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Prenatal Nutrition: The Role of Diet and Supplementation

Nutritional status during pregnancy and lactation is considered paramount for the long-term health of both mother and child. Yet, despite nearly universal agreement in the health care community on the importance of diet and nutrition during pregnancy, there exists no similar agreement as to the specific dietary advice to give to pregnant women, and whether nutrient supplementation should be advised. This confusion stems in part from the wider discussion amongst health care providers about what constitutes a healthy dietary pattern (for any subject), and whether the routine use of vitamin and mineral supplementation should be used to bridge the gap between optimal dietary advice and the individual's actual dietary habits.

Nonetheless, it is abundantly clear that neither mother nor infant are protected from an inadequate diet during pregnancy.[1] Today, the emerging knowledge of genomics and epigenetics adds to what has already been discovered about basic nutrient needs during fetal development, raising the stakes even higher when making nutrient recommendations to ensure optimal pregnancy and infant outcomes. In this paper, we summarize for the clinician the current evidence for making specific nutritional recommendations for healthy pregnant women in developed countries, and compare this evidence with currently available guideline recommendations. This discussion will also touch upon the role of pre-conception nutrition (for both mother and father) related to both pregnancy and infant outcomes; as well as the use of dietary changes and/or supplementation as preventative or interventional tools for certain common complications of pregnancy (e.g., preterm birth, low or high birth weight, poor fetal development, gestational diabetes or pregnancy hypertensive disorders). Included are suggestions for supplementing key prenatal nutrients, when appropriate, and for improved adherence to supplemental regimens.

Nutrition and Pregnancy Outcomes

There are clear and well-documented relationships between malnourishment and poor outcomes during pregnancy or infant development in under-developed countries. Worldwide, maternal undernutrition contributes to 800,000 neonatal deaths every year.[2] Children surviving maternal undernutrition often later succumb to the burden of stunted development, suboptimum breastfeeding and further undernutrition. The tragic result is 3.1 million childhood deaths annually.[3] Deficiencies in the intake of clean drinking water, protein, vitamin A, iodine, iron, folate and zinc play a major role in these outcomes. While this global perspective is outside the scope of this overview, we remain mindful of its impact (and the intervention programs used to combat these tragedies) as we discuss the role of nutrition during pregnancy.

In developed countries, where undernutrition is much less prevalent and severe, the relationship between specific dietary patterns and pregnancy outcomes is not as easy to discern. In fact, while observational data relating diet, pregnancy and maternal/infant outcomes are numerous; high-quality intervention studies testing diet and pregnancy outcomes are uncommon in healthy women living in developed countries.[4,5] Recently, researchers from the University of Newcastle (NSW, Australia) have reviewed and analyzed the dietary patterns of pregnant women in relation to the dietary recommendations within developed countries over the past 60 years, including the United States and Canada, the United Kingdom, Western Europe, Japan and Australia/New Zealand.[6,7] In the United States and Canada, pregnant women in their first trimester appear to consume a similar diet and number of calories (~2,100 kcal) as non-pregnant women.[8] Traditional dietary recommendations for energy

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intake range widely (~1,800-2,400 kcal/day) depending on height, activity level and stage of life. In keeping with most developed nations, the Institutes of Medicine (IOM) recommends increasing daily energy intake by 340 kcals and 450 kcals from the baseline energy intake in the second and third trimesters, respectively. These guidelines are also tied to recommended gestational weight gains, based on pre-pregnancy BMI (See Table 1).

Table 1:
Recommended Gestational Weight Gains

If Pre-pregnancy BMI Is: (kg/m2)	Gain This Amount: (singleton)	Gain This Amount: (twins)
< 18.5	28 to 40 lbs	Ask your doctor*
18.5 to 24.9	25 to 35 lbs	37 to 54 lbs
25 to 29.9	15 to 25 lbs	31 to 50 lbs
≥ 30	11 to 20 lbs	25 to 42 lbs

Assuming a 1- to 4.4-lb weight gain during the first trimester.
*Insufficient evidence was available to make a determination.

— Source: Institute of Medicine

Today, however, more women enter their pregnancy overweight or obese, which can lead to a number of pregnancy- and offspring-related complications such as gestational diabetes, pre-eclampsia, pre-term birth, cesarean delivery and structural birth defects.[9,10] According to the Centers for Disease Control and Prevention (CDC) surveillance data, 24.7% of women are obese (BMI>30) during pregnancy, and another 25% are overweight (BMI 25.0-29.9).[11] Ideally, health care providers should help women reach a healthy BMI prior to conception. Since women often do not seek health care until after they are aware of their pregnancy, limiting excess weight gain during pregnancy in subjects who are overweight or obese at the time of conception should be stressed. According to the American College of Obstetricians and Gynecologists (ACOG), gestational weight gain below the IOM recommendations among overweight pregnant women appears to have no negative effect on fetal growth and neonatal outcomes.[12] Diet and lifestyle measures used to restrict weight gain in obese subjects during pregnancy has been reviewed and found to be successful in reducing some complications, especially gestational diabetes.[13,14]

Dietary Patterns for Successful Pregnancies

As mentioned previously, the general dietary habits of pregnant women in developed countries are similar to their non-pregnant peers. In the United States, this is known as the Standard American Diet (SAD), often cited as being strongly correlated with increased risk for many chronic disease patterns. Conversely, most dietary recommendations for improving prenatal health include the basic fundamentals of a healthy dietary pattern for all individuals: ample fluid intake, sufficient protein and fiber intake, and appropriate levels of healthy carbohydrates and fats. These recommendations usually include such things as lean animal and plant-based protein, fresh fruits and vegetables, whole grains, and healthy fats and oils.[15] The dietary pattern that, in our analysis, best meets the overall pattern of healthy dietary signals and has been widely tested as an interventional strategy amongst Western subjects is the Mediterranean Diet (MedDiet). This dietary pattern, or modifications of this pattern, is suitable and safe for all pregnant women.

In a study of women from 10 different Mediterranean countries, higher adherence to a MedDiet pattern (measured by a validated dietary questionnaire) was statistically correlated with a 35% reduction in gestational diabetes, as measured by an oral glucose tolerance test performed between the 24th-32nd weeks of gestation.[16] In addition, glucose tolerance was measurably better in the pregnant women without GDM, when higher adherence to the MedDiet was maintained. Pre-pregnancy adherence to a healthy eating pattern (e.g., MedDiet, Dash Diet or similar) is also strongly correlated with a lower risk of gestational diabetes.[17] In addition to its potential to improve glucose and insulin signaling, adherence to a MedDiet pattern during pregnancy has been linked, in several studies, with a reduced risk of asthma and other atopic conditions in offspring.[18,19,20]

Foods to Limit or Avoid During Pregnancy

- Processed foods and meals from fast food restaurants
- Processed lunch meats (may contain nitrates) and soft cheeses (often unpasteurized)
- Artificial colors, preservatives and flavorings
- Alcohol and caffeine
- Conventionally-grown produce, in favor of organic produce
- Fish known to contain high amounts of mercury (tilefish, shark, swordfish and king mackerel) and shellfish

Macronutrient Recommendations

Water

Water comprises 55-65% of total body weight in most human beings. It plays an important role in pregnancy as water assists in significantly building blood volume. Blood volume increases beginning in the first trimester at six to eight weeks and peaks with little change beyond approximately week 34. This increase is primarily in plasma, not red cell mass, which contributes to a potential decrease in hemoglobin concentration and increases the risk for maternal anemia, among other concerns.[21,22] During pregnancy, the current recommendation is 64 to 80 oz (8-10 glasses) daily of water for singletons.[23] It is important to reinforce that this amount should primarily be consumed as pure water; although a portion of the targeted fluid intake can include water-based soups and broths, herbal teas or low-sugar fruit juices. Caffeinated drinks, zero-calorie sodas and sugary beverages should be avoided during pregnancy.

Protein

According to the IOM, maternal protein requirements are much higher in pregnant women than their age-matched peers.[24] Owing to the expanded protein requirements of the fetus, uterus, expanded maternal blood volume, placenta, extracellular fluid, and amniotic fluid, the IOM recommends 71 g of protein/day. This is 25 g higher than the 46 g/day recommended for non-pregnant women weighing 57 kg (125 lbs). Recognizing that nearly half of all women enter pregnancy overweight or obese, these recommendations are often difficult to interpret for specific patients. Even so, according to data compiled by researchers at the University of Newcastle, pregnant women in the United States and Canada consume, on average, 87 g of protein per day (~16.5% of calories).[7] While this level appears to exceed the IOM's recommendation of 71 g, it is still well below the higher end of the IOM's protein intake range of 10-35% of energy. Our recommendation for protein consumption during pregnancy (as in men and non-pregnant women) is 20-30% of total calories from both animal and plant-based sources.

Many prenatal clients report that early morning protein intake and consistent and reasonable intake throughout the day, particularly when consumed with carbohydrates, can positively impact both morning sickness and blood glucose levels. Simple targets include nuts, seeds, legumes, grains, eggs, or lean animal protein at every meal. When working with vegan or vegetarian prenatal clients, it is beneficial to track and analyze ongoing protein intake and consider supplementation if a specific dietary protein deficiency exists. Counseling to increase protein intake, protein support products, or amino acid supplementation may be used to address this concern.[25,26]

Carbohydrates

The current IOM recommendation for carbohydrate intake during pregnancy are the same as they are for all adults, 45-65% of daily energy intake (allowing up to 25% of energy intake from "added sugars"). It is our recommendation that all individuals, including pregnant women, consume only 40-50% of their total energy as carbohydrates from healthy whole grain, vegetable, and fruit sources, and eliminate the regular consumption of added sugars. Health care providers should advise women about the glycemic impact of carbohydrates (glycemic index, glycemic load, fiber, etc.) and the role they play in altering metabolic status, especially during pregnancy. Impaired glucose tolerance, maternal gestational hyperglycemia, metabolic syndrome, gestational diabetes and offspring obesity (See sidebar on fetal programming) are all factors for concern in monitoring specific carbohydrate intake for prenatal clients.[27] Dietary interventions that emphasize a low glycemic index appear to be more successful for gestational diabetes reduction than those that merely emphasize carbohydrate restriction.[28] Most vegetables are considered to have low or very low glycemic impact, with the exception of potatoes, sweet potatoes, beets, and corn. Low glycemic fruits include bananas, berries, citrus fruits, apples, and pears. Grains with low glycemic impact include brown rice, oats, quinoa, and whole wheat. Counseling clients to remove or minimize consumption of simple and complex sugars and to avoid fruit juices can have a beneficial impact on blood glucose levels and lower the risk for gestational metabolic complications.

Fiber

The typical Western diet is generally low in dietary fiber. According to the IOM, only 3% of Americans consume the recommended 14 g/1,000 calories of daily dietary fiber. On average, Americans consume about 7 g of fiber for every 1,000 calories eaten.[29] According to data compiled by researchers at the University of Newcastle, pregnant women in the United States and Canada consume, on average, only 19 g/day of dietary fiber, 33% below the current IOM recommended intake for fiber during pregnancy (28 g daily).[7] Among a wide-range of benefits, dietary fiber is important to modulate the glycemic impact of foods, provides food for certain healthy commensal gut organisms (as a prebiotic), improves bowel function, and helps normalize healthy blood pressure. In a study of over 1,500 women living in Washington, those in the highest quartile of dietary fiber consumption (>21.2 g/day) had a 72% lower risk (RR=0.28) of preeclampsia, as compared to those in the lowest quartile of dietary fiber intake (<11.9 g/day).[30] The recommendation to increase fiber in the diet (or through fiber supplementation), along with increased water consumption and moderate physical activity, is considered basic therapy for prenatal constipation.[31] Common fiber sources used in supplemental products include psyllium, bran, flax seeds, inulin, fructooligosaccharides, chicory root, beta glucans, certain fruit pectins, acacia, and guar gums. Each ingredient has different total, soluble, insoluble and fermentable fiber content. Using combinations of multiple fiber sources may be more efficacious and tolerable for a wide range of subjects.

Fatty Acids

Healthy fats and oils are fundamental to the diet during pregnancy for a number of reasons, most notably for the development and function of the fetal central nervous system. Fatty acids are integral to the structure of all cell membranes and therefore support the structural integrity of most tissues, including the gastrointestinal tract, respiratory and immune systems. Fatty acids can also be transformed into signaling molecules (e.g., prostaglandins) that can modulate various cellular functions, especially those related to the inflammatory response.[32]

Maternal fat intake and measures of fatty acid stores have been documented to affect cognitive development, behavior and mood swings, in both mother and child.[33,34] Although there appears to be a need for an appropriate intake of all fatty acids (saturated, monounsaturated, polyunsaturated, and omegas-3, 6 and 9); epidemiological and animal study data have highlighted the particular need for docosahexaenoic acid (DHA; 22:6 omega-3) during pregnancy.[35] While conversion from the essential omega-3 fatty acid alpha linolenic acid (LNA; 18:3, omega-3) is possible (though limited), most body stores of DHA are provided by consuming seafood or DHA-containing supplements.[36] Even though the need for DHA consumption during pregnancy is well-known, and supplementation is often recommended, pregnant women are among the lowest in their dietary intake of DHA. This is perhaps related to previous government warnings against seafood intake due to the potential for mercury toxicity.[37] Recent recommendations by the Food and Drug Administration (FDA) through the Prenatal Nutrition Working Group (2014) now specifically encourage the consumption of 8-12 oz. of fish per week (allowing up to 6 oz. of albacore tuna) for fetal neurodevelopment.[38]

Dietary fat intake guidelines for women in pregnancy are somewhat fluid. They are based on total caloric intake and are generally a function of macronutrient distribution rather than a targeted intake amount. The IOM recommends intake of 20-35% of total energy as fat, and also advises a 9:1 omega-6 to omega-3 intake ratio. We generally agree with the percent of fat intake recommended by the IOM, but recommend a lower ratio of omega-6 to omega-3 intake, to around 5:1. This can be accomplished by increasing the prudent intake of oily fish, supplementing omega-3 fatty acids, and limiting packaged and processed foods containing high amounts of corn, soybean, sunflower and cottonseed oils. In addition, due to both the potential benefits and the extremely low risk of DHA supplementation, we recommend that pregnant and nursing women supplement their diet with 200-600 mg/day of DHA.[39,40,41,42]

Micronutrient Recommendations

The vast majority of nutrient recommendations for pregnant women focus on specific micronutrients, particularly folates/folic acid, iron, iodine, choline, vitamin D, calcium and DHA. In addition, nutrient-depletion related to preconception dietary patterns or diseases are also of concern for clinicians. For instance, it is well-documented that vegetarian women are likely to experience deficiencies related to important prenatal micronutrients (vitamin B12, iron, DHA and vitamin D), though specific nutrient deficiencies are also prevalent in obese individuals, women with eating disorders, and those with inflammatory bowel diseases.[43,44,45] According to data compiled by researchers at the University of Newcastle, pregnant women in the United States and Canada are most likely to be deficient in their dietary intake of folates, iron, vitamin D and magnesium (Note: The researchers did not collect data on either choline or iodine).[6]

Our general recommendation is that women should, in addition to a well-balanced and healthy diet, consume an appropriate multivitamin/mineral supplement during preconception, pregnancy and lactation to ensure adequate levels of most micronutrients. However, the best data supporting routine supplementation during pregnancy is generally limited to a handful of nutrients, which are outlined below.

Folates/Folic Acid

Dietary intake of folates during early pregnancy (especially 21-28 days after conception) is critical for fetal spinal cord development. Low folate intake is one of the leading causes of neural tube birth defects (NTD), the prevalence of which has been reduced in nations implementing mandatory fortification of cereal grains with folic acid.[46] Without food fortification or supplementation, deficiency of folate intake is high in the United States. The National Health and Nutrition Examination Survey (NHANES) data collected from 2003 to 2006 suggests that nearly 90% of Americans consume less than the estimated average requirement, which increases the likelihood that a woman enters her pregnancy with inadequate levels of folate for appropriate fetal neural development.[47] Yet, despite the common recommendation for

Nutrition, Epigenetics and Fetal Programming

The vast majority of research related to nutrition during pregnancy has focused on the effect of specific nutrients on fetal development, pregnancy outcomes and postpartum nutrient depletion. From this perspective, nutrients are considered to function mostly as building blocks for cellular and tissue formation, or as necessary cofactors for important enzymes. This is, of course, a very fundamental aspect of prenatal nutrition, but the importance of proper nutrition in preconception (mother and father) and during pregnancy is now greatly expanded by the emerging science of genomics and epigenetics.[1] Although a thorough review of this topic is beyond the scope of this paper, we provide a brief overview to help clinicians understand this growing field of study, and gain a perspective on how fetal programming and epigenetics influence chronic disease (or health) in offspring later in life and even from one generation to the next.

Epidemiological and animal studies have revealed that maternal caloric under-nutrition, as well as over-nutrition, predisposes the offspring to a range of fetal adaptations to glucose and fatty acid metabolism. These adaptations increase the risk for cardiometabolic outcomes in adulthood.[2,3] Though it is clear that the intrauterine environment (nutrient, hormonal, etc.) plays an immediate role in fetal gene expression (genomics), the long-term effects appear to be mediated by epigenetic alterations in the genome. In other words, genomic and epigenetic adaptations intended to avoid immediate metabolic danger during fetal development appear to be less- than- helpful adaptations for long-term metabolic functioning.[4]

Epigenetic changes, such as DNA methylation, chromatin/histone modification and programmed microRNA expression, may be inherited at the time of conception (by mother or father) or be triggered by the environment during gestation. In most cases, lifetime epigenetic-based disease risk is due to both inherited and gestational environmental influences, as well as early-life diet and environmental signals. Relevant to this discussion, then, is the fact that appropriate levels of dietary macronutrients and micronutrients influence genomic and epigenetic outcomes; and do so in ways that are not always easy to measure through traditional perinatal outcomes. Consequently, specific animal and human studies now focus on ways to measure various interventions in fetal programming due to diet, stress and other maternal signals affecting epigenetic outcomes.[5,6]

While some nutrient-epigenetic relationships are well-known as part of their nutrient function (e.g., methylation-folates, vitamin B12, vitamin B6, choline), many powerful genomic and epigenetic signals often come from food nutrients with no formal daily recommended intake values (e.g., phytonutrients). In fact, dozens of compounds found in a variety of plant foods have been shown to influence DNA methylation, histone modification (primarily acetylation and deacetylation) and microRNA expression and maturation.[7] The only way to ensure these signals will properly influence genomic and epigenetic signaling is to encourage daily consumption of a variety of vegetables, fruits and culinary spices,and to emphasize colored and aromatic foods based on tolerance (tomatoes, garlic, onions, broccoli, blueberries, cherries, raspberries, red grapes, turmeric, cinnamon, etc.).

The vital role of epigenetics should also be stressed when advising future parents about preconception lifestyle and dietary habits. Epigenetic adaptations made during the first few decades of life (in both the mother and father) have the potential to influence the epigenome of future offspring, and therefore predispose them to positive or negative risk potential. Animal models now clearly show that obesity and poor diet in a male prior to conception negatively impacts insulin sensitivity and obesity in his offspring. In a landmark study, researchers at the University of New South Wales showed that adult female offspring of male rats fed a chronically high-fat diet prior to fertilizing control mothers showed decreased insulin sensitivity and early beta-cell destruction.[8] Genomic analysis of the female offspring showed over 600 different alterations in pancreatic beta-cell gene expression when the father was fed a high-fat diet, an effect that was partially due to specific changes in DNA methylation. This study has spawned new avenues of research in the understanding of paternal influences on offspring health.[9] While such controlled intervention studies have not yet been performed in human subjects, the genetic principle is predicted by epidemiology. Therefore, men intending to become fathers should recognize that their health, metabolic status and current lifestyle (diet, physical activity, stress and exposure to toxins) are likely to impact the health of their child. Thus, along with advice aimed to promote healthy prenatal and gestational nutrition, both mother and father should be advised to maintain many of the same general recommendations of a prudent diet and lifestyle prior to conception. Though beyond the scope of this paper, it should be noted that this general advice, along with specific nutrient interventions, has also been shown to improve fertility in both men and women.

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women to consume folic acid supplements or multivitamins with folic acid *prior* to pregnancy, among American women ages 18-44 years with a recent live birth (2009), only 29.7% of women reported folic acid supplementation during the month before pregnancy.[11] Those reporting the lowest rate of supplementation were those ages 18-24 years (16.1%), Hispanic (22.5%) and non-Hispanic black women (19.5%). During pregnancy, reported use of folic acid supplementation increases to an overall 77% (average 817 mcg/day), although use appears to be lowest during the first trimester (55%), when folate need is greatest.[48]

The biologically active folate molecule is the fully reduced and methylated mono-glutamate form called 5-methyltetrahydrofolate (5-MTHF). The common synthetic fortificant, folic acid, must be converted after ingestion to 5-MTHF via a multi-step enzymatic process that terminates with the enzyme 5,10 methyleneTHF reductase (MTHFR). Numerous polymorphisms exist for the gene that encodes the MTHFR enzyme. The most common of these single nucleotide polymorphisms occurs at base pair number 677, where a C (cytosine) is replaced by a T (thymidine), resulting in a different amino acid sequence (alanine to valine) at position 222 of the enzyme producing a less stable and less active enzyme. A woman homozygous at the MTHFR C667T position (677TT) produces a protein that is about 50% less active than a woman with a MTHFR genotype of 677CC. In general, pregnant women with a MTHFR 677TT genotype are at higher risk for fetal NTD, although other MTHFR polymorphisms (e.g. A1298C) play only a minor role in NTD risk.[49]

For decades, folic acid was the primary folate used in dietary supplements and in nearly every clinical trial used to improve folate status in pregnant women. Dietary folates (most of which have multiple glutamate moieties attached), are considered less bioavailable than folic acid because they must first be fully hydrolyzed to their respective monoglutamate form and, in many cases, also undergo methylation via MTHFR. Today, several forms of 5-MTHF are available for use in dietary supplements and have been shown to be comparable, or superior, to folic acid for increasing folate status in women of childbearing age.[50,51] Pharmacokinetic studies evaluating *single doses* show that individuals carrying MTHFR 677TT genotypes have a statistically higher plasma folate when consuming supplemental 5-MTHF, compared to an equimolar amount of folic acid. These differences are much smaller, often clinically insignificant, when equimolar amounts are consumed daily for weeks or months.[52,53,54]

Nutrient	IOM DRI for Pregnant Women *(Age 19–30)*	Difference from Non-Pregnant Women	FDA's DV for Pregnant Women
Vitamin A	2567 IU (as retinol)	+10%	8000 IU
Vitamin C	85 mg	+13%	60 mg
Vitamin D	600 IU	NC	400 IU
Vitamin E	22.5 IU (as d-alpha tocopherol)	NC	30 IU
Vitamin K*	90 mcg	NC	-
Thiamin	1.4 mg	+27%	1.7 mg
Riboflavin	1.4 mg	+27%	2 mg
Niacin	18 mg	+29%	20 mg
Vitamin B6	1.9 mg	+15%	2.5 mg
Folate	600 mcg	+50%	800 mcg
Vitamin B12	2.6 mcg	+8%	8 mcg
Pantothenic Acid*	6 mg	+20%	10 mg
Biotin*	30 mcg	NC	300 mcg
Choline*	450 mg	+6%	-
Calcium	1000 mg	NC	1300 mg
Chromium*	30 mcg	+20%	-
Copper	1 mg	+11%	2 mg
Fluoride*	3 mg	NC	-
Iodine	220 mcg	+47%	150 mcg
Iron	27 mg	+50%	18 mg
Magnesium	350 mg	+13%	450 mg
Manganese*	2 mg	+11%	-
Molybdenum	50 mcg	+11%	-
Phosphorus	700 mg	NC	1300 mg
Selenium	60 mcg	+9%	-
Zinc	11 mg	+38	15 mg
Potassium*	4.7 g	NC	-
Sodium*	1.5 g	NC	-
Chloride*	2.3 g	NC	-

Table 2: Nutrient Intake Values for Pregnant Women. This table shows the Daily Reference Intake (DRI-Column 2) as recommended by the Institutes of Medicine (IOM) for pregnant women aged 19-30 years. Nutrients highlighted with an "*" have AI (Adequate Intake) values listed, the rest represent the RDA (Recommended Dietary Allowance) value. Column 3 shows the difference, by %, in the IOM recommendation (Column 2) from non-pregnant women aged 19-30 years. For example, the iodine recommendation for pregnant women is 220 mcg, which is 47% higher than that recommended for non-pregnant women. Finally, Column 4 shows the 100% daily value (DV), where available, that FDA requires manufacturers to use within the supplement facts panel of a prenatal supplement. Notice that the DVs (FDA) and the DRI (IOM) numbers are often quite different- confusing many clinicians and patients in understanding the role of supplemental nutrients and the use of multivitamin-mineral products.

While no intervention studies using 5-MTHF during pregnancy have been published to date, there are many researchers and clinicians recommending the use of 5-MTHF, rather than folic acid, for preconception and prenatal supplementation.[55] With the exception of additional cost, this recommendation should result in no harm and is likely to increase folate status in these women to a greater extent than a similar level of folic acid. This is especially true of women carrying the MTHFR 677TT or 677CT genotypes. While commercial 5-MTHF ingredients are "bio-identical" to the natural mono-glutamate folate from foods, they are organically synthesized from folic acid and extensively purified to remove the non-biological isomer, resulting in a raw material that can be up to 200 times more expensive than folic acid. Depending on the dose and other ingredients within the prenatal supplement, this can add a significant cost to the prenatal product.

Folate Recommendation: According to the IOM, the daily recommended intake for folate (defined as a dietary folate equivalent-DFE) is 600 mcg.[56] Technically, this is equal to 300 mcg of a folic acid supplement, since the IOM deems 1 mcg of folic acid equal to 2 DFEs. As of December 2014, the daily value (DV) used for folic acid by the FDA to label prenatal supplements (i.e., the 100% DV in the supplement facts box) is 800 mcg; differing both from the 600 mcg DFE recommendation or its 300 mcg folic acid equivalent.[57] Regardless of these discrepancies, the NHANES data discussed above shows that folate/folic acid intake in women of child-bearing age is well below the recommended amount. Therefore, we recommend 800-1,000 mcg/day of folic acid or 5-MTHF should be added through supplementation starting eight weeks before conception through the end of breastfeeding. While we do not believe folic acid is either unsafe or ineffective in such patients, those with MTHFR 677CT or 677TT polymorphisms may realize additional benefits using 5-MTHF rather than folic acid.

Choline and related methylation support

Choline is an essential nutrient that is critical for fetal development, partly due to its intersection with methylation pathways.[58,59] Dietary choline can be oxidized to betaine (trimethylglycine), which in turn, can act as a methyl donor in the conversion of homocysteine to methionine. Lower choline (and betaine) intake during pregnancy has been linked to reduced cognitive development in the child.[60] Choline is also the precursor for the important membrane phospholipid, phosphatidylcholine, and the vital neurotransmitter, acetylcholine. During pregnancy, a mother shuttles large amounts of choline across the placenta to the fetus, and later, through her milk during breastfeeding. Although pregnant women have higher amounts of endogenous choline production (via conversion of estrogen-stimulated production of phosphatidylcholine), choline levels are often still diminished due to low dietary choline stores prior to pregnancy and low dietary intake during pregnancy.[61] In fact, according to recent NHANES data, only about 8% of the United States population consumes the adequate intakes of choline through their diet and supplementation.[62]

Besides eggs, food sources of choline include beef liver (highest), wheat germ, cooked beef and cod, and cooked cruciferous vegetables, especially broccoli and Brussels sprouts. Choline found in dietary supplements is often delivered as choline bitartrate, an ingredient derived from the synthetic conversion of tartaric acid. Lecithin or pure phosphatidylcholine (PC) is another popular supplement that provides choline. Pure PC is only about 13% choline by weight, as compared to the more commonly used choline bitartrate, which is 40% choline. Many commercially available "lecithins" are actually blends of PC with other phospholipids from soy, lowering the choline content even further. We recommend that women consume IOM's adequate intake levels of choline (450 mg/day) through their diet, if possible. Prenatal supplements containing either choline bitartrate or PC may also be another way to add choline to the diet, though these are unlikely to contain adequate intake levels. Since there is no established DV for labeling choline levels on prenatal supplements, most of these ingredients are expressed by total compound weight (rather than choline content). For instance 200 mg of choline bitartrate delivers approximately 80 mg of choline, while 200 mg of pure PC only delivers about 26 mg of choline.

Vitamin B12, in the methylcobalamin form, is a cofactor for methionine synthase, an enzyme that converts homocysteine to methionine using 5-MTHF as a methyl-donor. Although important for this methylation pathway, most women generally consume adequate levels of vitamin B12 in their diet to meet these basic nutritional needs (This is not generally true of vegetarians or those talking proton pump inhibitors). The role of added vitamin B12 to prenatal supplements is minor, although vitamin B12 should be included whenever folic acid is used to prevent folic acid-masking of a B12-deficiency. Methylcobalamin, now available as a supplement ingredient, is preferred by many functional medicine clinicians over cyanocobalamin, though data comparing these forms for efficacy or safety is lacking. Prenatal supplements should generally contain 10-100mcg of vitamin B12. Additional vitamin B12 supplementation (800-1,000mcg/day) should be considered in women with low vitamin B12 status.

Iron

Iron is a key nutrient during pregnancy, contributing a key component for the increased blood volume needed for oxygenation of tissues in both the mother and growing baby.[63,64] Low iron status during pregnancy increases the risk of preterm delivery and also increases the risk of low birth weight deliveries.[65] Additionally, babies born to mothers who are anemic are more prone to anemia themselves, and often require iron supplementation after birth.

Since NHANES data suggest that 20% of American women have low haemoglobin and iron levels, evaluation of low iron levels should be a focus prior to conception.[47] The RDA for iron intake in pregnant women is 27 mg/day, although the DV used for labelling prenatal supplements is much lower, at 18 mg. According to data compiled by researchers at the University of Newcastle, pregnant women in the United States and Canada consume an average of 16 mg of iron from dietary intake alone.[6] Although the use of iron supplementation is common during pregnancy, meeting the United States RDA requirement through dietary intake is possible if the mother follows a nutrient-dense diet of iron-rich foods. Organ meats such as beef liver, red meat such as beef and bison, poultry, seaweed, dark leafy greens, and blackstrap molasses are all good sources of iron. Almonds, pumpkin seeds, quinoa, and dried fruits such as apricots, dates, and prunes are also good sources of dietary iron. Adequate intake of vitamin C/ascorbic acid is known to improve iron absorption from both foods and supplements.[66]

Iron deficiency is one of the most common nutrient deficiencies worldwide, and the most common risk factors for anemia during pregnancy.[67] According to the American College of Obstetricians and Gynecologists "perinatal iron supplementation is important because the typical American diet and endogenous stores are insufficient sources for the increased iron requirements during pregnancy."[68] In the United States, low socioeconomic status and poor dietary habits may increase the likelihood of iron-deficiency anemia.[69,70] Even so, while the use of supplemental iron has been shown to improve pregnancy outcomes and is universally recommended in iron-deficient women worldwide, routine iron supplementation is not universally recommended within many guidelines for healthy (non-iron deficient) women within *developed* countries.[71,72,73]

In the United States and the United Kingdom, anemia is defined as haemoglobin levels of <11 g/dl (<110 g/L) during the first trimester and <10.5 g/dl (<105 g/L) during the second and third trimesters. However, serum ferritin levels are considered to be the best test for assessing iron deficiency during pregnancy. While many laboratories report ferritin levels above 10 mcg/dl as "normal," levels <15 mcg/dl indicate iron depletion in all stages of pregnancy.[73] A serum ferritin of <30 mcg/dl is also considered by some to be a good cut-off when screening women for iron-deficiency anemia and the need for iron supplementation during pregnancy.[74] Since ferritin, like C-reactive protein (CRP), is also an acute phase reactant; concurrent measurement of CRP may be helpful when interpreting higher levels of ferritin (>30mcg/dl) as they can inadvertently be a sign of an inflammatory condition.

Iron-containing supplements and prenatal vitamin/mineral supplements contain a range of doses and forms of iron. Most prenatal supplements contain 25-30 mg of elemental iron, although higher doses (50-100 mg) are often used for iron-deficiency anemia. The most common forms of iron used are: ferrous fumerate (33% iron), ferrous sulfate (monohydrate, 33% and heptahydrate, 22%), ferrous gluconate (12%), ferrous oxide (77%) and ferrous amino acid chelate (bisglycinate, 20%). Several studies have looked at the relative safety, side-effect profile and bioavailability of these forms, all of which are non-heme iron compounds. Since iron bioavailability is highly regulated by a person's iron status, only subtle differences in iron bioavailability have been demonstrated in clinical trials, favoring bisglycinate chelates. Recently, Milman, et al. showed that 25 mg of elemental iron from ferrous bisglycinate chelate was just as effective in maintaining iron status during the second and third trimester of pregnancy as 50 mg of elemental iron from ferrous sulfate.[75] The bisglyinate chelate form was also associated with fewer gastrointestinal side effects.[76]

Accidental overdose of iron-containing products is the single largest cause of poisoning fatalities in children under six years old. For this reason, products containing appreciable amounts of iron are required to have childproof packaging and appropriate warnings. Clinicians should remind those taking iron supplements, including prenatal supplements, to close the childproof packaging and keep these products away from children. The use of blister cards or single-use daily packaging may lower such risks.

Iodine

The requirement for iodine is higher during pregnancy due to a 50% increase in maternal thyroxin (T4) production, the need to transfer iodine to the growing fetus for its own thyroid hormone production and a slight increase in maternal renal iodine clearance.[77] Low maternal iodine stores can progressively lead to hypothyroid-related issues in the mother and poor brain development in the growing fetus.[78,79] This increased prenatal iodine requirement is reflected in the difference between the IOM's recommended daily iodine intake for non-pregnant women (150 mcg) and that during pregnancy (220 mcg) and lactation (290 mcg). The World Health Organization now recommends 250 mcg of iodine daily for pregnant and lactating women.

In the United States, the primary source of dietary iodine comes from the use of fortified iodized salt, although in some regions fish, shellfish and seaweed add a portion of the daily iodine intake. However, kosher salt, sea salt and most salt added to packaged foods rarely contain added iodine. In addition, the American diet and environment contain many compounds known to inhibit iodine/thyroid function.[80,81] Iodine deficiency in the general population (based on IOM's intake criteria) is uncommon in the United States because of the ubiquitous use of iodized table salt. Nonetheless, the American Thyroid Association recommends that women receive 150 mcg of iodine through supplements daily during pregnancy and lactation and that all prenatal vitamin/mineral preparations contain 150 mcg of iodine (The DV for iodine for prenatal supplement labels is 150 mcg).[82]

The most common source of iodine used in dietary supplements and prescription prenatal products is potassium iodide (75% iodine). Kelp is also a common ingredient used for iodine supplements, although the lack of consistent iodine content and the potential for heavy metal contamination make potassium iodide a preferable ingredient for prenatal supplementation.[83,84]

Vitamin D

The growing awareness of both the physiological importance and the nearly ubiquitous nutritional deficiency of vitamin D, have increased the concern for monitoring vitamin D status during pregnancy.[85,86] Low vitamin D status during pregnancy has been associated with adverse pregnancy outcomes including preeclampsia, gestational diabetes, and preterm or small-for-gestational age births.[87,88] The fetus is dependent on the mother as its only source for 25(OH)D, which readily crosses the placenta.[89] Low vitamin D status during pregnancy is associated with measures of fetal skeletal bone formation which may persist through adolescence.[90]

In the United States, vitamin D insufficiency is common prior to and during pregnancy, particularly among vegetarians, those with low sunlight exposure due to clothing or latitude, and those with darker skin.[91,92,93] Still, the IOM's current RDA for pregnant women is the same as for all adults (600 IU/day). We believe this level of vitamin D intake, in the absence of routine sunlight exposure to the skin, is inadequate to maintain appropriate vitamin D-related functions in adults, including pregnant women (For further discussion on this topic, download our whitepaper at www.pointinstitute.org).[94] According to the ACOG, most experts agree that supplemental vitamin D is safe in dosages up to 4,000 IU per day during pregnancy and lactation.[95] Although ACOG believes there is insufficient evidence to recommend the screening of all pregnant women for vitamin D deficiency, they agree that routine supplementation of 1,000-2,000 IU of vitamin D should be considered safe in those identified with vitamin D deficiency. Since the prevalence of vitamin D deficiency is so common and the risk of vitamin D supplementation is virtually non-existent at these doses, we believe that routine supplementation of vitamin D (1,000-4,000 IU/day of vitamin D3) should be recommended for all women during pregnancy and lactation.

Should prenatal supplements be recommended to all pregnant women?

With the exception of folic acid, iron and iodine, there is a general reluctance by health organizations to recommend the routine use of prenatal multivitamin/mineral products in "healthy" pregnant women living in developed countries. However, both the American Dietetic Association and the IOM recommend the use of multivitamin/mineral supplements in pregnant women who smoke, abuse alcohol or drugs, are iron deficient, or have a ***poor quality diet***.

According to NHANES data, greater than 40% of adults living in the United States consume less than the IOM's estimated average requirement (EAR) of vitamin D, calcium, vitamin A, vitamin C, vitamin E, thiamin, folate and magnesium.[47] Most nutrient needs during pregnancy are higher, which is reflected in the increased DRI recommendation of 19 of the 29 essential micronutrients (Table 2). Nutrient needs are also higher in overweight and obese subjects; and half of all pregnant women are overweight, while 25% enter pregnancy obese. Finally, CDC data shows that approximately 43% of pregnancies in the United States are unintended (61% of women aged 18-24), that only 30% of women consume a folate-containing supplement prior to conception and only 25% of these same women consumed the recommended daily servings of fruits and vegetables.[11] This data, we believe, suggests that the average pregnant women in the United States is likely to have a poor or less than optimal quality diet and enters her pregnancy with an insufficiency of one or more micronutrient. **In addition to the sound dietary advice we have outlined above, we agree with the majority of health care providers in recommending the daily use of a comprehensive multivitamin/mineral product before, during and after pregnancy, preferably one designed to adequately meet the needs of a perinatal woman (e.g., folate, iron, iodine, vitamin D3, choline and DHA).**

Achieving Adherence to Prenatal Supplementation

Advising a healthy woman about appropriate dietary choices and helping her choose an appropriate prenatal supplement is often complicated by low adherence to such recommendations.[96] In many populations, the use of dietary supplements is unfamiliar and adherence to recommended prenatal vitamin/mineral product may be challenging. Nonetheless, the limited data that has been collected over the years suggest that pregnant women are generally the highest users of multivitamin.[97] Many factors can influence the use of prenatal supplementation during pregnancy. These include patient care and education,[98] maternal depression and anxiety,[99] substance abuse,[100] morning sickness,[101] tolerance of iron supplementation, and general attitudes toward the use of supplements.

Research conducted in 2008 with 12 focus groups, including Hispanic and African-American prenatal clients, indicated that access to supplementation, experience of positive side-effects, client education, affordability, and social groups reinforcing prenatal supplementation compliance were all positively influential in successful use for clients.[102] Many challenges can be addressed and low adherence can be mitigated through effective client communication and education. Concerns such as forgetfulness can be addressed through scheduling tools, and knowledge of need for supplementation can be addressed through specific patient education in a face-to-face fashion and in supporting documentation. Open lines of communication can ameliorate concerns associated with negative side effects (constipation as a result of iron supplementation, for example). Practitioners working with pregnant women should focus on providing easily understandable guidelines, including the rationale and evidence for prenatal vitamin/mineral support. Informal studies indicate that accountability tools provided by clinicians to set goals, track daily intake, and monitor success are useful in supporting prenatal clients. In sum, physicians can positively affect adherence to lifestyle changes and compliance to supplement regimens through increased and better communication.[103]

Gut Microbiota and the Role of Probiotics During Pregnancy

The health and integrity of the gastrointestinal tract, along with its microbiota, is now recognized as a major factor in maintaining an individual's health. Beneficial microbial organisms help to protect the gastrointestinal (GI) environment from certain pathogenic organisms, provide important nutrients through fermentation and direct synthesis, improve gut barrier function, and helps to mature and fine-tune immune cell functions. The reproductive tract is also a microbial-rich environment. While this feature is often considered negative during pregnancy (e.g., vulvovaginal candidiasis, urinary tract infections, bacterial vaginosis), there is now a better understanding of the protective effect of "good" commensal organisms protecting the reproductive tract during pregnancy.[104] In fact, maternal gastrointestinal and placental microbiota have been shown to play a role in fetal metabolic programming as well as gut and immune maturation in the fetus prior to delivery.[105,106,107]

Due to these and other recent discoveries, the microbial environments of both the GI and reproductive tracts during pregnancy have only just become the focus of clinical research. Along with observational studies, several interventional studies have examined the role of nutritional, prebiotic and probiotic modulation of the maternal microbial environment on a range of perinatal and infant development outcomes.[108,109] Beyond the obvious support for both gastrointestinal and immunological health in the mother, prenatal probiotics have been evaluated for their effects on preeclampsia, maternal depression, gestational diabetes, maternal and fetal metabolic functions, and even heavy metal and pesticide sequestration.[110,111] Some, though not all, studies have shown that prenatal probiotic use significantly increased levels of both GI and vaginal *Lactobaccilli* populations, reduced the incidence of bacterial vaginosis, altered immune markers in serum and breast milk, improved maternal glucose metabolism, and reduced the incidence of gestational diabetes.[112,113,114,115,116,117]

Due to the wide-range of doses ($1x10^7$ to $2x10^{10}$ CFU), probiotic strain combinations used, delivery mechanism (e.g., capsules, yogurt, fermented milk) and different outcomes measured; definitive probiotic recommendations for specific outcomes are difficult to make. However, consistent among all these clinical trials was the fact that no adverse events were reported and there was strong evidence of safety and tolerability for the use of prenatal probiotic supplements, as well as fortified foods. While future studies are still needed to strengthen the outcome-based evidence for using prenatal probiotics for specific interventional purposes, the use of supplemental probiotics containing *Lactobacilli* and *Bifidobacteria* strains should be considered safe and beneficial during pregnancy and lactation. Studies using the common yeast probiotic, *Saccharomyces boulardii,* during pregnancy have not been published. While the use of this strain appears to be common during pregnancy in Europe,[118] some are still reluctant to recommend its use due to a lack of published clinical data.[119] However, with the exception of immunocompromised patients or individuals with central venous catheters, there is no reason to believe the use of *Saccharomyces boulardii* would be unsafe during pregnancy or lactation.[120]

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Ginger for Nausea During Pregnancy

While the use of certain botanical ingredients (i.e., herbal medicines) during pregnancy is common in a variety of healing traditions; the published efficacy and safety data of their use during pregnancy are very limited. One notable exception is the use of ginger root (and related extracts) for pregnancy-related nausea.[1] Ginger (*Zingiber officinale*) root is a pungent spice commonly used in both foods and medicines worldwide, and often used as an antiemetic.[2] The use of ginger root preparations for pregnancy-associated nausea and vomiting has recently been reviewed.[3] Using data from twelve randomized controlled trials (1,278 subjects), ginger preparations were able to significantly reduce nausea compared to placebo or control ($p=0.0002$), though the strong trend toward reducing vomiting episodes did not reach statistical significance ($p=0.06$). These studies also showed a very low incidence of side-effects or measured perinatal adverse effects with the use of these ginger root preparations.

The majority of these studies used capsule preparations that delivered 1,000-1,950 mg/day of ginger root powder,[4,5,6,7,8,9,10,11] though two studies delivered 1,000 mg of a powdered ginger root extract[12] or ginger syrup.[13] Generally, those trials using doses above 1,500 mg of ginger powder were no more effective than those using 1,500 mg or less. These data, coupled with the long history of safe use, suggest that ginger root preparations are a safe and possibly effective option for reducing nausea and vomiting associated with pregnancy.

A review of the safety and efficacy of other herbal preparations is beyond the scope of this article. We recommend the following publications to help the clinician determine the safety and efficacy of particular herbal preparations for pregnant subjects:

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