2002;13(6):625-30. Maternal multivitamin use and orofacial clefts in offspring. Teratology. 2001;63(2):79-86. Neural tube defects associated with maternal periconceptional dietary intake of simple sugars and glycemic index. Am J Clin Nutr. 2003;78(5):972-8. Oral clefts and vitamin supplementation. Cleft Palate Craniofac J. 2001;38(1):76-83. Maternal diet during pregnancy and risk of brain tumors in children. Int J Cancer Suppl. 1998;11:23-5. Neural tube defects associated with maternal periconceptional dietary intake of simple sugars and glycemic index. Am J Clin Nutr. 2003;78(5):972-8. Effects of retinoic acid on the neural crest-controlled organs of fetal rats. Pediatr Surg Int. 2003;19(5):-355-8. Marginal biotin deficiency is teratogenic in ICR mice. J Nutr. 2003;133(8: 2519-25. Folic acid and neural tube defects in pregnancy: a review. J Perinat Neonatal Nurs. 2003;17(4): 268-79.]

4. Assure adequate magnesium, calcium, vitamin D and iodine intake in particular; these are nutrients that are often inadequate in the diets of Americans and they are often needed in amounts beyond that provided by most multivitamin/mineral supplements.

Maternal magnesium status has been shown to be related to pregnancy outcome. Dietary magnesium inadequacy has been demonstrated to be quite common among American women, although it is rarely recognized or evaluated. Consider a magnesium supplement at about the RDA levels (e.g. 250-500 mg) especially if the woman has any of the following conditions:

- a magnesium-poor diet (not uncommon)
- a need for generous calcium supplements (to maintain a normal Mg:Ca ratio)
- preeclampsia,
- a medication that causes magnesium loss (e.g. thiazide diuretics).
- leg cramps,
- diabetes, or
- PMS when not pregnant

The best dietary sources include: peanuts, bran, wheat germ, nuts, legumes. If a supplement is used, try Mg oxide or chloride instead of sulfate or hydrochloride for better absorption and less of a laxative side-effect. Most prenatal vitamins contain only 10-25% of the RDA for magnesium. Please see "Aunt Cathy's Guide to Nutrition: Magnesium" for more detail.

Some researchers feel that prenatal magnesium adequacy has a higher priority than even iron supplementation because of the over 300 enzyme systems in the body that depend on magnesium to function properly. Several measures of pregnancy outcome such as **higher frequency of spontaneous abortions (miscarriage), fetal growth retardation, maternal hospitalizations, preterm delivery, SIDS and referrals to NICUs** have been found to be associated with poor magnesium status in pregnancy. These issues are related to general nutrition and are quite separate from issues related to the acute therapeutic i.v. magnesium sometimes used in the treatment of pre-eclampsia or premature labor, and even from the magnesium levels as measured in blood tests. The laboratory values often do not reflect cellular levels at all, primarily reflecting the ability of the kidney to hormonally regulate magnesium levels in the blood.

Other studies have shown a benefit of assuring magnesium adequacy (i.e. providing the RDA level of magnesium) in the reduction of **leg cramps** in pregnancy. **Pregnant women with diabetes** need special attention to adequacy of magnesium intake because of the potential for increased losses and the common finding of poor magnesium status among people with diabetes in particular. In addition, inadequacy of magnesium is a risk factor for the **development of gestational diabetes** as well as Type II diabetes. One

contributing factor may be the role magnesium plays in ATP production in the TCA Cycle, and another is very likely its key role in the functioning of insulin receptors.

[Magnesium intake and risk of type 2 diabetes in men and women. Diabetes Care. 2004;27(1):134-40. Role of cellular magnesium in health and human disease. Front Biosci. 2004 1;9:262-76. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. Diabetes Care. 2004;27(1):59-65. Randomised, cross-over, placebo controlled trial of magnesium citrate in the treatment of chronic persistent leg cramps. Med Sci Monit. 2002 May;8(5):CR326-30.Interventions for leg cramps in pregnancy. Cochrane Database Syst Rev. 2002;(1):CD000121; Magnesium in drinking water and the risk of delivering a child of very low birth weight. Magnes Res. 2002;15(3-4):207-13; Magnesium deficit and sudden infant death syndrome (SIDS): SIDS due to magnesium deficiency and SIDS due to various forms of magnesium depletion: possible importance of the chronopathological form. Magnes Res. 2002;15(3-4):269-78. Gestational diabetes and its impact on the neonate" Neonatal Netw. 2001;20(6):17-23. The apparent impact of gestational magnesium (Mg) deficiency on the sudden infant death syndrome (SIDS). Magnes Res. 2001;14(4):291-303. Micronutrients in pregnancy. Br J Nutr. 2001;85 Suppl 2:S193-7. Gestational magnesium deficiency is deleterious to fetal outcome. Biol Neonate. 1999;76(1):26-32. Nutritional and antimicrobial interventions to prevent preterm birth: an overview of randomized controlled trials. Obstet Gynecol Surv. 1998;53(9):575-85.Vitamin and mineral deficiencies which may predispose to glucose intolerance of pregnancy.J Am Coll Nutr. 1996;15(1):14-20. The effect of oral magnesium substitution on pregnancy-induced leg cramps. Am J Obstet Gynecol. 1995;173(1):175-80.]

Calcium and vitamin D intake status. Be sure that AT LEAST the RDA level is usually provided for calcium. Give dietary guidance to correct inadequacy (see "Aunt Cathy's Guide to Nutrition: Calcium Supplements" for more detail.) Supplement with calcium and vitamin D if unable to meet goals with foods (ideally without using bone meal, dolomite, or oyster shell calcium.) **Remember that the RDA for vitamin D (400 iu) appears to be inadequate for people in the northern latitudes or for those whose skin is dark or covered; some researchers are now suggesting that 1000 - 2000 iu may be needed by these people in order to maintain appropriate blood levels.** Interestingly, after years of continually increasing recommendations for calcium intake, it appears that the old RDA level of 800 mg calcium may well be adequate IF the adequacy of vitamin D is assured.

The critical point is that "assuring adequacy" is quite different from "assuring an intake at the RDA level." There is now a large effort on the part of experts in this field around the world to induce an increase in the officially recommended intake levels. Such things are notoriously slow to become official, but the data is very clear that such a change is needed.

The role of vitamin D inadequacy and risk of perinatal problems is now beginning to be explored. Remember that the amount of vitamin D currently included in a standard prenatal vitamin is 400 iu … the same as in a standard vitamin for when one is not pregnant. This is clearly an amount insufficient to meet the needs of both Mom and Baby. **Here are some new reports:**

J Clin Endocrinol Metab. 2007 Sep;92(9):3517-22. **Maternal vitamin d deficiency increases the risk of preeclampsia.** … Results: Adjusted serum 25(OH)D concentrations in early pregnancy were lower in women who subsequently developed preeclampsia compared with controls [geometric mean, 45.4 nmol/liter, and 95% confidence interval (CI), 38.6-53.4 nmol/liter, vs. 53.1 and 47.1-59.9 nmol/liter; $P < 0.01$]. There was a monotonic dose-response relation between serum 25(OH)D concentrations at less than 22 wk and risk of preeclampsia. After confounder adjustment, a 50-nmol/liter decline in 25(OH)D concentration doubled the risk of preeclampsia (adjusted odds ratio, 2.4; 95% CI, 1.1-5.4). Newborns of preeclamptic mothers were twice as likely as control newborns to have 25(OH)D less than 37.5 nmol/liter (adjusted odds ratio, 2.2; 95% CI, 1.2-4.1). Conclusions: Maternal vitamin D deficiency may be an independent risk factor for preeclampsia. Vitamin D supplementation in early pregnancy should be explored for preventing preeclampsia and promoting neonatal well-being.

J Nutr. 2007 Feb;137(2):447-52. **High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates.**

In utero or early-life vitamin D deficiency is associated with skeletal problems, type 1 diabetes, and schizophrenia, but the prevalence of vitamin D deficiency in U.S. pregnant women is unexplored. We sought to assess vitamin D status of pregnant women and their neonates residing in Pittsburgh by race and season. Serum 25-hydroxyvitamin D (25(OH)D) was measured at 4-21 wk gestation and predelivery in 200 white and 200 black pregnant women and in cord blood of their neonates. Over 90% of women used prenatal vitamins. Women and neonates were classified as vitamin D deficient [25(OH)D<37.5 nmol/L], insufficient [25(OH)D 37.5-80 nmol/L], or sufficient [25(OH)D>80 nmol/L]. At delivery, vitamin D deficiency and insufficiency occurred in 29.2% and 54.1% of black women and 45.6% and 46.8% black neonates, respectively. Five percent and 42.1% of white women and 9.7% and 56.4% of white neonates were vitamin D deficient and insufficient, respectively. Results were similar at <22 wk gestation. After adjustment for prepregnancy BMI and periconceptional multivitamin use, black women had a smaller mean increase in maternal 25(OH)D compared with white women from winter to summer (16.0+/-3.3 nmol/L vs. 23.2+/-3.7 nmol/L) and from spring to summer (13.2+/-3.0 nmol/L vs. 27.6+/-4.7 nmol/L) (P<0.01). These results suggest that black and white pregnant women and neonates residing in the northern US are at high risk of vitamin D insufficiency, even when mothers are compliant with prenatal vitamins. Higher-dose supplementation is needed to improve maternal and neonatal vitamin D nutriture.

The vitamin D research has critical implications for pregnancy as well as neonatal health and a wide range of health problems. For example, **recently, vitamin D deficiency was shown to be associated with increased risk of death from ALL causes.**

Arch Intern Med. 2007;167:1730-1737. (Sept. 10) Vitamin D Supplementation and Total Mortality: A Meta-analysis of Randomized Controlled Trials Arch Intern Med. 2007;167:1709-1710. (Sept. 10) Can Vitamin D Reduce Total Mortality?

Recently it has been suggested that the vitamin D deficiency during pregnancy **<u>may</u>** be related to the increasing prevalence of autism. This is certainly just a very interesting hypothesis at this stage, but because assuring adequacy has MANY other benefits during pregnancy and throughout life, it is reasonable to simply assure (not assume) adequacy among pregnant women … and everyone else. There are likely many benefits that have not yet been recognized related to preventing vitamin D deficiency.

Here's an abstract of a paper that describes why this issue worth looking into:

Med Hypotheses. 2008;70(4):750-9. **Autism and Vitamin D.** Any theory of autism's etiology must take into account its strong genetic basis while explaining its striking epidemiology. The apparent increase in the prevalence of autism over the last 20 years corresponds with increasing medical advice to avoid the sun, advice that has probably lowered vitamin D levels and would theoretically greatly lower activated vitamin D (calcitriol) levels in developing brains. Animal data has repeatedly shown that severe vitamin D deficiency during gestation dysregulates dozens of proteins involved in brain development and leads to rat pups with increased brain size and enlarged ventricles, abnormalities similar to those found in autistic children. Children with the Williams Syndrome, who can have greatly elevated calcitriol levels in early infancy, usually have phenotypes that are the opposite of autism. Children with vitamin D deficient rickets have several autistic markers that apparently disappear with high-dose vitamin D treatment. Estrogen and testosterone have very different effects on calcitriol's metabolism, differences that may explain the striking male/female sex ratios in autism. Calcitriol down-regulates production of inflammatory cytokines in the brain, cytokines that have been associated with autism. Consumption of vitamin D containing fish during pregnancy reduces autistic symptoms in offspring. Autism is more common in areas of impaired UVB penetration such as poleward latitudes, urban areas, areas with high air pollution, and areas of high precipitation. Autism is more common in dark-skinned persons and severe maternal vitamin D deficiency is exceptionally common the dark-skinned. Conclusion: simple Gaussian distributions of the enzyme that activates neural calcitriol combined with widespread gestational and/or early childhood vitamin D deficiency may explain both

the genetics and epidemiology of autism. If so, much of the disease is iatrogenic, brought on by medical advice to avoid the sun. Several types of studies could easily test the theory.

Other related recent reports: Prevalence of autism in children born to Somali parents living in Sweden: a brief report. Dev Med Child Neurol. 2008 Aug;50(8):598-601. Increased occurrence of autism among Somali children--does vitamin D deficiency play a role? Tidsskr Nor Laegeforen. 2008 Sep 11;128(17):1986-7. **Stay tuned!**

For more on vitamin D issues please see my on-line handouts
"Vitamin D: It's Not Just for Bones Anymore!" and
"My Current Top Five Easy Ways to Improve Your Family's Nutrition."

Vitamin D is added to milk and for many people it is not well known that it is rarely added to other dairy products. Only in the recent past has vitamin D begun to be added to a few brands of yogurt, cheese, and calcium-fortified orange juice [Fortification of orange juice with vitamin D: a novel approach for enhancing vitamin D nutritional health. Am J Clin Nutr. 2003;77(6):1478-83.] Because the amount of vitamin D added to milk is 100 iu/cup, it is quite unrealistic to expect that most people would obtain that the RDA for vitamin D from food. Also, note that the Food Guide Pyramid suggests 3 servings daily "from the dairy group." Women following that pattern would not be likely to obtain the RDA of 400 iu of vitamin D, much less the higher amounts suggested in the north or among those with dark skin.

Unfortunately, many people (including health professionals) are unaware of these fine points, and for this reason (when it is actually checked) serum vitamin D levels are often found to be inadequate even when calcium intake is appropriate and the RDA for vitamin D is provided. The new version of the Food Guide Pyramid fails to address the problem. It shows a sample2000 kcal diet that provides the (too low) RDA for vitamin D obtained in a week only by being heavily weighted with fortified milk and salmon. There is no caveat included regarding supplementation being important especially for those who do not drink a lot of milk or eat salmon . . . quite a lot of folks. The problem is completely ignored because of the simple fact that the pyramid planners chose not to even list vitamin D at all on the list of essential nutrients! [Vitamin K – another nutrient of increasing concern because of its newly discovered role in bone formation and the poor utilization of the form we have relied on from intestinal bacteria -- is not on the list either.]

Poor vitamin D status is now identified as a risk factor for such diverse conditions as pre-eclampsia, breast cancer, prostate cancer, colon cancer, multiple sclerosis, diabetes (both Type I and Type II), depression, rheumatoid arthritis, osteoarthritis, osteoporosis, impaired fetal development, schizophrenia, myopathy (muscle damage, including heart muscle damage), lupus, increased absorption of lead, schizophrenia and fibromyalgia. This is due to the fact that vitamin D is activated by converting it into a key steroid hormone (the 1,25dihydroxychole-calciferol form) that is structurally very similar to estrogen and testosterone. Inadequacy has great potential for serious health consequences. **So far, over 200 different tissues throughout the body have been determined to have receptors for vitamin D hormone.**

A few of the many references on this topic: Vitamin D deficiency in recently pregnant women. Rev Med Liege. 2008 Feb;63(2):87-91. Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metab. 2007 Sep;92(9):3517-22.Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. Schizophr Res. 2004 1;67(2-3):237-45. Beneficial effects of vitamins D and K on the elastic properties of the vessel wall in postmenopausal women: a follow-up study. Thromb Haemost. 2004;91(2):373-80. Vitamin D deficiency in early life accelerates Type 1 diabetes in non-obese diabetic mice. Diabetologia. 2004 31. Maternal blood lead concentration, diet during pregnancy, and anthropometry predict neonatal blood lead in a socioeconomically disadvantaged population. Environ Health Perspect. 2003;111(2):195-200. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr. 2004;79(3):362-71. Vitamin D status of middle-aged women at 65-71 degrees N in relation to dietary intake and exposure to ultraviolet radiation. Public Health Nutr. 2004;7(2):327-35. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. The prostate 25-hydroxyvitamin D-1{alpha}-hydroxylase is not influenced by parathyroid hormone and calcium: implications for prostate cancer chemoprevention by vitamin D. Carcinogenesis. 2004 Jan 16. Vitamin D intake and incidence of multiple sclerosis. Neurology. 2004;62(1):60-5. The pleiotropic actions of vitamin D. Bioessays. 2004;26(1):21-8. Vitamin D and vitamin D analogs as cancer chemopreventive agents. Nutr Rev. 2003;61(7):227-38. The potential benefits of dietary and/or supplemental calcium and vitamin D. Urol Oncol. 2003;21 (5):384-91. Can vitamin D

supplementation in infancy prevent type 1 diabetes? Nutr Rev. 2002 60(4):118-21. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet. 2001;358(9292):1500-3. Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. Am J Clin Nutr. 2003;78(6):1128-34. Nutritional risk predictors of beta cell autoimmunity and type 1 diabetes at a young age. Am J Clin Nutr. 2003;78(6):1053-67. In utero dietary exposures and risk of islet autoimmunity in children. Diabetes Care. 2003;26(12):3237-42. Nutrition. The vitamin D deficit. Science. 2003 12;302(5652):1886-8. Vitamin D status as a determinant of peak bone mass in young Finnish men. Arthritis Rheum. 2004;50(1):72-7. J Clin Endocrinol Metab. 2004;89(1):76-80. Vitamin D insufficiency in Greenlanders on a westernized fare: ethnic differences in calcitropic hormones between Greenlanders and Danes. Calcif Tissue Int. 2004;74(3):255-63. High prevalence of vitamin D insufficiency in healthy elderly people living at home in Argentina. Eur J Clin Nutr. 2004;58(2):337-42. Vitamin D and prostate cancer prevention and treatment. Trends Endocrinol Metab. 2003;14(9):423-30. Vitamin D: its role and uses in immunology. FASEB J. 2001;15(14):2579-85.. Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia. J Rheumatol. 2001;28(11):2535-9. Preeclampsia is associated with low circulating levels of insulin-like growth factor I and 1,25-dihydroxyvitamin D in maternal and umbilical cord compartments. J Clin Endocrinol Metab. 2000;85(5):1828-33.]

Because of the explosion of information on the critical functions of vitamin D hormone, adequacy is an issue that must be looked at carefully both for a healthy pregnancy and for the long-term health of the mother and child. This is also behind the 2008 recommendation of the American Academy of Pediatrics that all infants and children should receive at least 400 iu vitamin D daily starting soon after birth, and that breast-fed infants in particular are at risk of inadequacy without supplementation. This is in part a reflection of the newly recognized reality that many babies are actually born vitamin D deficient because of inadeqacy during pregnancy. **Whether or not the disease relationships described above are confirmed by subsequent research, it does illustrate the potentially broad implications of inadequacy (or excessive intake) of this important hormone, and suggests that it would be prudent to assess maternal intake carefully.** [Prevention of rickets and vitamin D deficiency in infants, children and adlescents. Pediatrics October 13, 2008. 2008;122:1142-1152. The Canadian recommendation is 400 iu for infants. Vitamin D-deficiency rickets among children in Canada. CMAJ. 2007 Jul 17;177(2):161-6. Bones and beyond: an update on the role of vitamin D in child and adolescent health in Canada. Appl Physiol Nutr Metab. 2007 Aug;32(4):770-7.]

A newly recognized problem with perinatal iodine deficiency in the US (and elsewhere) with serious reproductive consequences:

Iodine deficiency is a nutrition problem with well-known potential to harm fetal and infant neurologic development. Since salt was iodized in the US it has been assumed that this problem was eradicated and it has essentially gone off our radar screen. Emerging research (beginning in 2005) is demonstrating that this problem continues to be a very serious threat. The issue is new enough and important enough that I have put together a separate paper with current recommendations and descriptions of some key research.about this critical topic.

Please see "Aunt Cathy's Guide to Nutrition: New Attention to an Old Problem: Iodine Deficiency in Pregnancy and Lactation. 2009"

5. Evaluate the ratio of a woman's intake of omega 6: omega 3 fatty acids, with a ratio of 4:1 as a goal, and consider providing a generous amount of the omega-3 fatty acids as pre-formed EPA and DHA.

Most Americans consume these fats in a 10:1 ratio. A considerable body of research suggests that as a start there are major health advantages associated with consuming these fats at a 4:1 ratio. The ratio appears to be very important in areas such as risk of heart disease, cancer, HIV, depression, epilepsy, and degenerative eye diseases. **In each case, the direction of change that shows benefit is <u>increasing the proportion of dietary fats that are rich in oils of the omega-3 family</u> in relation to the intake of fats from the omega-6 family.** In addition to the <u>ratio</u> of these two families of fat, consumption of some of them as <u>preformed</u> 20-22 carbon long chain fatty acids appears to have special benefit in general and in pregnancy in particular. The long chain omega-3 fats **(EPA = eicosapentaenoic acid; DHA = docosahexa-enoic acid)** are found in fish and fish oil supplements.

Various advisories regarding hazardous levels of mercury or other toxins in certain fish have made it more difficult to recommend fish consumption in general, especially during pregnancy. However, a recent report on EPA-DHA (NOT on cod-liver oil, which is different in a number of ways) supplements available in the U.S. appeared in Consumer Reports (2003.Jul;68(7): 30-2.) They evaluated the safety of products on the market (e.g. related to mercury concerns, etc.,) the actual content of each product, and the price. The good news is that they found all to be safe, and all products contained what the label said was in there. However **the price** per 300 mg of supplemental fish oil ranged from 6 to 60 cents each!

[FDA warns on mercury in tuna. JAMA. 2004 Jan 14;291(2):171. Toxicology. Salmon survey stokes debate about farmed fish. Science. 2004 Jan 9;303(5655):154-5. Weighing health benefit and health risk information when consuming sport-caught fish. Risk Anal. 2003 Dec;23(6):1185-97. Decline in fish consumption among pregnant women after a national mercury advisory. Obstet Gynecol. 2003 Aug;102(2):346-51.]

Oils rich in omega-3 fatty acids appear to have important implications in pregnancy and infant nutrition in particular. DHA (a 22 carbon omega-3 fatty acid) is a **major fat of the brain**, and the research is growing that suggests that providing some pre-formed DHA is often advantageous. In a study over infants in various parts of the world, values of arachidonic acid and docosahexaenoic acid showed two-fold variability in cord blood of full term infants. The highest values of docosahexaenoic acid were observed in countries with apparently higher consumption of dietary fat from sea fish. DHA is also known to be essential for **retinal development** in infants.

Maternal essential fatty acid status declines during pregnancy, and as a result, neonatal concentrations of docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (AA, 20:4n-6) may not be optimal. Importantly, maternal supplementation with the essential fatty acids linoleic and alpha linolenic acid did not promote neonatal DHA+AA status. Maternal DHA supplementation significantly increases maternal DHA status and limits the last trimester decline in maternal status, aiding preferential transfer of DHA from mother to fetus. Long-chain PUFA (EPA, DHA, ARA) are therefore **conditionally essential** substrates during early life that are related to the quality of growth and development. The amount of DHA in human milk varies widely and is positively correlated with visual and language development in breast-fed infants. A dietary supply during pregnancy, lactation, and early childhood that avoids the occurrence of LC-PUFA depletion is desirable, as was recently recommended by an expert consensus workshop of the Child Health Foundation. **Fetal growth** requires n-3 docosahexaenoic acid (DHA), which is derived from the n-3 fatty acids in the maternal diet. Intrauterine growth restriction is associated with changes in polyunsaturated fatty acid fetal-maternal relationships. DHA can be formed in the liver from alpha linolenic acid, but it is unclear if the rate of DHA synthesis in humans is sufficient to support optimal brain and retinal development.

Differences in DHA status between women both in the non-pregnant state and in pregnancy may reflect variations in metabolic capacity for DHA synthesis. One group of researchers noted that available estimates suggest that 67 mg DHA/d is accumulated by the fetus during the third trimester of gestation. Human milk concentrations of DHA have been noted to decrease in recent years and a low intake of DHA among some pregnant women has been observed. The balance between the n-6 and n-3 PUFA in the maternal diet rather than amount of n-6 or n-3 PUFA per se could be important for adipose tissue growth and for maintaining adequate serum leptin levels in the offspring. In **multiple pregnancies**, fetal demand for '-docosahexaenoic acid may not be entirely satisfied. It may be that a greater maternal intake of docosahexaenoic acid should be encouraged for optimal tissue perfusion. Omega-3 fats are also associated with **decreased risk of premature delivery**. As premature delivery is the most common cause of low infant birth weight, and infant morbidity and mortality, this is a very important observation.

There may be a role for omega-3 fatty acids in **allergy** development, and possibly beneficial effects of n -3 PUFAs in **diabetic pregnancy** and in the prevention and treatment of long-term metabolic abnormalities associated with **macrosomia**. It has also been reported that maternal alcohol intake can alter fatty acid transport by the human placenta, decreasing fetal availability of polyunsaturated fats in general and of DHA

especially. It may be that this decreased DHA transport is one of the (many) mechanisms of **FAS (Fetal Alcohol Syndrome.)**

There is not an official pregnancy-specific recommendation as yet, but the following recommendations from the American Heart Association provide an idea of the range suggested in yet another health condition for which these issues are being found to be important:

American Heart Association Recommendations for Omega-3 Fat Intake (2002)

People without documented heart disease	**Eat a variety of (preferable oily) fish at least twice a week. Include oils and foods rich in alpha-linolenic acid (flaxseed, canola and soybean oils; flaxseeds; and walnuts.**
People with documented heart disease	**Eat about a gram of EPA+DHA daily. This can come from oily fish or from fish-oil supplements.***
People with high triglycerides	**Take 2-4 grams of EPA+DHA provided as fish oil supplements.***

*As always, you should discuss this with your physician, since in certain situations (like people on certain medications) there may be reasons to do things differently.

Rev Obstet Gynecol. 2008 Fall;1(4):162-9. **Omega–3 Fatty Acid supplementation during pregnancy.**

Omega-3 fatty acids are essential and can only be obtained from the diet. The requirements during pregnancy have not been established, but likely exceed that of a nonpregnant state. Omega-3 fatty acids are critical for fetal neurodevelopment and may be important for the timing of gestation and birth weight as well. Most pregnant women likely do not get enough omega-3 fatty acids because the major dietary source, seafood, is restricted to 2 servings a week. For pregnant women to obtain adequate omega-3 fatty acids, a variety of sources should be consumed: vegetable oils, 2 low-mercury fish servings a week, and supplements (fish oil or algae-based docosahexaenoic acid).

Some references on this topic: [Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. Acta Paediatr. 2009 Jun 1.Systematic review of fatty acid composition of plasma phospholipids of venous cord blood in full-term infants. Eur J Nutr. 2002;41(3):125-31. Effect of alpha-linolenic acid supplementation during pregnancy on maternal and neonatal polyun-saturated fatty acid status and pregnancy outcome. Am J Clin Nutr. 2004;79(2):251-60. Maternal docosahexaenoic acid supplementation and fetal accretion. Br J Nutr. 2003;90(1):135-45. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. Pediatrics 2003; 111(1):e39-44; Maternal docosahexaenoic acid supplementation during pregnancy and visual evoked potential development in term infants: a double blind, prospective, randomised trial. Arch Dis Child Fetal Neonatal Ed.2003;88(5):F383-F390. Long chain polyunsaturated fatty acids improve cognitive development. Perinatal biochemistry and physiology of long-chain polyunsaturated fatty acids. J Pediatr. 2003;143(4 Suppl) :S1-8. J Fam Health Care. 2002;12(6 Suppl):5. Higher maternal plasma docosahexaenoic acid during pregnancy is associated with more mature neonatal sleep-state patterning. Am J Clin Nutr. 2002;76(3):608-13. Neuroprotective effect of developmental docosahexaenoic acid supplement against excitotoxic brain damage in infant rats. Neuroscience. 2003;119(4):999-1012. Determinants of polychlorin-ated biphenyls and methylmercury exposure in Inuit women of childbearing age. Environ Health Perspect. 2001;109(9):957-63. Long-chain polyunsaturated fatty acid requirements during pregnancy and lactation. Am J Clin Nutr. 2000;71(1 Suppl):307S-11S. Perinatal biochemistry and physiology of long-chain polyunsaturated fatty acids. J Pediatr. 2003;143(4 Suppl):S1-8. Synaptic lipid signaling: significance of polyunsaturated fatty acids and platelet-activating factor. J Lipid Res. 2003;44(12):2221-33. Effect of dietary n-3 fatty acids on the composition of long- and very-long-chain polyenoic fatty acid in rat retina. J Nutr Sci Vitaminol (Tokyo). 2003;49(3): 210-3. Protective effect of docosahexaenoic acid on oxidative stress-induced apoptosis of retina photoreceptors. Invest Ophthalmol Vis Sci. 2003;44(5):2252-9. Visual acuity and retinal function in infant monkeys fed long-chain PUFA. Lipids. 2002;37(9):839-48. Scotopic electroretinogram in term infants born of mothers supplemented with docosahexaenoic acid during pregnancy. Invest Ophthalmol Vis Sci.2003;44(8):3685-9. Docosahexaenoic and arachidonic acid influence on preterm baboon retinal composition and function. Invest Ophthalmol Vis Sci. 2003;44(10):4559-66. Retinal sensitivity loss in third-generation n-3 PUFA-deficient rats. Lipids. 2002;37(8):759-65. Perinatal biochemistry and physiology of long-chain polyunsaturated fatty acids. J Pediatr. 2003; 143(4 Suppl):S1-8.] Perinatal supply and metabolism of long-chain polyunsaturated fatty acids: importance for the early development of the nervous system. Ann N Y Acad Sci. 2002;967:299-310. Pediatr Res. 2002;52(5):750-5. Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. Br J Nutr. 2002 88(4):411-20. Supplementing lactating women with flaxseed oil does not increase docosahexaenoic acid in their milk. Am J Clin Nutr. 2003;77(1):226-33. Intakes of essential n-6 and n-3 polyunsaturated fatty acids among pregnant Canadian women. Am J Clin Nutr. 2003;77(2):473-8. Leptin levels in rat offspring are modified by the ratio of linoleic to alpha-linolenic acid in the maternal diet. J Lipid Res. 2002 Oct;43(10):1743-9. Maternal and umbilical cord erythrocyte omega-3 and omega-6 fatty acids and

haemorheology in singleton and twin pregnancies. Arch Dis Child Fetal Neonatal Ed. 2003;88(2):F134-8. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. Obstet Gynecol. 2003;101(3):469-79. J Nutr.2003133(5 Suppl 2): 1606S-1625S. Exp Biol Med (Maywood).2001;(226(6):498-506; BMJ.2002;324(7335): 447; Obstet Gynecol Serv.2001;56(5 Suppl 1):S1-S13; Pediatrics. 2001;108(2):359-71; Obstet Gynecol Surv. 2001;56(5 Suppl 1):S1-13; Pediatr Clin North Am.2001;48(1):173-88; BJOG.2000;107 (3):382-95.) [Maternal and umbilical cord erythrocyte omega-3 and omega-6 fatty acids and haemorheology in singleton and twin pregnancies. Arch Dis Child Fetal Neonatal Ed. 2003;88(2):F134-8. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. J Allergy Clin Immunol. 2003;112(6):1178-84. Implication of lipids in macrosomia of diabetic pregnancy: can n-3 polyunsaturated fatty acids exert beneficial effects? Clin Sci (Lond). 2003;105(5):519-29.] Fish oil supplementation of rats during pregnancy reduces adult disease risks in their offspring. J Nutr. 2003;133(10):3170-4. Decline in fish consumption among pregnant women after a national mercury advisory. Obstet Gynecol. 2003;102(2):346-51 Maternal docosahexaenoic acid supplementation during pregnancy and visual evoked potential development in term infants: a double blind, prospective, randomised trial. Arch Dis Child Fetal Neonatal Ed. 2003;88(5):F383-90. Effects of n-3 polyunsaturated fatty acid supplementation in pregnancy on maternal and fetal erythrocyte fatty acid composition. Eur J Clin Nutr. 2004;58(3):429-37. The effect of maternal smoking and ethanol on fatty acid transport by the human placenta. Br J Nutr. 2002;87(3):247-52. The role of docosahexaenoic acid in brain development and fetal alcohol syndrome. Biochem Soc Trans. 1998;26(2):246-52. Dietary fatty acids and alcohol: effects on cellular membranes. Alcohol Alcohol. 1993;28(5):607-8. Effects of prenatal ethanol and long-chain n-3 fatty acid supplementation on development in mice. 1. Body and brain growth, sensorimotor development, and water T-maze reversal learning. Alcohol Clin Exp Res. 1990;14(3):405-12. Effects of prenatal ethanol and long-chain n-3 fatty acid supplemen-tation on development in mice. 2. Fatty acid composition of brain membrane phospholipids. Alcohol Clin Exp Res. 1990;14(3):413-20.

Because the omega-3 PUFAs contain a greater number of double bonds, a **generous antioxidant intake** is advisable. In addition to the well-known nutrient antioxidants (vitamins C and E, selenium, etc.) the pigments of brightly colored fruits and vegetables are now known to be especially potent antioxidants. These include lycopene in tomatoes, lutein in leafy greens, anthocyanins in beets and raspberries, beta-carotene in orange-colored foods, allicin and SAC in garlic, and many others. **Because conditions like diabetes (or other conditions involving altered metabolism, auto-immunity or inflammation) result in a greatly increased production of free radicals, generous antioxidant intake is also recommended in these situations. It appears to be protective at least against the <u>increased</u> risk of fetal damage due to the free radical component.** There are, of course, many additional health benefits for everyone associated with a generous intake of brightly colored fruits and vegetables as well. See "Aunt Cathy's Guide: Nutrition in Eye Health" for some specifics about antioxidant sources and amounts.

Oxidative and antioxidative status in pregnant women with either gestational or type 1 diabetes. Clin Biochem. 2004;37(4):293-8. Changes in plasma lipids and markers of oxidative stress in normal pregnancy and pregnancies complicated by diabetes. Clin Sci (Lond). 2004;106(1):93-8. Glutathione metabolism and oxidative stress in neonatal rat tissues from streptozotocin-induced diabetic mothers. Diabetes Metab Res Rev. 2004;20(1):72-8. Ascorbic acid, glycation, glycohemoglobin and aging. Med Hypotheses. 2004;62(2):275-9. Antioxidant, antidiabetic, antihyperlipidemic, reproduc-tion stimulatory properties and safety of essential oil of Satureja Khuzestanica in rat in vivo: a oxicopharmacological study. Med Sci Monit. 2003;9 (9):BR331-5Reduced SOD activity and increased neural tube defects in embryos of the sensitive but not of the resistant Cohen diabetic rats cultured under diabetic conditions. Birth Defects Res Part A Clin Mol Teratol. 2003;67(6):429-37.Lipid peroxidation and vitamin E status in gestational diabetes mellitus. J Obstet Gynaecol Res. 2003;29(5):300-4. Circulating biomarkers of oxidative stress in complicated pregnancies. Arch Gynecol Obstet. 2003;267(4):189-95. Maternal diabetes in vivo and high glucose in vitro diminish GAPDH activity in rat embryos. Diabetes. 2003;52(5): 1222-8. The role of reactive oxygen species in diabetes-induced anomalies in embryos of Cohen diabetic rats. Int J Exp Diabetes Res. 2002;3(4):247-55. gamma-Linoleic acid and ascorbic acid ameliorate the effects of experimental diabetes on electrolyte and bone homeostasis in pregnant rats. J Endocrinol. 2002;173(2):273-84.Effects of ergothioneine on diabetic embryopathy in pregnant rats. Food Chem Toxicol. 2002;40(12):1751-5. Com-bined treatment with vitamin E and vitamin C decreases oxidative stress and improves fetal outcome in experimental diabetic pregnancy. Pediatr Res. 2001;49(6):755-62.Vitamins C and E improve rat embryonic antioxidant defense mechanism in diabetic culture medium. Teratology. 2001;64(1):33-44. Lipid peroxidation and scavenging enzyme activity in streptozotocin-induced diabetes. Acta Diabetol. 2000;37(4):179-83. Antioxidant therapy and streptozotocin-induced diabetes in pregnant rats. Acta Diabetol. 1999;36(3):113-7. Lipoic acid prevention of neural tube defects in offspring of rats with streptozocin-induced diabetes. Am J Obstet Gynecol. 1999;180(1 Pt 1):188-93.Role of reactive oxygen species (ROS) in the diabetes-induced anomalies in rat embryos in vitro: reduction in antioxidant enzymes and low-molecular-weight antioxidants (LMWA) may be the causative factor for increased anomalies. Teratology. 1999;60(6):376-86. Teratogenic effects of diabetes mellitus in the rat. Prevention by vitamin E. Diabet-ologia. 1996;39(9):1041-6.Dietary vitamin E prophylaxis and diabetic embryopathy: morphologic and biochemical analysis. Am J Obstet Gynecol. 1996;175(4 Pt 1):793-9. Maternal antioxidant treatments prevent diabetes-induced alterations of mitochondrial morphology in rat embryos. Anat Rec. 1998;251(3):303-15The effect of vitamin E on antioxidant tissue activity in pregnant rats with streptozocin-induced diabetes Przegl Lek. 1998;55(6): 320-4. Prevention of diabetic embryopathy in offspring of diabetic rats with use of a cocktail of deficient substrates and an antioxidant. Am J Obstet Gynecol. 1997;176(4):790-7Vitamin E decreases the occurrence of malformations in the offspring of diabetic rats. Diabetes. 1997;46(6):1054-61. Congenital malformations in experimental diabetic pregnancy: aetiology and antioxidative treatment. Minireview based on a doctoral thesis. Ups J Med Sci. 1997;102(2):61-98.Antioxidant status and lipid peroxidation in diabetic pregnancy. Br J Nutr. 1997;78(4):523-32.Vitamin C supplement-ation of the maternal diet reduces the rate of malformation in the offspring of diabetic rats. Diabetologia. 1997;40(12):1416-24.6):320-4.

6. If blood pressure begins to go up in the second half of pregnancy: Do not automatically decrease sodium intake, and never recommend a diet restricted to 2 g sodium/day or less during pregnancy unless special conditions like renal disease or congestive heart failure are involved and the physician has a special reason for needing such a low level. In women with pre-eclampsia, a severe sodium restriction can actually

precipitate a seizure. Puffy feet and ankles in pregnancy are not caused by diet. With physician approval, increase calcium to 2000 mg supplement (in addition to diet) and give magnesium at the RDA Ca:Mg ratio (e.g. about 400 mg, since the RDA ratio is 300 mg Mg to 1200 mg Ca, the ratio with supplemental calcium described above = 400 Mg : 2000 Ca.) High dose calcium in the absence of adequate magnesium may increase risk of thrombotic events. In addition, remember to assure adequacy of vitamin D in order for the calcium to be absorbed appropriately. This plan may or may not be helpful in the prevention or control of PIH based on conflicting results from studies, but some individuals may respond favorably, and the intervention appears to be benign. And since prevention is always preferable to treatment, there is evidence [described earlier] that nutrition issues in the periconceptional period may also play a role in risk of development of pre-eclampsia later in pregnancy.

7. For nausea/hyperemesis problems, have M. Erick's video "Morning Sickness: All Day and All Night" (Lemon-Aid Films), and book "No More Morning Sickness" available for clients. In addition, the following ideas may be helpful (many of which were initially published by Ms. Erick.)

- Continued use of a multivitamin (they actually decrease nausea), and as described earlier, since the prenatal type is not necessary in early pregnancy and they can be harder to tolerate, a standard multi-vitamin with minerals or a children's chewable product taken with food is the best choice. If she is "gun shy" about iron or vitamins in general because of poor tolerance of her prenatal vitamin, the psychological advantage of a children's vitamin can help ("It's so gentle it's for little children!") as can the use of a "silver" type product with little or no iron. In general, remember that the woman having problems with eating is precisely the woman who is most in need of supplemental vitamins and minerals, so it is all the more important to help her find one she can tolerate. Do not advise her to "just skip it until you feel better."

- Ms Erick found that sniffing lemons and eating citrus foods (grapefruit, lemonade, etc.) often have a marked diminishing effect on the feeling of nausea, especially among women whose nausea is triggered by increased sensitivity to odors. Avoiding strong smells is helpful, so eating outdoors in nice weather is pleasant, as is having someone else do the cooking while she goes for a walk. Cold foods usually are less aromatic than hot foods. Even cooking smells that are normally pleasant (coffee brewing, sauces simmering, etc.) can induce nausea in many pregnant women. And, of course, things that are unpleasant under any circumstances can be even worse (garbage, the cat box, dirty diapers, etc.) so these are excellent tasks for significant others who want to help. ☺)

- Do not restrict the diet or advocate "clear liquids" as a treatment. For many women, liquids like water, juice and pop are the most difficult to keep down. However, many can tolerate lemonade, and for some ginger ale or ginger tea are helpful. Ginger appears to be safe in the amounts tested in hyperemesis patients, and studies have supported that it apparently helps in some cases. In a survey of obstetricians, 51.8% reported using ginger in this context. "The most commonly cited herbs for morning sickness were ginger, chamomile, peppermint and raspberry leaf (55, 37, 44 and 63% cited respectively). There was no consensus in the popular literature about whether or not each of these herbs was safe for use in pregnancy. Seven sources (6%) cited chamomile and peppermint as unsafe, while 16 (12%) cited the use of ginger and 11 (15%) the use of raspberry leaf as unsafe during pregnancy." Another survey of 300 non-medical sources studied 75 cited the use of herbs in pregnancy.

[A randomized comparison of ginger and vitamin B6 in the treatment of nausea and vomiting of pregnancy. J Med Assoc Thai. 2003 Sep;86(9): 846-53. A survey on the management of nausea and vomiting in pregnancy by obstetrician/gynecologists. Prim. Care Update Ob Gyns. 2001 Mar; 8(2):69-72.] [What do we know about herbal morning sickness treatments? A literature survey. Midwifery. 2000 Sep;16(3):224-8.]

- Vitamin B6 (pyridoxine) and antihistamines have been shown to be helpful in some women, and the research available suggests that these interventions are safe. However, the amount of vitamin B6 in multi-vitamins is only the RDA level (2 – 2.5 mg) and not the therapeutic level. Oral therapeutic levels used range from 25-100 mg/day, and sometimes pyridoxine is administered as an injection. In any case, these interventions during pregnancy require the approval of the physician or other primary care professional. However, this level of intake IS available over the counter in the form of "B-100 Complex" supplements.

  [Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2003;(4): CD000145. Nausea and vomiting of pregnancy. Am Fam Physician. 2003 Jul 1;68(1):121-8. Comparison of three outpatient regimens in the management of nausea and vomiting in pregnancy. J Perinatol. 2003 Oct;23(7):531-5. Bendectin and birth defects. II: Ecological analyses. Birth Defects Res Part A Clin Mol Teratol. 2003 Feb;67(2):88-97. Overview of nausea and vomiting of pregnancy with an emphasis on vitamins and ginger. Am J Obstet Gynecol. 2002 May;186(5 Suppl Understanding):S253-5. The use of CAM by women suffering from nausea and vomiting during pregnancy. BMC Complement Altern Med. 2002 May 17;2(1):5. Health risks over the Internet: advice offered by "medical herbalists" to a pregnant woman. Wien Med Wochenschr. 2002;152(7-8):190-2. A survey on the management of nausea and vomiting in pregnancy by obstetrician/gynecologists. Prim. Care Update Ob Gyns. 2001 Mar;8(2):69-72.]

- Do not presume that her nausea has a psychological etiology. A few years back it was common in the medical literature to find that the woman was blamed for the puzzle of hyperemesis gravidarum. ("She is expressing her subconscious ambivalence about the pregnancy", etc.) Old textbooks may still refer to this sort of theory. The evidence that it was "all in her head" was sometimes based on her rapid improvement when hospitalized and hooked up to i.v. glucose, which was described as a placebo. ("She responded to simply getting attention.") However, in this situation, the i.v. glucose was definitely not a placebo, but an interruption of the fasting/nausea pattern. The glucose arriving in the bloodstream shuts off ketone production, which may be one of the triggers of nausea in pregnancy. Note that once the glucose has decreased the nausea, she needs to be told to begin "grazing" regularly on carbohydrate (and to eat other foods, too, of course, as able) and to avoid fasting.

- "Grazing," (eating a little bit frequently and especially keeping the carbohydrate coming in) is an important concept. It encourages small servings, which may be helpful, but it is the "frequent feedings" aspect that seems to be the most beneficial. Old advice like "eat 6 small dry meals with 6 servings of liquids half an hour after each meal" has been standardly given out and it can be helpful. However, it appears that its usefulness is related less to the specific juggling of liquids and solids than it is to the fact that she is taking in small meals of carbohydrate 12 times a day! Some women even set an alarm to go off every two hours to make sure that carbohydrate is provided regularly because they feel nauseated once they fast longer than that. The old advice about eating crackers or dry toast half an hour before getting out of bed is probably helpful in the sense that it sends some carbohydrate down. Interestingly, there are no studies showing a special benefit of dry toast or crackers at the bedside instead of any other carbohydrate-containing food, but this particular advice is regularly included in materials given to pregnant women. Instead of just the old "cracker" advice, give her a larger "menu" of carbohydrate-containing food suggestions. This is especially important if she is somewhat dehydrated; soda crackers can be unpleasant when the mouth feels dry. In this regard, even the "avoid high fat food" advice often given may have been useful (when it was helpful) primarily because if she ate isocalorically she would necessarily increase carbohydrate intake by displacing fat. Plus, the presence of fat in food decreases the speed of stomach emptying, thus delaying the absorption of carbohydrate and the shut-off of ketone production.

- As a rule, do not tell her to automatically avoid particular foods, because (for example) even though some women find greasy foods less palatable, others have good luck with them. In fact, one of the most well tolerated foods is potato chips. In some cases reported, consuming a small bag of potato chips about half an hour before supper significantly improved the women's ability to eat the meal. Interestingly, potato chips are less "empty calories" than one might expect . . . they provide carbohydrate ("Yes!!"), sodium,

potassium, a little vitamin C, and energy to a woman desperately in need of all. At the very least, the chips are better than not keeping anything down! Wash them down a little later with some lemonade!

- Instead of telling her to avoid large numbers or types of foods, find out what foods she thinks she can eat, and then find ways to make them available to her. In addition to chips, many women report tolerating spaghetti, hard cooked eggs, chocolate milk, etc. At this stage the foods do not have to be particularly "nutritious" . . . breaking the fasting/nausea cycle is the goal. Good nutrition is the focus a bit later.

- Be aware of the potential serious danger from micronutrient deficiency (e.g. Wernicke's encephalopathy and other overt deficiency diseases have been documented), especially when primarily glucose or other carbohydrates are provided via i.v. or "clear liquid' diet without concomitant vitamin and mineral supplementation in a woman who has been unable to eat well. At least 12 cases of this unfortunate outcome have been reported in the literature, and all would have been prevented simply by the regular provision of a multivitamin (oral or added to the i.v.)

  [Memory loss and ataxia after hyperemesis gravidarum: a case of Wernicke-Korsakoff syndrome. Eur J Obstet Gynecol Reprod Biol. 2002 Apr 10;102(1):100-1. Hyperemesis gravidarum complicated by Wernicke's encephalopathy. Obstet Gynecol. 2002 May;99(5 Pt 2):875-7.]

- For heartburn, chewing gum has been shown to be helpful because it increases saliva production and helps neutralize stomach acid. Sugar-free gum is the choice from a dental perspective, but if a sugar-containing gum is found to help a woman suffering from nausea and vomiting to control it by "grazing" on carbohydrates, that would likely be the preferred product. The "acid bath" from regular vomiting would certainly be at least as detrimental to the tooth enamel as gum. There are also some new "antacid" gums available that utilize calcium carbonate. An expert panel in the Netherlands recommended calcium/ magnesium-based antacids as the treatment of choice for pregnant women because of their good safety profile.

  [Contemporary understanding and management of reflux and constipation in the general population and pregnancy: a consensus meeting. Aliment Pharmacol Ther. 2003 Aug 1;18(3):291-301 Clinical effectiveness of a new antacid chewing gum on heartburn and oesophageal pH control. Aliment Pharmacol Ther. 2002 Dec;16(12):2029-35. Effects of gum chewing on pharyngeal and esophageal pH. Ann Otol Rhinol Laryngol. 2001 Dec;110(12):1117-9. Walking and chewing reduce postprandial acid reflux. Aliment Pharmacol Ther. 2001 Feb;15(2):151-5.]

8. Advise women to avoid:

- **Caffeine:** Caffeine may increase risk of miscarriage and may affect fetal growth, although data are conflicting. There are many phytochemical substances in coffee besides caffeine, so there is quite a lot of sorting out to do. To the surprise of most people, several recent studies reported some benefits of both substances in relation to health conditions like diabetes and parkinsonism. In pregnancy, the prudent course is (and has been for some time) to "limit" intake of both substances. One recent publication had this to say: "Currently available evidence suggests that it may be prudent for pregnant women to limit coffee consumption to 3 cups/d providing no more than 300 mg/d of caffeine to exclude any increased probability of spontaneous abortion or impaired fetal growth." [Coffee and health: a review of recent human research. Crit Rev Food Sci Nutr. 2006;46(2):101-23. Association of maternal caffeine consumption with decrements in fetal growth. Am J Epidemiol. 2003 Mar 1;157(5):456-66. Maternal serum caffeine metabolites and small-for-gestational age birth. Am J Epidemiol. 2002 Jan 1;155(1):32-7.]

- **Alcohol: Alcohol is the number one preventable cause of mental retardation in America.** Note that the nutritional status of the mother is a critical variable in the degree to which exposure to potential teratogens damages the fetus. **For example, exposure to alcohol is significantly more damaging to the fetus when the mother also has poor zinc status (a common finding among heavy users of alcohol).** It also appears that providing a generous **antioxidant** intake may decrease some of the toxic effects. (References cited earlier.) Avoiding alcohol is the best advice, of course, but there is good that can be done

with nutrition interventions, even among those who are unable to stop drinking. Many "problem drinkers" WILL take nutritional supplements especially when the benefits to the fetus are explained. As a rule, regular heavy drinkers are frequently found to have poor nutrition status with extremely detrimental results, in particular in relation to zinc, folic acid, and thiamin. **Folic acid absorption is specifically inhibited by chronic alcohol use.** Many other nutrients are often inadequate as well, but they are less commonly recognized.

To optimize the care of this woman, don't WONDER if she might be poorly nourished . . . ASSUME that she is poorly nourished and ACT on it. If you are wrong and her nutritional status is actually excellent, no harm will be done by providing levels of nutrients at the levels usually regarded as appropriate for a healthy pregnant woman (i.e. RDA, RDI, etc.). But if she IS poorly nourished, there is the potential to do great good by implementing relatively small, simple, safe and inexpensive interventions. (For more information, see "Aunt Cathy's Guide to Nutrition: Fetal Alcohol Syndrome")

- **Smoking:** Smoking exposes the fetus to carbon monoxide, nicotine, lead, cadmium, and to transport of carcinogens. It reduces transport of nutrition and oxygen to the fetus, increasing risk of being born "small-for Gestational age" (SGA.) A recent study "found that moderate smoking mothers deliver neonates with decreased birth weight and highly correlated to placental cadmium concentration. Decreased metal nutrient/pollutant ratios, a condition here found in smokers, may indicate a placental dysfunction, contributing to impair birth weight." [Metals content in placentas from moderate cigarette consumers: correlation with newborn birth weight. Biometals. 2005 Jun;18(3):233-41.]

  Cigarette smoking during pregnancy generates free radicals (as it always does regardless of pregnancy status) and it has been implicated in oxidative cellular damage in fetuses. Two recent studies measured vitamin E in maternal and cord blood of smokers and nonsmokers (as a marker of antioxidants available to quench free radicals.) The women who smoked during pregnancy and the cord blood of their newborns had a lower concentration of vitamin E in plasma and in erythrocytes as compared with group of non-smoking women. The same researchers also measured malondialdehyde levels (a marker of lipid peroxidation.) They found that malondialdehyde was higher in plasma and in erythrocytes of mothers and babies in the "smoking" dyad, and concluded that smoking during pregnancy promotes free radical damage in growing fetus and newborns and stimulates metabolic disorders dependent on oxidative stress. This is likely an indication that antioxidant intake from vitamins, minerals and phytochemicals needs special attention in these women. [The effect of tobacco smoking during pregnancy on concentration of malondialdehyde in blood of mothers and in umbilical cord blood Ginekol Pol. 2005 Dec;76(12):960-5 The effect of tobacco smoking during pregnancy on concentration of vitamin E in blood of mothers and their newborns in umbilical cord blood Ginekol Pol. 2006 Apr;77(4):263-8.]

- **Unsafe Food and Water:** Undercooked meat, unpasteurized milk products, unpasteurized apple cider, raw oysters, swordfish, etc., are potential sources of listeria, E. Coli O:157, toxoplasma gondii, mercury and others organisms and substances that are especially dangerous in pregnancy. Avoid frequent consumption of liver during pregnancy due to the finding that the retinol content is much higher than was previously believed. Have well water checked for lead and other contaminants, along with the presence of submersible pumps or faucets with bronze fittings that can leach lead into the water. The EPA Safe Drinking Water Hotline has specific information about these issues: 1-800-426-4791. Poor nutrition also plays a part because it compromises the ability of the immune system to protect against infection, it impairs detoxification of harmful agents (e.g. by affecting the functioning of the cytochrome P450 system), and it also leads to greater absorption of certain toxic substances.

9. **Encourage weight gains within the currently accepted ranges** (25-35 lbs for the "average" woman, etc.) Weight gain in the first trimester has only recently been found to be very contributory to birth weight, so helping women avoid significant weight loss due to nausea may be more important than was realized earlier. This has huge public health implications, because low birth weight, specifically "small for

gestational age" (SGA), appears to be a significant predictor of risk of several chronic diseases of adulthood (diabetes, heart disease, etc.). This relationship is referred to as the "Fetal Origins Hypothesis" or the "Barker Hypothesis."

This topic has been the subject of a huge amount of research in the past few years, and just a small amount some is noted below. **Basically, it is quite clear that prenatal nutrition and other factors that affect the growth and metabolism of the fetus can contribute to a number of very significant health problems in later life.** Some of the most studied relationships have been related to SIZE of babies as a predictor of later health. At present the central research focus is teasing out exactly what factor is doing what to whom and when. This is an onerous task, however, as the factors do not operate in isolation.

It is clear that being either a large- for-gestational age infant or a small-for-gestational age infant is at higher risk of several negative outcomes in the long term. **Why** this is so is a tremendously complex question. For example, if an effect **is** seen with excessive caloric intake in pregnancy, is it a function of:

- the **amount of calories**?
- the **particular substances used** to provide the excessive calories?
- the **timing of the exposure** to excessive calories in relation to a critical fetal development period?
- the **genetic peculiarities** of the study subjects?
- the **underlying health conditions** of the subjects such as the **mother's metabolic state**?
- a **disruption of the ratios of calories to the nutrients** needed to appropriately metabolism them?
- an **interaction** with other related factors?
- the resultant **size** of the infant, or is size just a **marker** for some other problem?

How can we tell? Most studies can only chip away at a few questions at a time. However, we will need to keep working to determine some answers to these kinds of questions or we may embark on promotion of prenatal goals and policies that are not only unhelpful but potentially injurious.

Some references about the "Fetal Origins Hypothesis" concept: [Folate supplementation during pregnancy improves offspring cardiovascular dysfunction induced by protein restriction. Hypertension. 2006 May;47(5):982-7. Nutritional control of fetal growth. Nutr Rev. 2006 May;64(5 Pt 2):S50-1; discussion S72-91. Normal and abnormal fetal growth. Horm Res. 2006;65 Suppl 3:19-27. The late effects of fetal growth patterns. Arch Dis Child Fetal Neonatal Ed. 2006 Jul;91(4):F299-304. Wheezing & eczema in relation to infant anthropometry: evi-dence of developmental programming of disease in childhood. Matern Child Nutr. 2006 Jan;2(1):51-61. The developmental origins of adult disease. Matern Child Nutr. 2005 Jul;1(3):130-41. Metabolic syndrome in childhood: association with birth weight, maternal obesity, & gestational diabetes mellitus. Pediatrics. 2005 Mar;115(3):e290-6. Experimental models of developmental programming: consequences of exposure to an energy rich diet during development. J Physiol. 2005 May 15;565(Pt 1). Life-long echoes--a critical analysis of the developmental origins of adult disease model. Biol Neonate. 2005;87(2):127-39. 39. Blood pressure, serum lipids, fasting insulin, & adrenal hormones in 12-year-old children born with maternal preeclampsia. J Clin Endocrinol Metab. 2003;88(3):1217-22. Maternal dietary ethanol consumption is associated with hyper-triglyceridemia in adult rat offspring. Alcohol Clin Exp Res. 2002;26(6):848-55. Impaired glucose tolerance & elevated blood pressure in low birth weight, nonobese, young South African adults: early programming of cortisol axis. J Clin Endocrinol Metab. 2000;85 (12):4611-8. Does birth weight predict adult serum cortisol concentrations? 24-hour profiles in the United kingdom 1920-1930 Hertfordshire Birth Cohort. J Clin Endocrin-ol Metab. 2002;87(5):2001-7. Striking variation in the sex ratio of pups born to mice according to whether maternal diet is high in fat or carbohydrate. Proc Natl Acad Sci. 2003;100(8):4628-32. Low birth weight & weight in infancy are associated with adult insulin resistance & type 2 diabetes. A proposed mechanism is programming of the hypothalamic-pituitary-adrenal axis by intrauterine undernutrition, leading to persistently elevated cortisol concentrations. Long-term programming of blood pressure by maternal dietary iron restriction in the rat. Br J Nutr. 2002 88(3): 283-90. Maternal blood lead concentration, diet during pregnancy, & anthropometry predict neonatal blood lead in a socioeconomically disad-vantaged population. Environ Health Perspect. 2003;111(2):195-200. Increased systolic blood pressure in rats induced by a maternal low-protein diet is re-versed by dietary supplementation with glycine. Clin Sci (Lond). 2002;103(6):633-9. Gender-linked hypertension in offspring of lard-fed pregnant rats. Hypertension. 2003;41(1):168-75. Maternal energy stores & diet composition during pregnancy program adolescent blood pressure. Circula-tion. 2001;104(9):1034-9 Maternal nutrition during gestation & blood pressure in later life. J Hypertens. 2001;19(1):29-34. Size at birth, gestational age & cortisol secretion in adult life: foetal programming of both hyper- & hypocortisolism? Clin Endocrinol (Oxf). 2002;57 (5):635-41. A deficient maternal calcium intake during pregnancy increases blood pressure of the offspring in adult rats. BJOG. 2002;109(5): 540- 5. Insulin resistance in

adult rat offspring associated with maternal dietary fat & alcohol consumption. J Endocrinol. 2002;173(1): 63-71. Diet in late pregnancy & glucose-insulin metabolism of the offspring 40 years later. BJOG. 2000;107(7):890-5. Maternal consumption of a high-meat, low-carbohydrate diet in late pregnancy: relation to adult cortisol concentrations in the offspring. J Clin Endocrinol Metab. 2003;88(8): 3554-60. Whole body insulin resistance in rat offspring of mothers consuming alcohol during pregnancy or lactation: com-paring prenatal & postnatal exposure. J Appl Physiol.2004; 96(1):167-72. Olive oil consumption during pregnancy & lactation in rats influences mammary cancer development in female offspring. Nutr Cancer. 2003;46(1):59-65. Effects of maternal ethanol consumption on hematopoietic cells in the rat fetal liver. Alcohol. 2002;28(3):151-6.]

Be wary of nutritionally inadequate weight loss diets undertaken prior to conception in order to be at a "healthier" weight going into pregnancy. Weight may be more "ideal" but nutrient stores could be severely compromised at a time when the fetus is most vulnerable to inadequacy.

For example, there is a higher risk of neural tube defects (NTDs) seen among the offspring of obese women. However, it is unlikely to be corrected by a diet that provides inadequate folic acid, vitamin B-12, vitamin B-6 and selenium, all of which have been shown to have a role in the prevention of NTDs. Some studies find the folic acid – NTD relationship to be quite different among overweight mothers. This may be because several other threats to a healthy pregnancy have not been corrected. **Preconceptional weight loss is not contraindicated, but it must be undertaken with careful attention to nutritional adequacy, and appropriately planned vitamin/ mineral supplementation is advisable.**

Another related issue is pregnancy after gastric bypass surgery. As this "bariatric" [weight reduction] surgery is becoming more common, subsequent pregnancy is becoming a much larger issue. Serious micronutrient inadequacies are appearing in the scientific literature in this population, including devastating conditions like Wernicke's encephalopathy from thiamine deficiency (multiple references cited below.) Wernicke's Encephalopathy has very overt symptoms and it is therefore far more recognizable than deficiencies of many other nutrients. I believe the multiple cases reported of overt thiamine deficiency after gastric bypass to be the "canary in the mine-shaft" -- it is likely a marker for other serious problems that are much less visible. Bottom line: careful consideration of micronutrient intake levels and absorption factors are especially critical in pregnancy post-bypass.

It is also useful to note that research is just in its infancy (no pun intended) regarding understanding of the issues involved in post-bariatric surgery pregnancy and of bariatric surgery in general. **Some reports indicate that after weight-loss surgery certain pregnancy complications were indeed less than those found in control groups of women similarly obese but not undergoing surgery**. Obesity is well known to be associated with an increase in many risks to a successful pregnancy, such as diabetes, pre-eclampsia, diabetes complications and c-section**. However, reports describing pregnancy after bariatric surgery as "safe" have so far only compared those immediate pregnancy complications as the outcome measurement of the study.** Additionally, the number of cases studied in this way is still quite small, and the women were (by definition) those receiving prenatal health care. **Its "safety" in terms of the optimal health and development of the fetus and the continued health of the mother in terms of nutrient adequacy (and not just changes in degree of fatness) is only beginning to be investigated.**

A recent report demonstrated that individuals who are morbidly obese and planning gastric bypass surgery are ALREADY deficient in a number of nutrients before the surgery takes place. [Preoperative Nutritional Status of Patients Undergoing Roux-en-Y Gastric Bypass for Morbid Obesity. J Gastrointest Surg. 2006 Jul-Aug;10(7):1033-7.] One might reasonably extrapolate from this situation as well to question whether the overall nutritional status of other seriously obese individuals might be similarly affected (whether planning surgery or not,) and to consider what might be done to correct things prior to conception.

Again, the first critical step is simply recognizing that:

- micronutrient inadequacies in the general public are not uncommon;

- women are generally at higher risk;
- people who battle with overweight could easily be at additional risk because of a history of food restricting weight-loss attempts, and the use of medications or purging to induce weight loss;
- "malnutrition" includes micronutrient inadequacy and not just calories and protein; in America malnutrition is not at all limited to people who are underweight.

Some additional references on this topic: Pregnancy after bariatric surgery: a comprehensive review. Arch Gynecol Obstet. 2008 May;277(5):381-8. Reproductive Considerations and Pregnancy after Bariatric Surgery: Current Evidence & Recommendations. Obes Surg. 2008 Apr 8. Pregnancy Following Gastric Bypass Surgery for Morbid Obesity: Maternal & Neonatal Outcomes. Obes Surg. 2008 Mar 4. Pregnancy outcomes after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2008 Jan-Feb;4(1):39-45. Reproductive implications of bariatric surgery: pre- & postoperative considerations for extremely obese women of childbearing age. Curr Diab Rep. 2007 Aug;7(4):281-8. Effect of Body Mass Index on pregnancy outcomes in nulliparous women delivering singleton babies. BMC Public Health. 2007 Jul 24;7(147): 168 Nutritional consequences of bariatric surgery. Curr Opin Clin Nutr Metab Care. 2006 Jul;9(4):489-496. Acute psychotic disorder after gastric bypass surgery: differential diagnosis & treatment. Am J Psychiatry. 2006 Jan;163(1):15-9. Wernicke encephalopathy after bariatric surgery: losing more than just weight. Neurology. 2005 Dec 27;65(12):1987. Eating avoidance disorder & Wernicke-Korsakoff syndrome following gastric bypass: an under-diagnosed association. Obes Surg. 2005 Sep;15(8):1207-10. Wernicke encephalopathy--an emerging trend after bariatric surgery. Am J Med. 2004 Nov 15;117(10):804-5. Wernicke's encephalopathy after Roux-en-Y gastric bypass. Obes Surg. 2004 Sep;14(8):1135-7. Stroke & seizure following a recent laparoscopic Roux-en-Y gastric bypass. Obes Surg. 2004 Jun-Jul;14(6):857-60. Acute Wernicke's encephalopathy following bariatric surgery: clinical course & MRI correlation. Obes Surg. 2004 Jan;14 (1):129-32. Rapid onset of Wernicke's encephalopathy following gastric restrictive surgery. Obes Surg. 2003 Aug;13(4):661-2. .A cluster of polyneuropathy and Wernicke-Korsakoff syndrome in a bariatric unit. Obes Surg. 2002 Jun;12(3):328-34. Wernicke encephalopathy in non-alcoholic patients. Am J Med Sci. 2002 Feb;323(2):107-11. Wernicke's syndrome after bariatric surgery. Clin Nutr. 2000 Oct;19(5):371-3. Wernicke-korsakoff encephalopathy & polyneuropathy after gastroplasty for morbid obesity: report of a case. Arch Neurol. 2000 Sep;57(9): 1356-9. A rare complication of adjustable gastric banding: Wernicke's encephalopathy. Obes Surg. 2000 Jun;10(3):274-5. A case of Wernicke-Korsakoff syndrome with dramatic improvement in consciousness immediately after intravenous infusion of thiamine No To Shinkei. 2000 Jan;52(1):59-63. Alcohol & poor compliance as factors in Wernicke's encephalopathy diagnosed 13 years after gastric bypass. Can J Surg. 1998 Oct;41(5):389-92. Starvation injury after gastric reduction for obesity. World J Surg. 1998 Sep;22(9):1002-7. Wernicke's encephalopathy developed several years after total gastrectomy. Report of 2 cases Rinsho Shinkeigaku. 1997 Nov;37(11):1027-9. Wernicke's encephalopathy after vertical banded gastroplasty for morbid obesity. Eur J Surg. 1997 Jun;163(6):473-4. Wernicke's encephalopathy after vertical banded gastroplasty for morbid obesity. BMJ. 1996 Feb 17;312(7028):434.]

10. **Pregnant women with metabolic conditions such as diabetes (Type I or II or gestational), Lupus, Crohn's disease, Celiac disease, MS, Epilepsy or multiple allergies have special nutrition problems that are often unrecognized.**

These include **altered requirements for specific nutrients, and drug/nutrient interactions** of special concern in pregnancy. These metabolic conditions result in significantly more inflammation and a greater production of injurious free radicals.

It has been shown that women with diabetes can decrease the risk of birth defects and other complications by maintaining good glycemic control prior to and throughout pregnancy. However, careful attention to micronutrients such as providing generous antioxidants, an appropriate omega-3 to omega-6 ratio, and adequacy of vitamins and minerals (e.g. selenium and magnesium) has been shown to further decrease the risk.

B vitamin adequacy appears to be even more important in women with insulin resistance / gestational diabetes in regulating homocysteine levels. As there are pregnancy complications specifically associated with elevated homocysteine in women with gestational diabetes, attention to this interaction may be very important. [Total plasma homocysteine correlates in women with gestational diabetes. Arch Gynecol Obstet. 2008 Jan 31. Teratogenicity associated with pre-existing and gestational diabetes. J Obstet Gynaecol Can. 2007 Nov;29(11):927-44.]

Other examples and references were included earlier (such as epilepsy control medications and their interactions with folic acid, vitamin D, vitamin K and carnitine.)

Here are a few additional references regarding nutrition and epilepsy treatment: [Carnitine status of pregnant women: effect of carnitine supplementation and correlation between iron status and plasma carnitine concentration. Eur J Clin Nutr. 2009 Jun 3. Importance of monotherapy in women across the reproductive cycle. Neurology. 2007 Dec 11;69(24 Suppl 3):S10-6. Pregnancy and epilepsy : Retrospective analysis of 118 patients. Nervenarzt. 2008 Apr 4. Antiepileptic drug use, folic acid supplementation, and congenital abnormalities: a population-based case-control study. BJOG. 2008 Jan;115(1):98-103. Management of epilepsy in women of childbearing age: practical recommendations. CNS Drugs. 2006;20(5):373-87. Valproic acid in epilepsy : pregnancy-related issues. Drug Saf. 2006;29(1):1-21. Recent advances on neural tube defects with special reference to Valproic Acid. Endocr Metab Immune Disord Drug Targets. 2006 Mar;6(1):25-31.Antiepileptic drugs: a case report in a pregnancy with a neural tube defect. Pediatr Neurol. 2006 Apr;34(4):323-4. Best practice guidelines for the management of women with epilepsy. Epilepsia. 2005;46 Suppl 9:117-24.]

Note that the standard recommended nutrient intakes for pregnant women are (by definition) based on the needs of "98% of the healthy population" and they simply cannot be relied upon to meet the needs of women who are not members of that group. Carefully assessing and adjusting the diet or supplement regimen can significantly improve outcomes for these women and their babies, especially when any necessary adjustments are made prior to conception.

Stay Tuned!