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Routine vitamin, mineral and micronutrient supplementation

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INTRODUCTION

Little doubt exists in the minds of the medical profession and much of the public that the connection between maternal nutrition and fetal outcome is important. There is, however, much confusion about the most efficient method to achieve an adequate nutritional status at the start of pregnancy, especially if a nutritional deficiency is present. No consensus regarding the definition and/or understanding of 'adequate nutrition' exists, and even less uniformity of opinion is present for a definition of 'optimal nutrition', even though some authorities might suggest that diet alone supports health and longevity. The components of diet are inexorably tied to culture.

Beginning with birth, each of us eats foods which are usually chosen by individuals who have had no formal training in domestic sciences, dietary technology, or food preparation. Mothers and grandmothers sanctioned food choices determined by local availability, budget, accessibility of refrigeration and community or religious practices that often stretch back to antiquity. The nutritional value of these diets is highly variable.

Under such circumstances, when healthcare professionals speak with clients in developed nations, their words may provoke head-shaking to signify some degree of understanding, but it is highly likely that patients differ in their understanding of adequate nutrition. This scenario is only part of the problem. In the authors' opinions, a far greater problem exists in that the science of nutrition is relatively young in the spectra of medical disciplines and often gets short shrift in the educational process. Despite a vast body of research into specific dietary problems, much of the available literature is confusing because of lack of standardization of methodologies of study, indecision about whether specific nutrients should be evaluated alone or in combination, and absence of agreement as to whether the dose should be tested in relation to what a normal person might consume in a 24-hour period or as a megadose that exceeds anything that can be found in a supposedly normal diet.

The same may be said regarding optimal vitamin supplementation in pregnancy, be it the type or the dose. Table 1 has been prepared to provide health care professionals a handy guide that they can share with their patients. Not only are the nutrients and their respective doses listed, but also cited are the appropriate sources of the information. It is hoped that practitioners will feel free to copy this table, from either the printed or electronic version, and share it with patients and their families. A careful perusal of recommended dosages reveals a lack of consistency even among those agencies that deal with these issues on a daily basis. Where more than one source may be considered authoritative, both are listed.

Table 1 Recommended nutrient intakes, deficiency effect on expectant mother and offspring, authority source and effect of excess

Nutrient	*Recommended intake for pregnant women*	*Deficiency effect on expectant mother*	*Deficiency effect on offspring*	*Source*	*Effect of excess*
Fiber	28 g	Constipation	None known	National Academy of Sciences[1]	Malnutrition and depletion of vitamins
Folate	600 μg per day DFE*	Folate-deficiency anemia: tiredness, breathlessness, palpitations, depression	Neural tube defects	*Food and Nutrition Board[2]	Toxicity from folate is low because it is water soluble and is regularly removed from the body through urine
Iodine	220 μg* 150 μg**	May be accompanied by catastrophic consequences, including spontaneous abortion, stillbirth and increased perinatal mortality	Newborns: may exhibit goiter, mental retardation and cretinism, the most extreme form of neurological damage from hypothyroidism	*Food and Nutrition Board[3] **American Thyroid Association[4,5] † National Institutes of Health[6]	†Thyroid dysfunction and skin irritation
Iron	27 mg/day* 30 mg/day**	Anemia	Premature delivery, low birth weight	*Food and Nutrition Board[3]* *Centers for Disease Control[7]	Gastrointestinal distress
Omega 3 - DHA/EPA	1200 mg* 1400 mg**	Fatigue, poor memory, dry skin, heart problems, mood swings or depression and poor circulation	Adverse effects on visual and neurological development	*The DHA/Omega-3 Institute[8] **Food and Nutrition Board[9]	None known
Omega 3 - DHA	200 mg/day* 300 mg/day**	Fatigue, poor memory, dry skin, heart problems, mood swings or depression and poor circulation	Adverse effects on visual and neurological development	*World Association of Perinatal Medicine, the Early Nutrition Academy and the Child Health Foundation[10] **National Institute of Health and the International Society for the Study of Fatty Acids (NIH/ISSFAL)[11,12]	None known

continued

Table 1 *Continued*

Nutrient	*Recommended intake for pregnant women*	*Deficiency effect on expectant mother*	*Deficiency effect on offspring*	*Source*	*Effect of excess*
Selenium	60 µg	Pre-eclampsia, first-trimester miscarriages and recurrent miscarriages	Weakens the immune system; severe deficiency associated with Keshan disease, Kashin-Beck disease and myxedematous endemic cretinism	Food and Nutrition Board[13]	Selenosis: fatigue, gastrointestinal upset (nausea, vomiting, stomach pain, diarrhea, garlic breath, metallic taste in the mouth), hair and nail loss or blotchy nail beds and mild nerve damage
Vitamin A	750–770 µg RAE (retinol activity equivalent)	Night blindness, xerophthalmia	Impaired immunity, impaired vision	Vitamins, Food and Nutrition Board[14]	Birth defects
Vitamin B3 (niacin)	18 mg/day for pregnant and breastfeeding women* 30 mg/day for women under 18 and 35 mg/day for women over 18**	Hyperemesis gravidarum, pellagra	No human studies	*Food and Nutrition Board[15] **WebMD[16] †Drugs.com[17]	Nausea, vomiting, severe sensory neuropathy Assigned pregnancy category C by the FDA when given in doses above the RDA†
Vitamin B6 (pyridoxal phosphate, pyridoxamine phosphate)	1.9 mg/day	Overt symptoms are rare	May result in lower APGAR scores	Food and Nutrition Board[2]	None known
Vitamin B12	2.6 µg†	Pernicious anemia	Irritability, failure to thrive including falling off in growth rate, apathy, anorexia, developmental regression, limited hepatic reserves, refusal of solid foods, megaloblastic anemia* †Increased risk of neural tube defects	*Dror and Allen[18] **†National Institutes of Health[19] †Centers for Disease Control and Prevention[20]	**None known
Vitamin D	4000 IU*	Increased risk of cesarean delivery, muscle weakness, poor muscle performance*	Rickets	Centers for Disease Control and Prevention[21] *WebMD[22]	*No evidence of toxicity

continued

Table 1 *Continued*

Nutrient	*Recommended intake for pregnant women*	*Deficiency effect on expectant mother*	*Deficiency effect on offspring*	*Source*	*Effect of excess*
Zinc	40 mg for women >19 years, 34 mg for women 14–18 years*	Impaired growth and development, preterm deliveries, pre-eclampsia, hemorrhage, infections and prolonged labor	Congenital anomalies	*National Institutes of Health[23]	*Ingestion of 2 g of or more can cause nausea, vomiting and fever

DFE, dietary folate equivalent; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid

Even as recently as 10 years ago, it might have been deemed superfluous to discuss vitamins, minerals and micronutrients in a monograph devoted to preconception counseling. This is not the case for three important reasons.

First, people are beginning to recognize that previously prepared foods, stored at a low temperature and then reheated or maintained at a constant warm temperature for hours before consumption, may lose a significant, albeit unknown, portion of their expected values compared to what would have been present had they been eaten immediately or shortly after cooking. Such food is found in cafeterias, steam lines, hotel buffets, etc. This problem exists totally apart from other issues related to 'fast foods' that are eaten shortly after their preparation. Other problems that affect food nutrient content include the use of artificial light and hormones during the growing period, the need to pick fruits and vegetables in a pre-ripened state for transport to the point of sale, and the addition of chemicals or processes that prolong shelf life.

The second reason relates to a continually increasing awareness that dietary inadequacy that exists before pregnancy cannot immediately be rectified once pregnancy commences. A prime but not exclusive example is the relationship between serum folate levels and neural tube defects. Much of the existing literature fails to stress that it is ineffective and perhaps disingenuous to exhort patients to take folic acid only when they are pregnant, because 50% of pregnancies are unintended and any folic acid taken after the 28th day following conception does not affect the neural tube which is already formed by that time. Recent publications and governmental advice center on the need to provide entire populations with adequate folate supplementation before pregnancy because (1) patients are not routinely tested for folate levels, meaning that those who are deficient are unknown, and (2) many patients, especially those in their second pregnancy or higher, tend to come for their first prenatal visit some time after the 28th day following conception because they believe they know the 'routine' or, in the case of grandmultiparas, are burdened with childcare responsibilities. Moreover, physicians now recognize that folic acid is of benefit throughout the remainder of a pregnancy because of cellular development and synergy with B vitamins.

Third, it is clear that governmental decisions to fortify specific foods are not sufficient to eliminate all problems. Here again, folate is a prime example. In 1992, the United States Public Health Service issued a recommendation that all women of childbearing age consume 400 μg of folic acid on a daily basis for the prevention of neural tube defects. Six years later, the Institute of Medicine offered similar advice. Women were informed they could obtain adequate amounts of folate by taking a folic acid supplement, taking a multivitamin containing the requisite amount of folic acid among other constituents, or eating cereal grain products fortified by 100% of the RDA (recommended daily allowance) of folic acid. In 1998, the US Food and Drug Administration required mandatory fortification of cereal grains with 140 μg of folic acid per 100 g of cereal grain product, including those grain products that were imported, such as Italian pastas. This enormous effort resulted in a 27% reduction in the incidence of neural tube defects in 1999–2000 compared to 1995–1996[24]. The decline in incidence continues, but it has not been total, perhaps because the fortification process was confined to wheat grains and a large percentage of the American Hispanic population consistently eat products made from corn meal, something not considered at the time of publication of the original fortification guidelines. Not fortifying corn products may not be the entire reason for the smaller response in the American Hispanic population, but it is significant that the largest manufacturer of corn tortillas in Mexico has voluntarily added folate fortification (Linda Van Horn, personal communication, July 20, 2009). The information cited here contrasts with the public health considerations relating to food fortification and/or comprehensive multivitamin products for pregnant women that provide the internationally recommended levels of folic acid rather than relying on obtaining folate and other essential vitamins, minerals and micronutrients in dietary choices.

CRUCIAL ISSUES FOR HEALTH-CARE PRACTITIONERS

Although health-care practitioners generally are familiar with the reputed value of adequate maternal nutrition in terms of its effect on pregnancy outcomes, often they are less familiar with the value of supplementation during pregnancy. Any meaningful discussion of supplementation must address three crucial issues – who to supplement, how to supplement and what to supplement.

Who to supplement

Once again, the profession is confronted by a dichotomy. Much of the literature strongly recommends that only those with known deficiencies receive supplements. This would be reasonable if it were possible to test for all essential pregnancy-related vitamins, minerals and micronutrients in a cost effective and universally applied manner. Such testing routinely is not available in most hospitals where the majority of deliveries are conducted. Even if it were, the unpredictability of pregnancy means that testing could not be carried out in a rational and/or cost effective manner.

Faced with these limitations, routinely supplementing women of childbearing age is a rational means of ensuring that women have adequate levels of essential vitamins, minerals and micronutrients when they become pregnant. In the long run, such therapy is capable of circumventing the dietary variations that exist within populations and between individuals, each of whom may be convinced that her particular diet is adequate, if for no other reason than it may be prepared by someone outside her home and/or at great expense. Of great importance, supplementing that is begun before pregnancy can be continued during the pregnancy by changing to a traditional prenatal vitamin, continuing into lactation and the time before the next conception.

How to supplement

There is no simple explanation regarding this issue, because neither the medical profession nor pharmaceutical manufacturing associations have determined whether it is more advantageous to supplement with single or multiple components in a given pill. Either is possible, and in the early days of supplementation practice, it was common to prescribe separate tablets for iron and for vitamin supplementation. Knowledge of the essential pregnancy-related requirements for specific vitamin constituents has increased exponentially since 1990, and many clinicians have begun to see the value of prescribing a 'balanced palate' of components that includes vitamins, minerals and micronutrients in one pill or capsule. Thus, the concept of 'monotherapy' has evolved, although admittedly monotherapy is reasonable if one holds to the concept that supplements should be advised only when specific deficiencies are present. In the authors' opinions, however, this line of thinking fails to protect the public health in terms of pregnancy well-being because, with rare exceptions, clinicians are unaware of the relative states of deficiency or adequacy of circulating levels of vitamins, minerals and micronutrients in their patients. Moreover, clinics and hospitals that are very proficient in conducting obstetric deliveries are not at all equipped to accurately analyze blood samples for circulating levels of important vitamins, minerals and micronutrients.

What to supplement

Given the circumstances cited above, all women of childbearing age who engage in sexual relations could become pregnant and should be advised to take a vitamin supplement that contains folate in the requisite dose, along with vitamin B12. In this regard, it is noteworthy that as of early 2009 one of the major worldwide producers of birth control pills is adding folic acid fortification to each pill. We believe it is not practical to assume a good diet will provide everything needed for a healthy pregnancy, because (1) there is no agreement on what constitutes a good diet for everyone, (2) evidence suggests that significant numbers of the literate public do not follow the written guidelines and recommendations concerning healthy eating as they relate to pregnancies, and (3) such advice is without meaning for those segments of the population that are marginalized, living below the poverty level, and who seek prenatal care late in pregnancy. Folate is not the only vitamin that may be deficient in the general population, as shown by a recent national dietary survey in the United States that sampled women aged 19–49 and showed that 90% had daily iron intake that was below the reference nutrient intake (RNI)[25].

We agree with other authors[26,27] that it is necessary to anticipate the increased need for micronutrients, because the only rational way to ensure that these essential elements are present during the critical times of pregnancy is to provide them before pregnancy. This simple concept can and should be part of the counseling provided to every women of reproductive age when she has a medical encounter for whatever reason.

DEFINITIONS

Dietary reference intakes were developed by the Institute of Medicine. The acronym 'DRI' generally characterizes a set of reference values used for planning and assessing nutrient intake for healthy people. Three important types of reference values in the DRI include recommended dietary allowances (RDA), adequate intakes (AI) and tolerable upper intake levels (TUIL) (often shortened to UL). The RDA recommends an average daily dietary intake level sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals in each age group and sex. An AI is set when there are insufficient scientific data available to establish an RDA. Commonly, AI meet or exceed the amount needed to maintain a nutritional state of adequacy in nearly all members of a specific age group and sex. On the other hand, the UL is the maximum daily intake unlikely to result in adverse health effects.

PROBLEMS IN THE LITERATURE

The accumulated literature on vitamins, minerals and micronutrients is impressive, to say the least. Terms that describe the quantity and variety of research and opinions might include 'staggering' or 'daunting', and therein lies the problem. The average practitioner has little time or inclination to read even a small quantity of what is available and thus may turn to reviews and committee opinions for clinical guidance. Even these are not in agreement, as evidenced by the heterogeneity of information in reviews that are judged as authoritative, such as the Cochrane database.

The recitation of each controversy surrounding the vitamins, minerals and micronutrients mentioned below will add nothing to the clinical acumen of any health-care professional who may read this chapter. On the other hand, we believe it useful to mention our biases at this time. Simply stated, we believe that modern diets can be deficient in vitamins, minerals and micronutrients for several reasons – overproduction in some farming areas, the use of chemical fertilizers, the need to harvest unripe produce and allow ripening under controlled environmental conditions, and the need to pack foodstuffs in CO_2 for transport, etc., among others. We also believe that supplementation should be started before conception in young women who may or may not be contemplating pregnancy. Finally, we believe that supplementation should be continued after pregnancy throughout lactation and into the interconceptional period, so supplementation becomes a way of life based on the recognition of the inherent deficiency of modern diets in most individuals.

STRATEGIES TO IMPROVE NUTRITION

Recent concerns about dietary inadequacy have led to various strategies to improve nutrition; these range from changing dietary components to reducing social isolation as a means of encouraging better food intake. Each is discussed below.

Functional foods

Functional foods are provided to confer a 'benefit' to the diet beyond that of simple nutrition. In this regard, the nutritive value of common foods can be enhanced by several means, including but not limited to probiotics, prebiotics, synbiotics, omega-3 fatty acids and fibers. The catch-all term for this type of additives is nutraceutical, which can also be used to denote vitamin supplements.

Fibers

Fibers are either readily fermentable by colonic bacteria or only slowly fermentable. They act in several manners, not least of which is exerting a 'mop and sponge effect' in the colon and assisting in the formation of the fecal contents.

Nutraceutical

Dr Stephen DeFelice coined the term 'nutraceutical' in the 1990s and defined it as 'any substance that is a food or a part of a food and provides medical or health benefits, including the prevention and treatment of disease'[28]. Such products may range from isolated nutrients, dietary supplements and specific diets to genetically engineered designer foods, herbal products and processed foods such as cereals, soups and beverages. It is important to note that this definition applies to all categories of food and parts of food, ranging from dietary supplements such as folic acid, used for the prevention of spina bifida, to chicken soup, taken to lessen the discomfort of the common cold. This definition also includes a bioengineered designer vegetable food, rich in antioxidant ingredients, and a stimulant functional food or 'pharmafood' and fibers.

Prebiotics

Prebiotics are 'non-digestible food ingredients' that selectively stimulate a limited number of bacteria in the colon to improve the health of the host. Present-day prebiotic research is concerned with enhancing probiotic flora.

Probiotics

A probiotic is defined as a 'live microbial food supplement' that beneficially affects the host by improving its intestinal balance. Lactic acid bacteria, particularly *Lactobacillus* spp. and *Bifidobacterium* spp., are the best-studied probiotics at the time of this writing and can be combined with food products such as cereals, bioyogurts and drinks for benefit of gastrointestinal (diarrheal and irritable bowel syndrome) and non-gastrointestinal conditions (candidiasis and urinary and respiratory tract infections).

Synbiotics

These substances contain complementary probiotic and prebiotic ingredients that interact synergistically toward maintenance of a desirable microbial population in the intestine.

The Mediterranean diet

Simply stated, this diet contains high quantities of vegetables, legumes, fruits and cereals (largely unrefined); a moderate-to-high intake of fish; a low intake of saturated fats in contrast to a high intake of unsaturated fats, especially olive oil; a low-to-moderate intake of dairy products, mostly in the form of cheese and yogurt; a low intake of meat; and a modest intake of alcohol mostly in the form of wine. This diet is widely viewed as promoting healthier aging, increasing longevity, and possibly reducing the risk of developing Alzheimer's disease later in life.

Reducing social isolation

Regardless of age, dining with other individuals has many advantages compared to dining alone. Granted that many women of reproductive age are single and often employed, special efforts must be made as part of the counseling process when pregnancy is desired to inform patients that reliance on modern fast foods is not a means to enhance nutrition and that eating with co-workers and/or family has numerous intangible benefits. Most research in this area has been confined to older individuals, many of whom were residing in institutional facilities. Be this as it may, there is no reason to believe that the positive effects of communal consumption that have been observed in older individuals would not pertain to the young, regardless of whether they are pregnant[29].

'ESSENTIAL MATERNAL/ FETAL BUILDING BLOCKS

Folate

- General – folic acid (pteroglutamic acid or PGA) is a synthetic form of folate. Naturally occurring folate is abundant in dark green leafy vegetables, orange juice, legumes (beans), nuts, asparagus and other select foods. Meat, with the exception of liver, is not a good source of folate. Folic acid, as contained in commercial products or fortified foods, is generally more bioavailable than when consumed from food alone. Indeed, it has been suggested that without supplementation, one would need to ingest enormous quantities of green leafy vegetables to even approximate daily requirements. It also has been suggested that the actual content of folate in foods known to contain high amounts has been declining on an annual basis for some years because of overproduction and the use of artificial fertilizers.

- DRI – folate requirements increase during pregnancy, a fact that has been appreciated for decades. What has not been appreciated until recently is that folate deficiencies must be addressed before the woman becomes pregnant, because many women do not receive medical care until after the 28th day of conception, at which time deficiency cannot be corrected in time to prevent neural tube defects [which] may have already occurred.
- The RDA for folate during pregnancy, as established by the Institute of Medicine in 1998, is 600 μg per day DFE [dietary folate equivalent], this being approximately 50% higher than that of non-pregnant women. Prenatal vitamin supplements contain from 400 to 1000 μg of folic acid. The higher doses are in excess of the 600 μg per day folate DFE for pregnant women.

Deficiency

- Neural tube defects (NTD) occur more frequently in the presence of folate deficiency. The most common include anencephaly and spina bifida, which result from failure of closure of the developing neural tube as it overlies the developing embryonic brain and spinal cord, respectively. This closure occurs by the 28th day of embryogenesis (42 days after the onset of the last menstrual period). Approximately 3000 NTD-affected pregnancies occur on an annual basis in the US alone[1], and the worldwide numbers may still be as high as 300,000 per year, although the incidence ranges widely (0.8 per 1000 births in certain areas of the US to 13.8 per 1000 births in north central China)[26,27].
- Cardiac defects – folic acid containing supplements consumed early in pregnancy have been associated with reduced risks for offspring with heart defects, especially ventricular septal defects and conotruncal defects (e.g. tetralogy of Fallot and transposition of the great arteries)[30]. Although controlled intervention trials are lacking, secondary analysis of a Hungarian randomized controlled trial (RCT)[31] showed reduced occurrence of both cardiovascular anomalies (OR = 0.42) and urinary tract anomalies. Studies in other jurisdictions have reported similar decreases.
- Other positive associations have been reported, including reductions in the incidences of colorectal cancer, breast cancer and possibly vascular disease[26,27]. Of perhaps greater interest to obstetricians/gynecologists is the report that preconceptional folic acid supplementation [for] 1 year or longer was associated with a 50–70% decrease in the risk of early spontaneous preterm delivery between 20 and 28 weeks, a finding that remained after adjustment for maternal age, race, BMI [body mass index], education, marital status, smoking, parity and history of preterm birth[32].

Supplementation

- In 1992, the US Public Health Service recommended that all women of childbearing age consume 400 μg/day of folic acid from supplements, fortified foods, or both, in addition to consuming a varied diet to reduce the likelihood of their having an NTD-affected pregnancy[33]. The Institute of Medicine followed in 1998, advising that all women capable of becoming pregnant consume this important vitamin[2]. Other countries have agreed, with some including the recommendation that supplementation begin in the preconceptional period. This change is considered of great importance because numerous investigations worldwide document that policies advocating supplementation beginning in pregnancy alone are not sufficient to produce the desired reduction in NTD prevalence.
- The 400 μg dose is the amount observed to be associated with NTD risk reduction in most epidemiological studies, supporting the conclusion that periconceptional folic acid use significantly reduces the [incidence] of NTD. It is also the dose [used] in the large scale Chinese intervention trial (N = 250,000)[26,27].
- The 400 μg dose is accepted worldwide even though the only genuine occurrence RCT (NTD in the absence of prior-affected offspring) used a dose of 800 μg folic acid. In this study, the frequency of NTD was zero among 2471 women receiving 0.8 mg, compared to six among 2391 not so receiving[34], in which the expected NTD cases were 6.9 and 6.7, respectively. This study used 800 μg of folic acid, not because the authors had any scientific evidence of its superiority, but because this dose was provided gratis to the investigators. In the Chinese study mentioned above, 400 μg of folic acid was used selectively in specific geographic regions and reduced NTD occurrence by 79% in high incidence regions (0.65% background NTD incidence) and 41% in low incidence regions (0.08% background NTD incidence)[35].
- Although the 400 μg/day is a reasonable dose of folic acid for reducing NTD in the general population, it is considered insufficient for women who have previously had an infant with an NTD. Here the recommended dose is 4 mg per day[36] (ten times the normal), based on a Medical Research Council trial that resulted in a 72% reduction in NTD recurrence[37].

Fortification

- Folic acid fortification programs (i.e. adding folic acid to food) are justified because most women of reproductive age still do not take folic acid supplements (especially before becoming pregnant) and because educational efforts pertaining to NTD risk reduction have not been completely effective in modifying behavior related to supplement use. By 2007, 54 countries had regulations regarding mandatory wheat flour fortification[38]. In the US, as noted above, folic acid also is added in specified amounts to all cereal grain products (bread and pasta, for example) that then are labeled “enriched”. Even so, it is estimated that, of US women of reproductive age, only 8% consume equal to or greater than 400 μg/day[39], thus supporting the conclusion that most US women need to take a folic acid supplement to achieve the US Public Health Service/Institute of Medicine (USPHS/IOM) recommendation of 400 μg/day.

- Racial and ethnic disparities exist, with Hispanic women having the highest rate of NTD and the lowest use of folic acid supplements[40,41]. To what extent this disparity exists because of the propensity of Hispanic women to preferentially consume products containing corn flour on a daily basis as would occur with tortilla consumption is unknown. It is a reasonable conjecture, although it also is reasonable to presume that other factors may be working concomitantly.
- The incidence of NTD was inversely associated with folate status in a large Irish cohort study in which the lowest prevalence of NTD was associated with a mean serum folate of ≥7 ng/dl and a mean serum red blood cell (RBC) folate concentration of approximately 400 ng/ml[42].
- Effect of excess – the Institute of Medicine[43] found no substantiated evidence of toxic effects, although other potential adverse effects are: (1) potential interference with the diagnosis of vitamin B12 deficiency-based neurological disease (masking); and (2) potential increase in numbers of twins, a finding ultimately thought to be related to confounding by a high preponderance of fertility interventions.

Iodine

- General – iodine is an essential element that is required for the synthesis of the thyroid hormones of thyroxine (T4) and tri-iodothyronine (T3) that play pivotal roles in metabolism. Deficiency (hypothyroidism) and excess (hyperthyroidism) are well known to medical practitioners throughout the world. Iodine in the form of iodate commonly is used as an additive to salt to prevent iodine deficiency disorders. It is also a common additive of supplements. Upon ingestion, iodate is reduced to iodide that is absorbed and available metabolically as active iodine[26,27].
- DRI – World Health Organization[44], United Nations Children's Fund and the International Council for Control of Iodine Deficiency Disorders consider a daily intake of 100 μg of iodine per day for adults as being sufficient to provide typical urinary iodine levels of 100 μg/l. This is not the case in the US where the RDA is 150 μg/day for both men and women. The tolerable upper intake level (TUIL) for adults is 1100 μg/day (1.1 mg/day). This is because a large portion of the country is landlocked, and those inhabitants do not consume seafood regularly.
- Many regions throughout the world lack sufficient dietary iodine which is dependent on seafood, particularly salt water fish, and, to a certain extent, milk. It is fortunate that iodine is the simplest micronutrient to fortify; [this] is usually accomplished by the addition of potassium and/or calcium iodate to salt[26,27]. Iodine requirements in pregnancy are higher than for the non-pregnant woman. The RDA must be 220 μg/day to achieve a urinary iodine excretion of >150 μg/day.

Deficiency

- Deficiency is present worldwide and often remedied by fortification, although this latter process is variable. In the US, addition of iodate to salt began in the 1920s, but as recently as 1988–1994 the National Health and Nutrition examination survey determined that 15% of women aged 15–40 and 17% of pregnant women had urinary concentrations of iodine amounting to only 50 μg, indicating <100 μg daily intake[45].

- Deficiency during pregnancy may be accompanied by catastrophic consequences, including spontaneous abortion, stillbirth and increased perinatal mortality. Newborns may exhibit goiter, mental retardation and cretinism, the most extreme form of neurological damage from hypothyroidism. The brain is particularly sensitive to deficiencies, because thyroid hormones are responsible for myelinization of the central nervous tissue.
- Effect of excess – when the recommended intake is vastly exceeded, the excess intake of iodine may rarely result in goiter, thyrotoxic crisis and hyperthyroidism. This does not occur after digestion of physiological quantities of iodized table salt or from low-dose supplements during pregnancy (1–200 or 100–200 μg/day). WHO recommends upper intake levels of 600 μg/day[46], while the US Institute of Medicine[47] considers the safe upper limit for iodine intake to be 1000 μg/day for pregnant women. Reasons for this wide variation are not clear but illustrate the complexity of attempting to define upper limits of intake that are appropriate for all patients.

Iron

- General – the use of iron in pregnancy has a long history. It was probably first prescribed as a restorative in ancient days in the form of wine (an alcoholic tincture of iron) before the association of alcohol and fetal anomalies was appreciated. Certainly it was known to obstetricians practicing by the middle of the 20th century, at which time it was often prescribed as a separate pill in doses far in excess of what could be reasonably be absorbed and as such was often cited as the cause of gastrointestinal discomfort that ranged from pain and cramps to diarrhea or vomiting. It is not surprising that many women, especially multiparas, are all too happy to deposit their prescriptions for iron products in the waste basket when leaving the clinic or doctor's consultation.
- Iron holds the dubious distinction of simultaneously being an essential trace mineral, the source of the world's most common deficiency, and a potential cause of anemia in pregnancy if its level is insufficient. Its ability to convert between the ferrous (Fe^{2+}) and the ferric (Fe^{3+}) states accounts for its role in oxidative metabolism. When free iron is present, it can lead to the generation of active oxygen species and free radicals that may cause oxidative damage.
- Dietary iron consists of heme and non-heme (inorganic) forms. Heme iron is supplied by meat, fish and poultry, whereas plant-based foods (vegetables, fruits and grains) are the sources of non-heme iron, although bioavailability varies greatly (high from broccoli and cabbage, and low from legumes, rice and maize). Fortified foods always use the non-heme inorganic form, and absorption is enhanced by ascorbate and stomach acid, and inhibited by calcium and a number of food constituents. The

average estimated iron absorption from an adequate diet is 10%, a figure that increases to 18% in individuals with depleted stores.

- The numbers cited above relating to absorption cloud the clinical picture. About 4 mg is the maximum that can be absorbed on a daily basis regardless of whether the woman has adequate or inadequate stores. This number is of great importance when advising patients regarding a prenatal supplement that contains iron, because many contain quantities far in excess of that which can be absorbed and which may be the cause of gastrointestinal disturbances.
- Iron status is often measured by hemoglobin levels, with deficiency being defined as <13 g Hb/dl for men and <12 g Hb/dl for women (WHO criteria[48]). There are numerous biomarkers that are better indicators of iron stores, however, especially the total serum iron binding capacity, with levels of more than 450 μg/dl indicating deficiency.
- DRI – the RDA as set by the IOM for pregnancy is 27 mg/day[49]. This represents an approximate 50% increase over the RDA for adult females (18 mg). The need for increased iron is based on the increases in the red cell mass, a 50% expansion of the plasma volume and the growing fetal requirements. Estimations of the amount of iron that needs to be absorbed in the second and third trimester are 4–5 mg/day and 6–7 mg/day, respectively. These needs are partially addressed by existing iron stores even when the woman is anemic. The RDA for lactating women was set at 10 mg/day[26,27].
- Deficiency – although it is clearly beneficial to enter pregnancy with an adequate iron store, WHO estimates anemia is present in 18% of pregnant women in industrialized countries and 56% in developing countries[50]. Most of these anemias had their onset before conception, and the presence of iron deficiencies *per se* as measured by low ferritin far exceeds the prevalence of anemia. The literature on the adverse effects of anemia is copious, with low birth weights, premature delivery and low neonatal iron stores being prominent.

Supplementation

- Given the circumstances described above, it is disconcerting that international organizations have not reached a consensus about the value of supplementation. The recommendations of the Institution of Medicine are complex[51]. The American College of Obstetricians and Gynecologists recommends that all pregnant women should be screened for anemia and those with iron deficiency anemia be treated with supplemental iron in addition to prenatal vitamins[52].
- The authors believe that pronouncements such as these make a simple proposition unnecessarily complex for busy practitioners who often see patients who come for antenatal care with the presumption that they will be given vitamin and iron supplementation. Because most modern prenatal supplements contain rational amounts of iron, it seems reasonable to prescribe them to all pregnant women.
- A final word of caution is necessary. The most common cause of poisoning fatality in young children is accidental

overdose by ingesting iron-containing products. The oral lethal dose is approximately 200 mg/kg, although less can be fatal. Early symptoms include vomiting, nausea, hypotension and respiratory difficulties; later, multiple organ failure or central nervous system (CNS) failure may occur. Maternal oral medications with iron contents clearly should be kept out of children's reach.

- Effect of excess – the upper intake level (UL) is 45 mg/day, a figure based on the likelihood of gastrointestinal distress from higher amounts.

Omega 3 fatty acids

- General – three main types of omega 3 essential fatty acids, with distinctly different functions, are important in perinatal nutrition. Eicosapentaenoic acid (EPA), found primarily in fish and fish oil, helps the body manufacture eicosanoids and has controlling effects on hormones and the immune system, both of which are known to affect brain function. Docosahexanoic acid (DHA) also is found primarily in fish and represents about 97% of all omega 3 fats in the brain and 93% of all omega 3 fats in the retina. As such, it is particularly important for fetal brain and retinal development during the third trimester and up to 18 months of life. DHA is involved in visual and neural function and neurotransmitter metabolism. Alpha-linolenic acid (ALA), found mostly in seeds, vegetable oils and leafy green vegetables, is converted into EPA and then into DHA in the body.
- These omega 3 fatty acids and the omega 6 fatty acid, arachidonic acid (AA), recently have gained attention in the field of prenatal nutrition because of their important functions in fetal and newborn neurodevelopment and inflammation. DHA and AA are critical to fetal and infant central nervous system growth and development[53,54]. All of the omega 3 and omega 6 fatty acids accumulated by the fetus are derived from the mother by placental transfer. During the last trimester, the fetus accrues about 50–70 mg/day of DHA. Both maternal DHA intake and circulating DHA concentrations are important determinants of fetal blood concentrations of DHA.
- Recommendations – pregnant women have an increased need for essential omega 3 fatty acids compared with women who are not pregnant[55]. Supplementation is imperative because pregnant women often do not get adequate omega 3 fatty acids when seafood, the major source, is restricted to two or fewer servings per week. Supplementation is particularly critical for pregnant women who do not have any means of getting omega 3 oils from their diets[56]. No requirements have been established for omega 3s for pregnant women.
- As macronutrients, omega 3s are assigned an AI and AMDR (acceptable macronutrient distribution range) instead of RDAs. The AI for omega 3s is 1.1 g/day for women[57,58], while the AMDR is 0.6–1.2% of total energy[59]. The physiological potency of the various omega 3s differs so widely that it is not possible to estimate one AMDR for all omega 3 fatty acids. Approximately 10% of the AMDR can be consumed as EPA and/or DHA. At the time of this writing, lack of evidence prevents [the] setting [of] a UL

(upper tolerable limit) for omega 3 fatty acids[59,60].

- The unified recommendation for pregnant and lactating women is 1200 mg of omega 3s daily. Supplementation is the only way to achieve this, and supplements may be fish oil supplying EPA and DHA or algae-derived DHA in combination with fish oil.
- Omega 3 supplementation in food has become a significant part of food fortification, with food companies around the world launching omega 3 fortified bread, mayonnaise, pizza, yogurt, orange juice, pasta, milk, eggs and confections. In the US, infant formula is regulated as a unique food category by the Food and Drug Administration, and omega 3 enrichment is mandated for all infant formula. This practice increasingly is being adopted by food regulators around the world.
- Excesses – consuming either large or inadequate amounts of omega 3 fatty acids during pregnancy and lactation seems unwise because of the potential for adverse effects on infant development. Whereas evidence shows the detrimental effects of omega 3 deficiency on the health status of babies[61], no evidence has established the effect of consuming excessive amounts of omega 3 during pregnancy or lactation.

Selenium

- General – selenium is an essential trace mineral required only in small amounts[62,63]. Selenium forms selenoproteins with an antioxidant role to prevent cellular damage from free radicals. Selenoproteins also help regulate thyroid function and play a role in immunity[64–66]. The major dietary sources of selenium are plant foods. The selenium content of soil affects the selenium levels in food (plant or animal origin) and food distribution across regions with disparate levels of selenium in the soil helping prevent selenium deficiency in people living in low-selenium geographic areas. Selenium deficiency is, however, a common issue with populations that consume only foods grown locally in low selenium regions.
- Recommendations – pregnant women have a higher need for selenium than do most adults. Food labels do not list selenium content, and the selenium content of foods varies widely depending on food type and area where grown. Because Brazil nuts are unusually high in selenium, with as much as 544 μg per ounce (780% DV [daily value]), it is wise to eat Brazil nuts only occasionally.
- The RDA for pregnant and lactating women is 60 μg and 70 μg selenium, respectively. Information is insufficient to establish an RDA for infants; however, an AI of 15 μg selenium has been established for 0–6-month-old healthy infants who are breastfed and 20 μg for infants 7–12 months old.

Deficiency

- Low selenium levels may be linked to pre-eclampsia, first-trimester miscarriages and recurrent miscarriages[67]. The researchers reported that women with low levels of selenium had up to four times the risk of developing these conditions.
- Selenium deficiency occurs in regions with low selenium soil content,

notably in China and parts of Russia. Selenium deficiency usually does not manifest in illness; rather, it weakens the immune system, rendering the body vulnerable to illnesses caused by other nutritional, biochemical, or infectious diseases. Three diseases are associated with severe selenium deficiency in children: Keshan disease that results in an enlarged heart with poor function, Kashin-Beck disease that results in osteoarthropathy, and myxedematous endemic cretinism that results in mental retardation.

- Women with Crohn's disease and surgical removal of part of the stomach have increased susceptibility to selenium depletion or deficiency, which further exacerbates neurological effects of iodine deficiency on thyroid function[64,68]. Malabsorption owing to HIV/AIDS can deplete levels of selenium, and selenium deficiency is associated with decreased immune cell counts, increased disease progression, and mortality in HIV/AIDS populations[69,70], so much so that physicians often prescribe selenium supplements as part of an overall maternal nutrition plan for such patients.

Supplementation

- Selenium occurs in foods as selenomethionine and is incorporated into body proteins along with the methionine. On the market, selenium supplements often are based on sodium selenite and sodium selenate, forms that are not absorbed or utilized as optimally as is the organic form. "High selenium yeasts" contain as much as 1000–2000 μg of selenium organically bound per gram[71] and are more effective because of greater bioavailability. Only high-selenium yeast has been shown to lower cancer incidence and prostate specific antigen (PSA) and is recommended over the organic form for supplementation.
- European crop survey data indicate selenium levels in British and European wheats to be generally 10–50 times lower than in American or Canadian wheats. Thus, foods made from such wheat, a staple grain for example, would fail to help consumers meet the recommended intake of selenium. Despite this, no uniform regulations mandating enrichment of staple foods with high-selenium yeast are available on a worldwide basis.
- Excess – high blood levels of selenium (>100 μg/dl) can result in a condition called selenosis[72], the symptoms of which include gastrointestinal upsets, hair loss, white blotchy nails, garlic breath odor, fatigue, irritability and mild nerve damage[62]. Selenium toxicity is rare.

Vitamin A

- General – vitamin A is a fat soluble nutrient that exists in several forms (known as retinoids), including retinol, retinal, retinoic acid and retinyl ester. Synthetic analogues also exist, as do about 600 provitamin A carotenoids that represent precursors of vitamin A. Only about 10% of the latter compounds can be converted to vitamin A, although both types are found in nature. Vitamin A is primarily present in animal-origin food stuffs, especially liver, dairy products (whole milk, cheese and butter), and fish, such as tuna, sardines and herring. Fish liver oils, in particular cod liver oil, are also high in vitamin A content. Carotenoids are synthesized by plants and found mainly in fruits and vegetables, the most abundant of which is beta carotene that has the greatest amount of provitamin A activity. Vitamin A is essential for vision, reproduction, immunity, skin and epithelial integrity, and the transduction of light into neural signals in the eyes. It is especially critical during periods wherein cells rapidly proliferate and differentiate.

- DRI – in 2001, the Institute of Medicine revised the RDA guidelines for vitamin A expressed as retinol activity equivalents (RAE)[73]. No such action was taken for carotenoids because they are not considered essential nutrients. The RDA for pregnant women is 750–770 μg RAE in which 1 μg of retinol equals 12 μg beta carotene. The tolerable upper intake (UL) is 3000 μg for preformed vitamin A. Doses of vitamin A present in supplements are usually reported in IU and need conversion to RAE to determine whether they meet the RDA.
- During pregnancy, requirements are predictively higher because of fetal growth needs. In well-nourished women, diet suffices to provide suggested requirements[74].

Deficiency

- Although deficiencies are rare in industrialized nations, they represent a major problem globally, and are most commonly manifest as night blindness and xeropthalmia. In pregnancy, especially during the third trimester, vitamin A starts to accumulate in the fetus. No correlation between deficiency and malformed infants has been established. After the first few weeks of life, neonatal deficiency may develop if the breastfeeding mother is vitamin A deficient.
- Toxicity – case reports of offspring with anomalies after mothers took high levels of vitamin A[75,76] have led to some concern about high doses during pregnancy. Although no consistent pattern of anomalies has been observed[74], caution has been raised against any dose greater than 2500 IU. The literature on anomalies is unclear, because doses have varied from 10,000 IU daily to 50,000 IU in the form of a supplement. Even when 10,000 IU was the dose utilized, the literature is divided as to whether increases in anomalies are seen[26,27]. In contrast to the equivocation regarding the effects of excess vitamin A, the literature is clear that retinoid analogues cause birth defects or embryonic demise, with pronounced teratogenicity ascribed to synthetic analogue 13 cisretinoic (isotretinoin), a compound used in a specific medication (Accutane) that is highly effective for severe cystic acne and may be used by women of reproductive age. The US FDA requires that female patients be informed that two types of contraception be used when retinoid drugs are prescribed[77]. Pregnancy should be avoided during drug administration and for 3 months thereafter, because the likelihood of deleterious effects is among the highest of the known teratogens. In contrast to the retinoids, toxicity because of beta carotene and other keratonoids in food is not considered a concern, and for this reason no UL has been set.

Supplementation

- Many authorities are of the opinion that vitamin A supplementation is not warranted in healthy women except perhaps in developing countries were deficiency is a problem. In such instances, the maximum daily supplement of vitamin A advised by World Health Organization is 300 μg or 10,000 IU[26,27].

Vitamin B3 (niacin)

- General – vitamin B3 or niacin (also known as, nicotinic acid and vitamin PP) is an essential human nutrient, other forms of which include the corresponding amide, nicotinamide or 'niacinamide'. The terms niacin, nicotinamde and vitamin B3 are often used interchangeably to refer to any member of this family of compounds, since they have the same biochemical activity. Niacin is converted to nicotinamide *in vivo* and, although the two are identical in their vitamin activity, nicotinamde does not have the same pharmacological effects as niacin. Nicotinamide does not reduce cholesterol or cause flushing. Niacin is involved in DNA repair and the production of steroid hormones in the adrenal gland.
- Niacin is found in a variety of foods including liver, chicken, beef, fish, cereal, peanuts and legumes, and is also synthesized from trytophan, which is found in meat, dairy and eggs. Niacin may also be derived from seeds and nuts, whole grains and enriched whole grain products, as well as from mushrooms and spent brewer's yeast (Vegemite or Marmite).
- The recommended daily allowance of niacin is 14 mg/day for women and 18 mg/day for pregnant or breastfeeding women. The upper limit for adult women is 35 mg/day, which is based on flushing as the critical adverse effect.
- In larger doses, niacin can reverse atherosclerosis by lowering low-density lipoprotein (LDL) and favorably affecting other compounds. In general, niacin status is tested through urinary biomarkers, which are believed to be more reliable than plasma levels.

Deficiency

- Severe deficiency of niacin is associated with a pandemic deficiency disease called pellagra. Pellagra is characterized by diarrhea, dermatitis and dementia, as well as 'necklace' lesions on the lower neck, hyperpigmentation, thickening of the skin, inflammation of the mouth and tongue, digestive disturbances, amnesia, delirium and eventually death, if left untreated. Niacin deficiency is rarely seen in developed countries, but it is apparent in conditions of poverty, malnutrition and chronic alcoholism. It tends to occur in areas where people eat maize or corn – the only grain low in niacin – as a staple food. A special cooking technique called nixtamalization is employed to increase the bioavailability of niacin during maize meal or masa production.

Supplementation

- The RDA for niacin is 18 mg for adult men and 14 mg for adult women, although more is needed for nursing (20 mg) and pregnant women (18 mg).

- Pharmacological doses of niacin (1.5–6 g/day) often cause skin flushing and itching, dry skin, skin rashes and gastrointestinal complaints, such as dyspepsia (ingestion). High-dose niacin may also elevate blood sugar, thereby worsening diabetes mellitus and gestational diabetes.
- Niacin at doses used in lowering cholesterol (>35 mg/day) has been associated with possible consequences for infant development, nausea and vomiting in pregnant women.

Vitamin B6

- General – vitamin B6 consists of a family of seven substituted pyridine derivatives, the major forms in tissue being pyridoxal phosphate (PLP) and pyridoxamine phosphate (PMP). The others are: pyridoxine (PN), the form that is given as vitamin B6 supplement; pyridoxal 5'-phosphate (PLP), the metabolically active form; pyridoxamine (PM); pyridoxamine 5'-phosphate (PMP); and 4-pyridoxic acid (PA), the catabolite which is excreted in the urine.
- All forms except PA can be interconverted. Bioavailability of B6 supplements is in excess of 90%, whereas food vitamin B6 is >75% bioavailable. Cereals, meat, fish and non-citrus fruits are the major contributors of vitamin B6. Rich sources include fortified cereals, beef liver and other organ meats.

Deficiency

- Overt clinical symptoms attributable to vitamin B6 deficiencies are rare. Numerous studies have assessed a variety of populations in an attempt to determine deficiency. Lack of supporting clinical evidence of deficiency makes it questionable whether biochemically defined relative deficiencies represent true vitamin B6 deficiencies.
- Pregnancy – maternal levels of B6 status as found in plasma/whole blood decrease as the gestation advances but more so in the last trimester. Whether observed changes represent poor vitamin status or physiological changes is not clear, because no clinical evidence of significant problems in vitamin B status is available even in the presence of levels of status markers. The only evidence suggesting doses in the range of 4–10 mg of pyridoxine are the few studies suggesting the APGAR scores of infants are higher when mothers take supplements containing more than 5 mg of pyridoxine[26,27].
- The limited number of studies regarding benefits of vitamin B6 and pregnancy complications are inconclusive, although these same supplements have been used to treat hyperemesis gravidarum for decades, usually in doses of 100 mg or more. Today pyridoxine is usually but not always given in combination with doxylamine. Controlled studies show a very effective response to pyridoxine, although the placebo often is equally as effective. In summary, supporting evidence for its effectiveness when administered alone is weak[26,27].
- Teratogenicity – older literature suggests that vitamin B6 can exert teratogenic effects of a variable nature in animals; however, this concern is of a limited nature in humans, primarily based on the extensive literature

relating to the combination of the antihistamine doxylamine and pyridoxine that was marketed worldwide for years for use during pregnancy as a treatment against nausea and vomiting.

Supplementation

- DRI – the RDA for the adult was set at 1.3 mg/day. The RDA for pregnant and lactating women was increased to 1.9 and 2.0 mg/day, respectively, based on an average estimated accretion by the placenta and fetus in addition to increased maternal metabolic demands through pregnancy of about 0.25 mg/day, mostly occurring in the second half of gestation. The median intake from food sources in the US was estimated at 2 mg for men and 1.5 mg for women of vitamin B6[26,27].
- Effect of excess – the IOM has set an upper limit of 100 mg/day of vitamin B6. Severe sensory neuropathy has been reported in individuals ingesting very large doses of pyridoxine (1–6 g/day) with some evidence of adverse effects at 500 mg/day. No credible adverse effects have been noted at doses of 300 mg or less[26,27].

Vitamin B12 (cobalamin)

- General – vitamin B12 (cobalamin) is an important co-factor for two key enzyme reactions – methionine synthase and L-methylmalonyl-CoA mutase. It is found only in foods of animal origin, and major dietary sources include but are not limited to red meat, chicken, fish, milk, yogurt, cheese and liver[78]. Dietary B12 possesses only approximately 50% of the bioavailability of crystalline synthetic B12[43]. Although synthetic B12 is used to fortify certain food products such as breakfast cereals, it is not one of the nutrients required to be added to the so-called enriched grain products used in the US and Canada[26,27].
- DRI – clinical symptoms of deficiency (neurological, cognitive, hematological) usually occur with serum or plasma levels < 148 pmol/l; biochemical signs of inadequacy begin when plasma/serum blood levels are <221 pmol/l. Accordingly, recommended cutoffs for diagnosing B12 deficiency and depletion are < 148 pmol/l (200 pg/ml) and <221 pmol/l (<300 pg/ml) in plasma or serum.

Deficiency

- General population – deficiency primarily results from low intake of animal-based foods or food-bound vitamin B12 with infrequent causation by pernicious anemia. The former deficiency most usually occurs in individuals older than 50 years of age, whereas malabsorption results from either decreased acid reduction or pancreatic insufficiency. Pernicious anemia results from the lack of intrinsic factor required for uptake of B12 into the intestinal lumen[78]. It is rarely seen in women of reproductive age.
- Population-based data from the US indicate that 16% of individuals aged 19–50 years of age are either deficient (< 148 pmol/l) or marginal (149–221 pmol/l). Avoiding consumption of all animal-based foods (strict vegan) is not necessary to develop deficiency, and deficiency is more prevalent in the

general population than previously thought. For example, a Canadian study of 10,622 women aged 15–46 found an overall prevalence of B12 deficiency of 7.4%[79], with a chemical deficiency (<125 pmol/l) present in 6.9% of non-pregnant women, 5.2% of those pregnant <28 days, and 10.1% of those pregnant >28 days.

- Infants commonly become B12 deficient because their mother's diet was restricted before pregnancy, during gestation, or during lactation[80]. Thus, pregnant women who limit consumption of animal-based products may have impaired vitamin B12 status that negatively affects delivery of sufficient B12 to the embryo[81]. Prenatal vitamin B12 supplementation is advisable for women who are not willing to increase their consumption of vitamin B12-containing food.
- Teratogenic effects – vitamin B12 deficiency is an independent risk factor for pregnancy complications and birth defects. Most often these defects mimic those found with folic acid deficiency. In particular, Irish investigations have provided strong support for a correlation between lower vitamin B12 status, independent of folate status, and an increased NTD risk in a population not exposed to folic acid fortification or supplement[82]. Specifically, Irish mothers with serum B12 concentrations in the lowest quartile had a 2–3-fold higher AOR [adjusted odds ratio] for having an NTD-affected infant compared to those in the highest quartile.
- Breastfeeding mothers who are vitamin B12 deficient are liable to have infants who, over time, show lethargy, irritability, or developmental delay if their mothers adhere to a vegan or vegetarian diet. Neonatal neurological abnormalities second to subacute combined degeneration of the spinal cord may be irreversible.

Supplementation

- The RDA for vitamin B12 is 2.4 μg/day[43]. During pregnancy, this increases by 0.2 μg/day, so that the RDA for pregnancy was set at 2.6 μg/day by the IOM in 1998.
- Effect of excess – there is no evidence that excess vitamin B12 has a teratogenic effect, and no reports of vitamin B12 toxicity exist in the general population or during pregnancy.

Vitamin D

- General – there are two chemical forms of vitamin D. Vitamin D2, ergocalciferol, is synthesized by plants. Vitamin D3, cholecalciferol, is synthesized by mammals. Dietary sources of vitamin D are numerous and primarily come from animal origin (liver oils and fatty fish such as salmon, herring and tuna). Many foods, including milk, yogurt, cheese, margarine and some brands of breakfast cereal are fortified with vitamin D. In the US, milk and selected brands of orange juice are fortified with 100 IU vitamin D per 8 oz.
- The primary source of vitamin D is the skin where ultraviolet light-B converts 7-dehydrocholesterol under the influence of exposure to sunlight. This is of particular importance for individuals living in northern latitudes with limited sunlight, in populations with heavily pigmented skin,

and in populations who cover exposed skin for religious or cultural reasons[83]. Serum 25-(OH) D3 is the best indicator of vitamin D status. Deficiency is defined in adults as serum/plasma concentrations of 25-(OH) D3 <50 nmol/l, although it is recognized that various investigators define this value differently.

- DRI – no RDA has been established because of lack of sufficient data; however, the AI for men and women (19–50 years of age) is 5 μg/day (200 international units)[43]. This value may be too low and possibly will be modified in the near future.

Deficiency

- General population – in non-pregnant women, vitamin D deficiency is not uncommon, although prevalence rates differ markedly on a racial basis (42% in African American women vs. 4% in white women). Part of this discrepancy may be on a genetic basis, because prevalence remains high (19%) among African American women who consume >200 IU vitamin D per day from supplements and eat fortified cereal >3 times/week. Such findings suggest that the AI may need adjustment on a "racial/ethnic basis"[26,27].
- Pregnancy – in general, 25–30 g calcium is transferred from the mother to the fetal skeleton, primarily during the latter stages of pregnancy. Under these circumstances, vitamin D deficiency during pregnancy may result in adverse outcomes in the fetus that persist long term, including rickets. Numerous studies of the maternal-fetal dyad have been conducted in the US and the UK from which there are several general conclusions: (1) pregnant women and their neonates who live in northern latitudes are at higher risk of vitamin D deficiency than are those who live in southern latitudes; (2) women with darker skin colors exhibit greater levels of deficiency than do women with lighter skin colors (this includes African Americans and many Hispanics of mixed race in the US and Africans, Indians and Caribbean islanders in the UK); (3) seasonal variations contribute little to vitamin status changes, particularly in women of color and their neonates; (4) current formulations of prenatal vitamin supplements may be inadequate to achieve desired serum levels of 25-(OH) D3; and (5) interconceptional intervals are too short.

Supplementation

- Evidence is rapidly accumulating that, in contrast to published guidelines, vitamin D supplementation may be necessary for all patients to achieve the desired 25-(OH) D3 concentration of >50 nmol/l in pregnant women. As recently as 2008, Wagner *et al.*[84] recommended assessing maternal vitamin D status by measuring 25-(OH) D3 concentrations in pregnant women to be followed by supplementation in the case of deficiency. However well meaning this advice, it is, in the opinions of the authors, impractical. We believe, from a public health point of view, that supplementation of higher amounts is more practical, because vitamin D in therapeutic doses does not appear toxic. A dose of 250 μg/day appears safe and represents the amount that can be synthesized only by total body sun exposure.

Zinc

- General – another essential trace element is zinc, which plays a structural and/or catalytic role in more than 300 enzymes and proteins involved in growth and development, neurological function, the immune system and reproduction.
- Bioavailability of zinc varies widely, with rich sources found in red meat, oysters and whole grains – primarily in the germ and bran, so milling or polishing grains such as rice leads to loss of most of the nutrients. Bioavailability is improved in vegetarian diets containing refined or fermented grains.
- Most zinc is stored in skeletal muscle and bone with primary losses in feces and only a small amount in urine, skin and hair. Zinc status indicators are lacking.
- DRI – the RDA is 8 mg for adult women, assuming 70% is absorbed from meat. In contrast, World Health Organization publishes two RDAs for adults, 5.6 mg/day for meat eaters and 18.5 mg/day for vegetarians. During pregnancy, the RDA is increased to 11 mg for adult women and 13 mg for pregnant teenagers. The upper limit is 40 mg/day for women and 34 mg/day for teenagers[85].

Deficiency

- Zinc deficiency is rare in North America but may be prevalent in other countries (Middle East and Latin America) and associated with impaired growth and development. Zinc bioavailability from vegetarian diets is lower than from non-vegetarian diets because vegetarians do not eat meat, which is naturally high in bioavailable zinc. Additionally, vegetarian diets are typically high in legumes and whole grains that contain phytates binding zinc and inhibiting its absorption. Vegetarians sometimes require as much as 50% more of the RDA for zinc than do non-vegetarians.
- Results of studies of poor zinc status in pregnancy are unclear, with adverse fetal outcomes being reported as congenital anomalies and preterm deliveries along with pre-eclampsia, hemorrhage, infections and prolonged labor. Randomized controlled intervention trials in pregnancy are mixed, in that half show positive effects and half show no effects in terms of growth retardation, preterm delivery, and increased birth weight.

Supplementation

- Evidence supporting the benefits of supplementation is mixed, although it is believed that supplementation with 15 mg/day in pregnancy may provide some benefit, especially for those whose diets contain food which have poor zinc availability[26,27].
- Teratogenicity – it is not clear whether zinc deficiency causes human structural malformations[86], because much of the early literature fails to consider decreased maternal folate levels as a confounder[26,27].'

SUMMARY

This chapter reminds readers of the important relationship between maternal diet and fetal outcome, comments on the difficulties of obtaining an adequate and nutritious diet in a modern society, and stresses that dietary inadequacies that existed before pregnancy cannot be rectified once pregnancy has begun. This latter point is illustrated by consideration of folic acid, which only recently has been recognized as being required in pre-pregnancy so the mother has adequate amounts during the critical time of neural tube formation in the first 28 days after conception.

A major problem facing today's health-care practitioners in terms of counseling their pregnant patients regarding diet and nutrition is that the available source documents vary so widely in their points of view. This is particularly true in the literature relating to supplementation, in which it is the rare article that mention its biases. This is unfortunate, because the biases and the context around which an article is written may never be understood by the public. For example, as our editorial team was finalizing this chapter, the senior author (LK) received a newsletter from an internationally renowned university directed to women. The lead article stated that obtaining one's micronutrients in pregnancy through diet requires planning, patience and knowledge about foods, in particular nutrient-dense foods (those packed with vitamins and minerals with relatively few calories). The article listed 18 nutrient-dense foods, most of which are not eaten by the general population, let alone pregnant women: leafy vegetables such as chard, collard greens, kale and mustard greens; brussels sprouts; crimini and shitake mushrooms; papaya; flax seeds; garbanzo and pinto beans; almonds; barley; oats; quinoa; halibut; and venison. Sample menus listed sliced kiwi, edamame, walnuts and salmon (commonly listed as a fish that supplies omega 3 oil, even though mackerel is a much richer source). We believe that this advice, however well meaning, is disingenuous at best, because it does not address the real needs of patients but rather presents them with theoretical solutions for problems over which they have little control.

That diets have changed in the past 150 years was described in great detail in a three-part series in the *Journal of the Royal Society of Medicine*[87–89]. Here the authors were careful to relate such changes to the social context that surrounded them, which included an increasing reliance on transportation as opposed to walking, the advent of refrigeration and food preservation, and incorporating ethnicities into UK society who brought their foods with them.

Physicians must view pregnant patients (and the diets they ingest) in the context of the society in which these patients live. This includes nuclear households of one or two, the necessity of two-income households, the demands of work and outside interests on available time, and the easy availability of food prepared outside the home. It is unrealistic to think that pregnant women eat all meals prepared at home, have the time or resources to shop and look for the exotic foods that may be nutrient dense and vitamin rich, and never resort to fast food or 'take out'. Also, it is important to remember that food choices often are based on inherent tastes, that tastes are at least to some degree related to culture, and that cultural food choices are intergenerational.

So where does that leave the physicians and the patients they serve? The simple answer relates to supplementation. If one is not inherently biased against supplementation, it is not difficult to envision circumstances whereby supplementation becomes a lifelong habit in which supplements change as the individual ages and life circumstances change. Thus, discussions of supplementation need not be confined to pregnancy alone but can be initiated during active teenage years and certainly when marriage and childbearing are anticipated.

Once supplementation is begun, it can be continued into lactation and the time between pregnancies, and maintained through and after menopause into the senior years with the caveat that supplements which are ideal for a teenager need to be changed for the geriatric population.

Although individuals eat to taste, they generally do not eat one or two nutrients on an exclusive basis. Thus, it is disheartening to see reports of pregnant women receiving high doses of single vitamins in the hope that this will be of therapeutic value. In the same sense, it is not surprising when trials using high doses of single vitamins do not achieve their desired goals. If health-care professionals advise patients to eat a balanced diet consisting of fruits, vegetables, meat, fish, grains, fat, etc., they should have no difficulty in strongly advising them to select high quality multivitamin, mineral and micronutrient supplements that represent a balanced palate of what is needed before, during and after pregnancy.

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