Lead Article

Safety and efficacy of supplements in pregnancy

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Pregnancy is a time where expectant mothers often focus on their diet to improve their own health and to preserve the future health of their children. There is much conflicting information in the public domain about the safety and/or efficacy of nutritional supplements during pregnancy. Despite this, the market for supplements is growing. This review discusses the roles of critical nutrients in pregnancy and the available evidence on the use of supplements to reduce risks and improve maternal and fetal outcomes. Recommendations are made for pregnant women, taking into account safety data and tolerable upper intakes set for pregnant women. It is important for dieticians, nutritionists, physicians, and other healthcare providers to be able to offer accurate and evidence-based advice on supplement use in pregnancy. Routine supplementation may not be necessary for all, but individuals at risk are identified.

INTRODUCTION

There is substantial evidence on the importance of maternal diet for the health of the fetus. The nutrient status of the fetus is mostly dependent on maternal intake and it has been known for many years that deficiencies in critical nutrients can lead to malformations and poor health outcomes for both the mother and offspring. It is because of this that, often, pregnancy is a time that expectant mothers will focus on their health and nutrient intake. Supplement use is very common in pregnancy. Studies show that multivitamin use (excluding folic acid alone)_ranges from 78% to 98% in different cohorts across the United States, Canada, and Australia.[1–3] However, knowledge about the safety or effectiveness of supplements is not widespread. Many supplement manufacturers err on the side of caution and use advisory labels to avoid use in pregnancy. Given the relatively high incidence of nutritional deficiencies, reduced nutrient density of food, and higher intake of nutritionally poor processed food, supplement use in pregnancy may be beneficial in some instances and reduce risks of negative outcomes.

The evidence for safety and efficacy of nutritional supplements in pregnancy is reviewed here. In many cases tolerable upper limits are already set based on rigorous reviews of adverse events.[4] Recommendations are made herein for particular at-risk groups or individuals that may benefit from supplementation in addition to a well-balanced diet. It is worth noting that significant limitations exist for assessing the correct level of evidence required to make nutritional recommendations,[5] and this could be argued to be more pronounced in pregnancy. Regarding the role of the randomized controlled trial in nutrition, it is clearly unethical to reduce intakes of nutrients in pregnancy for comparison as a "control" group. Studies on nutrition also differ from drug-intervention studies in that it is often more difficult to prove the effect of the absence of nutrients rather than the addition of a drug. Nutrient deficiencies may also develop over time, which are not always resolved during a short window of supplementation. It could be argued that this is even more important during pregnancy, as beginning supplements in the first or second trimester may not be a sufficient time frame in which to affect development of the fetus.

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Vitamins, minerals, and omega-3 fats will be discussed, in that order, with regard to function and identification of at-risk groups. Daily recommendations are included along with tolerable upper intakes, which are compared between the European Union (EU) (European Food Safety Authority) and the United States (Institute of Medicine) where available, or relevant evidence discussed. Table 1 provides a quick reference guide.

VITAMIN A

Vitamin A is likely the most controversial supplement in pregnancy and has largely been avoided by pregnant women and omitted from supplement formulations or replaced with beta-carotene owing to perceived risk of teratogenicity. However, vitamin A plays an essential role in embryogenesis, and the risk of teratogenicity is limited. When converted to retinoic acid, it acts as a ligand for the retinoid superfamily of receptors. Two retinoic acid–dependent transcription factors – retinoic acid receptors and retinoid X receptors – are expressed in a well-defined pattern in the developing embryo. An excess or deficiency of vitamin A can cause critical alterations in gene expression sufficient to cause developmental abnormalities.[34]

Retinoic acid plays a role in organogenesis, including of the lung. An intervention study demonstrated improved lung function in offspring of a deficient population who received vitamin A supplementation.[35] Vitamin A also plays a role in immune function, and neonatal deficiency in vitamin A increases the risk for infectious diseases such as diarrhea, measles, and respiratory illness.[36] Repletion may reduce rates of maternal infections[37] and improve early fetal lymphopoiesis.[38]

The recommended daily intake during pregnancy is 540 µg retinol equivalents (RE) in the EU,[7] with a higher level of 770 µg RE in the United States.[6] As a fat-soluble vitamin, preformed vitamin A is found in fish oil, meat, and dairy products. Beta-carotene, the primary plant source of retinol, is found in many fruits and vegetables, particularly orange-colored carrot, sweet potato, squash, and peppers. Deficiency is common in developing countries with poor access to fresh plant produce and limited dietary meat intake. However, in a World Health Organization (WHO) analysis, the prevalence of serum retinol <0.70 µmol/L in pregnant women was just 2% in the Americas but alarmingly high in Europe at 11.6%.[39] Of all the nutrients reviewed herein, it is important to dispel the myths around vitamin A supplementation to ensure that sufficiency is achieved in pregnancy. Currently, there is a common perception that any supplementation with retinoic acid should be strictly avoided and that even foods high in preformed vitamin A should be avoided – for example, liver. It could be said that the risk from supplementation has been overstated. An analysis of almost 23 000 pregnant women in the *New England Journal of Medicine* identified a highly conservative safe threshold of 3000 µg RE/d of preformed vitamin A from food and supplements.[40] At that, only a small number of cases satisfied this threshold, and the safe level could be higher than this according to a number of other studies.[4] The greatest risk is within the first 60 days of gestation. The tolerable upper limit is set at 3000 µg RE/d in the EU[4] and United States[6] without the need for an uncertainty factor calculation, acknowledging the caution already applied.

VITAMIN B6

Adequate supply of vitamin B6 in pregnancy plays an important role in neural development, synthesis of fetal neurotransmitters, and fetal metabolism.[41] Poor vitamin B6 status has been shown to correlate with reduced conception rates and increased risk of early pregnancy loss.[42] Intervention studies are rare, but a meta-analysis of 3 small studies showed a significant positive effect on birth weight but no effect on other neonatal health outcomes or maternal morbidity or mortality.[8] A later Cochrane review concluded that more evidence is needed to determine benefits to supplementation in pregnancy for critical maternal and neonatal outcomes.[43] Supplementation may reduce severity of mild nausea in pregnancy, however, at 30–75 mg/d in divided doses.[44] In addition, anemic pregnant women who are nonresponsive to iron supplementation may respond to vitamin B6, and it is important to consider this deficiency in the clinical setting of anemia.[45]

The recommended intake for pregnant women is 1.8 mg/d in the EU[7] and 1.9 mg in the United States.[9] Sources include fish, meat, poultry, eggs, legumes, and nuts. Supplements often contain much higher amounts. Doses of 50–510 mg/d taken during the first trimester have not been associated with adverse fetal outcomes.[8] Pyridoxine has been associated with neurotoxicity and neuropathy at doses above 50 mg/d,[46] although pyridoxal-5'-phosphate is a safer form of B6 and not associated with neuropathy.[47] Based on neurotoxicity alone, the tolerable upper limit in the EU was set for adults at a very conservative 25 mg/d – a limit that was determined in part from a study that was acknowledged to be flawed.[4] No evidence of adverse events or neurotoxicity has been shown at this level in pregnant women. The United States set a higher level of 100 mg/d, based on reports of neurotoxicity at 200 mg/d and of >500 mg/d in other reports, but acknowledging the variability of the evidence, used the uncertainty factor of 2 to arrive at 100 mg/d.[9]

Table 1 **Summary of recommended intakes of nutrients in pregnancy**

Nutrient	Food source	At-risk groups	Safety limit (tolerable upper limit) per day	Recommended intake level from food or supplements per day
Vitamin A	Retinol in meat, dairy, and fish oil. Beta-carotene in orange-colored carrot, sweet potato, squash, and peppers	Poor dietary intake of fresh plant produce and low meat intake	EU: and US: 3000 μg RE[4,6]	EU: 540 μg RE[7] US: 770 μg RE[6]
Vitamin B6	Fish, meat, poultry, eggs, legumes, and nuts	Poor dietary intake	EU: 25 mg,[4] although no harm has been shown with up to 50 mg[8] US: 100 mg[9]	EU: 1.8 mg[7] US: 1.9 mg[9]
Folic acid	Legumes, leafy green vegetables, broccoli, asparagus, and avocado	Recommended for all; history or family history of NTD	EU: and US: 1 mg,[4,9] although based on masking hematological abnormalities or B12 deficiency	EU: 600 μg[7] US: 400 μg[9]
Vitamin B12	Animal products such as meat, eggs, dairy, and fish	Vegans and vegetarians	None set; usual intakes 35 μg, but 1000 μg in malabsorption is a commonly administered[4,8]	EU: 4.5 μg[7] US: 2.6 μg[9]
Vitamin C	Kiwi fruit, citrus fruit, peppers, and lightly steamed or raw broccoli and cauliflower	Increased dietary intake recommended for all[11–14]	US: 2 g/d,[15] but excess intake via supplements may lead to elevated fetal plasma concentrations[16]	EU: 105 mg[7] US: 85 mg[15] Achievable from food alone
Vitamin D	Sun exposure	Winter pregnancies; residence at northern latitude; dark-skinned ethnicity[17]	EU: and US: 4000 IU[18,19]	EU: and US: 600 IU,[7,18] although this is highly conservative and 1500 IU may be better to reach optimal levels[20]
Vitamin E	Almonds, sunflower seeds, avocado, spinach, and eggs	Poor dietary intake	EU: 300 mg[4] US: 1000 mg[15]	EU: 11 mg[7] US: 15 mg[15]
Vitamin K	Vitamin K1 in dark-green leafy vegetables, broccoli, and Brussels sprouts; vitamin K2 in dairy and fermented foods	Poor dietary intake	None set; no studies carried out	EU: 70 μg[7] US: 90 μg[6]
Myo-inositol	Plant foods	At risk for NTD[21] or GDM[22]	None set; safe at usual clinical dose 4 g[23]	2–4 g in at-risk women[21,22]
Choline	Meat, fish, dairy, beans, cruciferous vegetables, nuts, and seeds	Possibly with genetic variants in choline or folate pathway[24]	EU: and US: 3500 mg[9]	EU: 480 mg, although could be higher in second and third trimester[7] US: 450 mg[9]
Calcium	Dairy, nuts, tofu, and tinned fish with bones	At risk for preeclampsia,[25] vegans	EU: and US: 2500 mg[26]	US: and EU: 1000 mg[7,18]
Iodine	Nonorganic dairy, eggs, freshwater fish, and iodized salt in countries where it is fortified	Subclinical hypothyroidism, vegans	EU: 600 μg[4] US: 1100 μg[6] Both should be considered excessive given risk/high incidence of thyroid disease	EU: 200 μg[7] US: US: 220 μg[6]
Iron	Red meat, plant source such as legumes, nuts and dark green vegetables is poorly absorbed	Vegetarian and vegans	None set in the EU: although supplementation in the absence of deficiency is not recommended[27,28] US: 45 mg based on gastrointestinal side effects only	EU: 16 mg[7] US: 27 mg[6]

(continued)

Table 1 **Continued**

Nutrient	Food source	At-risk groups	Safety limit (tolerable upper limit) per day	Recommended intake level from food or supplements per day
Magnesium	Nuts, seeds, legumes, and some fish and whole grains	Low dietary intake, which is common[29,30]	EU: 250 mg[4] based on side effect of diarrhea, which is usually minimal below 350 mg and can be minimized by dividing doses US: 350 mg[31]	EU: 300 mg[7] US: 350 mg[31]
Zinc	Meat, legumes, seeds, and nuts, though absorption is affected by high-phytate plant-based diet	Vegetarians and vegans	EU: 25 mg, although no studies have shown adverse reproductive effects up to 90 mg[4] US: 40 mg[6]	EU: 9.1 mg in a very low phytate diet to 14.3 mg in a high phytate diet[7] US: 11 mg[6]
Omega-3	Oily fish such as wild salmon, mackerel, herring, anchovies, and sardines	Vegans	Up to 2.7 mg omega-3[32]	EU: and US: 250 mg with an added 200 mg of DHA in pregnancy[7,33]

Abbreviations: DHA, docosahexaenoic acid; EU, European Union; GDM, gestational diabetes mellitus; IU, international units; NTD, neural tube defects; RE, retinol equivalents; US, United States.

VITAMIN B9 FOLIC ACID

The prevention of neural tube defects is the most widely known role for folic acid in pregnancy. A Cochrane review concluded that supplementation before conception and up to 12 weeks of pregnancy is effective for preventing first- and second-time occurrence neural tube defects.[48] Many countries worldwide – including the US, UK, and EU countries, Canada, New Zealand, and China – issued recommendations in the early 1990s that women planning a pregnancy should take 400 µg of folic acid daily. Despite this, suboptimal intake of folate remains high and there is a high incidence of unplanned pregnancies and noncompliance such that the rate of neural tube defects remains alarmingly high. True incidence is difficult to assess on account of reporting irregularities but ranges from approximately 5 to 20 per 10 000 births even in developed countries such as the United Kingdon.[49] There are continued efforts to educate, and recommendations in most countries have been expanded to all women of childbearing age.

Systematic reviews and meta-analyses of folic acid supplementation during pregnancy have also identified a reduced risk of preeclampsia,[50] preterm delivery, and small-for-gestational-age (SGA) outcomes.[51] However, a significant effect on preterm delivery was only seen when folic acid was initiated during the pregnancy and not with pre-conception supplementation, though the trend was still apparent.

Supplementation at 400 µg is largely considered safe. Evidence for adverse effects such as cancer, diabetes, thyroid disorders, and allergic disease below the tolerable upper intake level of 1000 µg is weak or inconclusive.[52] Experimental and observational evidence suggests that there may be risks related to changes in neurodevelopment with folic acid exposure above this level, but further studies are required in relation to dosage and timing.[53] Traditionally, doses of 4 mg have been used for high-risk patients; however, doses of 400–800 µg of folic acid lower risk of neural tube defects, with no further reduction in risk with doses >1000 µg.[54] 5-Methyltetrahydrofolate is also effective at increasing folate concentrations to levels that are considered effective and may be preferable in women with polymorphisms in folate-related enzymes, especially methylene tetrahydrofolate reductase and dihydrofolate reductase.[55]

Recommended daily intake in pregnancy is 600 µg in the EU[7] and 400 µg in the United States,[9] where the tolerable upper limit is set at 1 mg, although this is based on masking hematological anomalies and B12 deficiency.[4,9] Dietary sources are legumes including beans and lentils, leafy green vegetables, broccoli, edamame

beans, asparagus, and avocado. Almost 80 countries worldwide have a fortification policy, including the United States, which has led to a dramatic fall in the incidence of neural tube defects. Many EU member states do not have such a policy. In these countries, it may be recommended that 800 µg/d is required to achieve optimal red blood cell folate levels to prevent birth defects in women.[56]

VITAMIN B12

Vitamin B12 is a cofactor in the methylation cycle which is necessary to ensure adequate folate is available for deoxyribonucleic acid synthesis and cell replication. Vitamin B12 deficiency is associated with adverse maternal and neonatal outcomes, including spontaneous abortions, preeclampsia, low birth weight and developmental anomalies (particularly neural tube defects), and delayed myelination or demyelination.[57]

A common sign of B12 deficiency is a macrocytic anemia, which may be detected in pregnant women on a routine blood test where other markers such as homocysteine or methylmalonic acid are not frequently tested. Folate supplementation can resolve a B12 deficiency macrocytic anemia, however, which can leave B12 deficiency underdiagnosed.[58] This is sometimes termed "masking a B12 deficiency." Given that pregnant women are advised to take folic acid and some take high amounts, it may be important to routinely measure B12 levels in pregnancy or in prepregnancy. High folate status and low vitamin B12 status during pregnancy may predispose women to diabetes and children to low birth weight, insulin resistance, and adiposity later in life.[58]

The recommended daily intake for pregnant women is 4.5 µg in the EU[7] but lower in the United States, at 2.6 µg, based on evidence that absorption is more efficient during pregnancy.[9] Sources of vitamin B12 include animal products such as meat, eggs, dairy, and fish. Risk of deficiency is high in vegetarians and vegans, and the vegan lifestyle is becoming increasingly popular. B12 is also found in fortified foods, but vegans may need to supplement routinely. B12 deficiency is also commonly seen in digestive disorders such as celiac disease, inflammatory bowel disease, and irritable bowel syndrome as a result of small intestinal bacterial overgrowth.[59] Reduced absorption is also caused by impaired proteolysis, which is required to release B12 as observed in gastritis, hypochlorhydria, and use of proton pump inhibitors.

No adverse effects on pregnancy outcomes have been associated with a high vitamin B12 intake from supplements. Usual intakes from supplements in pregnancy are 35 µg, but up to 1000 µg are given to women with compromised absorption.[4,8] Therefore, no tolerable upper limit for vitamin B12 has been set for pregnant women in either the EU or the United States. For the treatment of deficiency, a range of 500–2000 µg of oral vitamin B12 per day may be recommended, which is as effective as sublingual or intramuscular routes.[60–62]

VITAMIN C

Clinical studies do not support routine supplementation with vitamin C for the prevention of important pregnancy outcomes such as fetal growth, preeclampsia, preterm birth, or fetal or neonatal death.[63] It is possible that vitamin C supplementation may reduce the risk of premature rupture of the membranes, as has been observed in a small number of observational and intervention studies.[16,64,65] Supplementation with 100 mg, a conservative dose, has also been shown to reduce the risk of urinary tract infection in pregnancy.[66]

The recommended daily intake in pregnancy is 105 mg in the EU,[7] with a more conservative 85 mg in the United States,[15] which could be achieved with an intake of 5 portions of fruit and vegetables per day. However, vitamin C deficiency is prevalent, with further increased risk for low-income populations, pregnant women, pregnant smokers, and pregnant women with type 1 diabetes.[11–14] These groups should be counseled to increase intake of fruits and vegetable high in vitamin C – namely, kiwi fruit, citrus fruit, peppers, and lightly steamed or raw broccoli and cauliflower. Extensive evidence supports an optimal vitamin C intake of at least 200 mg/d, with 400 mg/d required to reach near-maximal plasma vitamin C levels.[67] Focusing on high vitamin C food sources would be required to achieve this. There is little evidence to recommend vitamin C supplementation beyond this amount in pregnancy. Vitamin C is actively transported to the fetus via the umbilical cord,[16] so excess maternal intake may lead to elevated fetal plasma concentrations. Despite this, the United States maintain the tolerable upper limit in pregnancy at 2 mg/d.[15]

VITAMIN D

Vitamin D deficiency, defined by the WHO as <50 nmol/L, is found in pregnant women globally, with figures ranging from 35%–77% in Northern Europe to 33% in the United States and 70%–90% in Middle Eastern counties.[68] Deficiency has been associated with a number of negative pregnancy outcomes, including preeclampsia, gestational diabetes mellitus (GDM), emergency cesarean section delivery, low birth weight, and SGA.[69] There is also an association between

vitamin D deficiency and postpartum depression, with a 2.67 times risk with vitamin D levels <50 nmol/L.[70]

Vitamin D is an important immunomodulatory, and dysregulation of the immune system may play a role in recurrent pregnancy loss. An increase in T helper 1 and T helper 17 cell activity may increase risk, whereas promotion of T helper 2 cell populations may infer protection and vitamin D may play a direct role here.[71] Recurrent pregnancy loss affects 1%–2% of reproductive women and studies show an association with vitamin D deficiency.[72] Vitamin D level, therefore, may be an important clinical consideration, particularly as recurrent pregnancy loss is often unexplained.

Supplementation with 4000 IU in pregnancy has been shown to reduce the risk of asthma in the offspring, particularly in the most deficient mothers.[73] A Cochrane review and meta-analysis determined that, despite the associations, intervention with vitamin D supplementation did not decrease the incidence of preeclampsia, GDM, SGA, low birth weight, preterm birth, and cesarean section although it did have a positive effect on birth weight.[74] The included studies were heterogeneous in dosage, duration, and gestational age at commencement, which was an important limitation given that supplementation likely took place after the biochemical processes of many of these conditions had begun. Importantly, they did not account for baseline vitamin D status, seasonality, diet, ethnicity, and skin characteristics.

The recommended intake for pregnancy is a highly conservative 600 IU in both the EU and the United States.[7,18] There have been no published reports of teratogenic effects of vitamin D in humans. Supplementation with 1500 IU/d in pregnant and lactating women has been shown to raise blood levels of 25-hydroxyvitamin D consistently above 75 nmol/L.[20] The tolerable upper limit for pregnant women is 4000 IU, and this has been found to be safe with multiple safety assessment methods and more effective than lower doses in restoring sufficiency.[18,19] Testing serum levels of 25-hydroxyvitamin D is the ideal way to tailor recommendations, ensuring that those who are deficient receive personalized vitamin D supplementation. This is not always available as a routine test and thus considerations might include sun exposure, time of year, residence at high latitude, and race.[17]

VITAMIN E

As a fat-soluble antioxidant, vitamin E is proposed to be protective in conditions of oxidative stress, including preeclampsia, intrauterine growth restriction, and premature rupture of the membranes.[75] Vitamin E also mediates the release of prostacyclin, and levels of both vitamin E and prostacyclin increase with gestational age.[76] This may play a role in inhibiting uterine contractions and platelet aggregation and increasing vasodilation. Low plasma concentrations of alpha-tocopherol have been associated with increased risk for SGA,[77] preeclampsia, GDM,[78] and miscarriage.[79] A Cochrane review of intervention studies does not currently support a role for vitamin E supplementation in any of these conditions.[75] Baseline vitamin E status was not measured in any of the included studies, and populations that were assumed replete were grouped with populations with suspected inadequacy.

Other smaller studies have shown that vitamin E supplementation may be useful in the prevention of pregnancy-related leg cramps at a dose of 100 mg/d.[80] It may also play a role in preventing wheezing illness or asthmatic disease in children when supplemented at a conservative dose of 8–18 mg/d.[81]

The recommended daily intake of vitamin E for pregnancy is 11 mg in the EU[7] and 15 mg in the United States.[15] Good sources include nuts and seeds, with highest levels in almonds and sunflower seeds, avocado, spinach, and eggs. Intake of 12–15mg alpha-tocopherol per day has been shown to maintain adequate vitamin E status in healthy adults.[82]

No adverse events related to vitamin E supplementation have been documented in well-controlled clinical trials with the exception of a possible effect on coagulation at a dose of 540 mg/d, leaving the tolerable upper limit set at 300 mg/d in nonpregnant and pregnant women alike in the EU and 1000 mg/d in the United States.[4,15] Additional risk may apply in vitamin K–deficient individuals, and this safe upper limit does not apply to those on anticoagulant medications or suspected to be deficient in vitamin K due to malabsorption or reduced synthesis by gut flora.

VITAMIN K

Vitamin K is required for the biological activity of a number of coagulation factors, but no studies have assessed maternal bleeding as an outcome of vitamin K supplementation.[83] Neonates have a relative vitamin K deficiency at birth owing to limited synthesis of the vitamin in the gut, and it is important to note that maternal supplementation during pregnancy does not negate the requirement for intramuscular vitamin K administration to prevent hemolytic disease of the newborn.[83,84] Vitamin K is also essential for bone formation, either by direct interaction with receptors on osteoblasts or by supporting osteocalcin-/vitamin D-mediated mineralization.[85] Vitamin K2 at 45 mg/d has been used as a safe treatment option in a case series of pregnancy-associated osteoporosis.[86]

Recommended intake is set at 70 µg/d in the EU[7] and 90 µg/d in the United States.[6] The best sources of dietary K1 are dark-green leafy vegetables and vegetables of the brassica family such as broccoli, Brussels sprouts, and kale.[7] Vitamin K2 is found in small amounts in animal products but primarily produced by colonic bacteria and bacteria in fermented foods.[87] There is no known toxicity for vitamin K2, and no tolerable upper level has been set for either K1 or K2 in pregnancy as there have been no studies on reproductive or teratogenic risk.[4]

MYO-INOSITOL

Myo-inositol is a small sugar molecule considered part of the B vitamin family. Much research has focused on the role of myo-inositol as an insulin-sensitizing agent in polycystic ovary syndrome[88] and in improving oocyte quality and outcomes of assisted reproduction.[89]

Myo-inositol also has a functional role in mammalian gametogenesis and embryonic development.[90] As phosphatidylinositol, it plays a role in the closure of the neural tube. In mothers with a previous history of neural tube defects in pregnancy, 5 mg periconceptional folic acid plus 1 g myo-inositol has been shown in pilot studies to be superior for reducing risk compared with folic acid alone.[21] Further large-scale trials are warranted here to improve neonatal outcomes.

Another important role for myo-inositol is in preventing GDM. The prevalence of GDM ranges from 5.8% in Europe to approximately 10% worldwide.[91] Adverse outcomes include preeclampsia, preterm delivery, macrosomia, birth injury, and increased fetal and neonatal death. The risk for the mother of developing type 2 diabetes postnatally is well known, although the prevalence is extremely difficult to measure given variations in diagnostic techniques and wide variations in follow-up duration from months to many years. Six studies in the EU with >5-year follow-up yielded an average incidence of 16.5%.[91] Two Cochrane reviews have been published by the same group which analyzed myo-inositol supplementation in pregnancy at doses of 2–4 g/d. The first, in 2015, indicated that antenatal supplementation with myo-inositol reduces the risk of developing GDM by more than half, though the risk of bias was unclear.[22] The second review analyzed the use of myo-inositol as a treatment for diagnosed GDM, showing low-grade evidence for an effect on improved glucose metabolism and reduced maternal weight gain.[92]

Dietary myo-inositol is widely found in plant foods, and usual intakes range from approximately 115–1500 mg/d depending on the quantity of plant-based foods consumed.[93] As a supplement, myo-inositol is considered safe in humans at the typical clinical dose of 4 g/d.[23] The only adverse effects identified were at 12 g/d, which included nausea, diarrhea, and flatus. No adverse maternal or neonatal outcomes have been reported from antenatal supplementation.[94] Given that this supplement is widely available and has a good safety profile, it is imperative that further studies are carried out to confirm its benefits in GDM given the high incidence and associated morbidity of this condition.

CHOLINE

Choline is a vitamin-like nutrient that is required to synthesize cell membrane phospholipids and neurotransmitters and is critical for embryonic development, in particular brain development.[95] Along with folic acid, choline is involved in 1-carbon metabolism and is required in the conversion of homocysteine to methionine. Low dietary intake and serum levels of choline have been associated with increased risk for neural tube defects independent of folate intake.[96,97] As a methyl-donor, choline supplementation during the third trimester of pregnancy has been shown to epigenetically modify expression of cortisol-regulating genes, which may alter the hypothalamic-pituitary-adrenal axis of the child and impact stress reactivity.[98] Moreover, supplementation in the second trimester has been shown to be related to improved sensory gating, proposed to be associated with later attention deficits and psychological disorders.[99]

The recommended intake of choline is lower in the United States, at 450 mg/d,[9] while the European Food Safety Authority states a value of 480 mg/d, noting, however, that further study is required to determine whether there are increased requirements in the second half of pregnancy.[7] It is also worth noting that common genetic variants in the choline and folate pathways may lead to increased requirements.[24] Choline is predominantly sourced in the diet and present in a wide variety of foods from animal-source meat, fish, dairy, and eggs to beans, cruciferous vegetables, nuts, and seeds.[100] There are no known adverse effects of choline when consumed at levels below the recommended upper intake level of 3500 mg/d for adults, which is the level set in the EU and United States.[9] A dose of 930 mg/d in the third trimester was found to improve maternal and fetal biomarkers of choline metabolism with no adverse effects.[101] The choline and betaine metabolite trimethylamine N-oxide has been controversially implicated in cardiovascular disease; however, there is no association between dietary choline or betaine and cardiovascular disease.[102]

CALCIUM

The role of calcium in bone mineralization is well known and this is widely recognized as an important

consideration in pregnancy for both fetal bone mineralization and to prevent a reduction in maternal bone density in pregnancy and postpartum. Supplementation at 1200 mg calcium carbonate per day was found to markedly reduce bone resorption in pregnant women and at 1 month postpartum,[103] and at 2000 mg/d was shown to increase bone mineral content in the neonate.[104] Maternal supplementation in pregnancy has also been shown to reduce risk of dental caries in children at age 12 years.[105]

Calcium is also a critical factor in regulating blood pressure, via calcium-dependent hormones and the renin-angiotensin pathway, which maintains cellular calcium homeostasis.[106] Calcium supplementation at 1–2 g/d in high-risk populations is strongly recommended by the WHO as a means of preventing preeclampsia.[25] With regards to other pregnancy outcomes, one Cochrane review concluded that supplementation does not appear to prevent preterm birth but may have modest effects in preventing low infant birth weight.[26]

Recommended intake in pregnancy is 1000 mg/d in both the EU and the United States.[7,18] Globally, most countries fall below this level, except for a small number of northern European countries.[107] The most common source is dairy products, but dairy intake may be avoided by certain individuals because of intolerance or dietary choices such as veganism. Other good sources include nuts, tofu, tinned fish with bones, and also dark-green vegetables, although absorption is hindered in the latter by oxalate. Calcium absorption is also dependent on vitamin D status.[108] Given the aforementioned prevalence of vitamin D insufficiency, both calcium intake and calcium absorption are important considerations.

Pregnant women should be counseled to increase dietary calcium intake, and in cases where intake is suboptimal or dairy is excluded from the diet, supplementation may be recommended.[109] A number of large placebo-controlled trials using supplementation up to 2500 mg/d, exclusive of dietary intake, have shown no adverse effects in pregnancy.[109] Increased cardiovascular risk with calcium supplementation is controversial and not well supported.[110] Most studies examine risk between 500 mg/d and 1 g/d of calcium, but no risk is assumed with supplementation in generally healthy adults below the tolerable upper limit of 2500 mg/d, as set in the EU and United States.[4,18,111]

IODINE

Iodine is an essential nutrient for fetal growth and development, which may be widely misunderstood by the general population. Iodine is required for thyroid hormone synthesis, and delivery of thyroxine via the placenta is essential until fetal synthesis is sufficient at approximately 17–19 weeks' gestation.[112] Even subclinical hypothyroidism can double the risk of miscarriage and neonatal death.[113,114] Reduced maternal thyroid function and maternal iodine deficiency have been associated, in a number of large-scale studies, with impaired neurodevelopment, cognitive development, behavioral issues, learning skills, and intelligence quotient in children.[115–118]

Given these important findings, there has been much debate as to whether broad guidelines recommending iodine supplementation in pregnancy should be issued. Some countries, such as Australia and New Zealand, recommend intake of 150 µg/d for all pregnant women.[119] However, there are risks to over-supplementation in populations that may be replete. Excessive iodine intake may cause alterations in thyroid function, inducing hypothyroidism or hyperthyroidism in some, particularly those with antithyroid antibodies.[120] These risks are mostly associated with a sudden increase in iodine intake in those with thyroid disease and are unlikely to occur with moderate increases in normal pregnant women. Excess intake, however, has also been linked with impaired child neurodevelopment where supplementation at 150 µg/d was analyzed in a replete population in Spain.[121]

The recommended daily intake in pregnancy is 200 µg in the EU[7] and 220 µg in the United States.[6] The best sources are nonorganic dairy, eggs, freshwater fish, and iodized salt in countries where it is fortified.[7] Urine iodine clearance should increase in pregnancy from an optimal 150 µg/L to between 150 and 249 µg/L.[122] It would be ideal to measure thyroid function, including presence of antibodies along with urine iodine levels, in order to safely tailor supplementation. However, this is difficult in pregnant women, though an estimation might be achievable.[120,123] Where testing is not practical, dietary questioning is useful. Where dairy is avoided because of intolerance or choice, and in vegans who avoid eggs and fish also, iodine supplementation is usually required.[4] A dose of 200 µg/d of supplemental iodine in mildly iodine-deficient pregnant women increased iodine intakes into the sufficient range of 150–249 µg/L,[124] where other studies have shown that initiating 150µg/d during pregnancy is insufficient to reach this level.[125–127] The WHO recommends supplementing with 250 µg/d for pregnant women in countries without access to iodized salt.[128] Ideally, supplementation in deficient women before conception would help to optimize status during pregnancy.[129] It is important to note that where testing is not available, over-supplementation should be cautioned. The tolerable upper limit of 600 µg/d in the EU,[4] and even higher at 1100 µg/d in the United States,[6] is herein considered excessive given the high incidence of thyroid disease.[130]

IRON

Prevalence of iron deficiency is difficult to estimate given that there is poor distinction in some studies between iron-deficiency anemia and other forms of anemia. The WHO estimates the prevalence of anemia worldwide to be 41.8% in pregnancy, with approximately half of these cases attributed to iron deficiency.[131] Iron-deficiency anemia during the first 2 trimesters in pregnancy is a risk factor for preterm labor and low birth weight and predicts iron deficiency in infants.[132–134] A Cochrane review of the evidence has shown that iron supplementation can restore sufficiency and resolve anemia, but the evidence is unclear for other maternal or neonatal outcomes.[135]

Routine supplementation is not recommended as there are risks to elevated iron status also including impaired immunity, and evidence exists for a U-shaped curve with regards to iron status and both preterm labor and SGA.[27,28] It is important to add that hereditary hemochromatosis is a relatively common genetic condition, especially in Europe, which often is not clinically relevant or diagnosed until after pregnancy.[136]

The recommended intake is 16 mg/d in the EU[7] and higher, at 27 mg/d, in the United States.[6] All pregnant women should be counseled to increase dietary intake and optimize absorption. Heme iron – found in red meat, for example – has higher bioavailability, while in contrast, non-heme iron – found in plant sources such as legumes, nuts, and dark-green vegetables – is poorly absorbed. Vitamin C as ascorbic acid increases iron absorption from non-haem iron sources, while phytic acid in cereals, grains and legumes inhibits iron absorption.[137]

In pregnancy, a woman is considered anemic if her hemoglobin is <110 g/L in the first or third trimester or <105 g/L in the second trimester.[138] When supplementing, oral iron should result in an increase in hemoglobin within 2 weeks to be considered confirmation of iron deficiency.[139] There is no tolerable upper limit set for iron in the EU given sparse evidence regarding risk for serious adverse events, excluding those individuals with hereditary hemochromatosis, who should avoid supplementation.[4] Side effects, including gastrointestinal discomfort, nausea, and constipation, are commonly reported at levels of 40–50 mg/d, and the tolerable upper intake in the United States, of 45 mg/d, is based solely on this.[6] These are common complaints in pregnant women and iron supplementation may exacerbate discomfort. Intermittent (doses >80 mg weekly) rather than daily iron (doses >40 mg/d) supplementation is less likely to cause side effects.[140] Iron glycinate chelate at 15–25 mg/d is also better tolerated and is significantly more effective for treating iron deficiency in pregnant women than ferrous sulfate at doses of 40–50 mg/d.[141–143]

MAGNESIUM

Magnesium may inhibit preterm uterine contractions via calcium antagonism, and deficiency has been associated with increased risk of preterm labor or preterm birth.[144] Via this mechanism, magnesium supplementation may also be helpful for leg cramps.[145]

Magnesium also inhibits angiotensin II and has a vasodilatory effect. Intravenous magnesium sulfate is recommended in the treatment of preeclampsia, and lower magnesium levels have been observed in women with hypertensive disorders of pregnancy.[146] A randomized controlled trial showed that supplementation of 300 mg magnesium citrate per day, when commenced at 25 weeks' gestation, reduced the incidence of high blood pressure at 37 weeks.[147] In another study, supplementation in magnesium-deficient pregnant women at 300 mg/d significantly reduced multiple maternal and fetal outcomes, including preeclampsia, intrauterine growth restriction, preterm birth, low birth weight, and Apgar score below 7.[148]

Magnesium is involved in multiple steps of the insulin signaling pathways and impairment of magnesium-dependent channels is a proposed mechanism in GDM.[149] Supplementation in deficient pregnant women, at 250 mg/d for 6 weeks, significantly improved glucose control and insulin secretion, whereas the placebo group worsened over time.[150] Combined with vitamin E supplementation in another study, similar effects were observed with glucose control, insulin secretion, and homeostatic model assessment index, along with an improvement in serum lipids, although magnesium deficiency was not well established in this study group.[151]

A Cochrane review of clinical trials concluded that magnesium supplementation during pregnancy currently lacks strong evidence for maternal and child outcomes.[152] However, this review has been criticized for excluding several studies that demonstrate benefit such as reduced frequency of spontaneous abortion, premature deliveries and pregnancy complications.[153] In addition, it may be that magnesium supplementation is most effective for sub-groups with magnesium deficiency. Many studies utilize serum magnesium to measure adequacy which is highly unreliable and in turn reduces the power of meta-analyses.[144]

Accurate measurement of magnesium deficiency is challenging, but dietary analyses show that over half of women aged 19–50 years in the United States and United Kingdom do not meet the average requirements.[29,30] The recommended intake for pregnant

women is 300 mg/d in the EU[11] and 350 mg in the United States.[31] Good sources include nuts and seeds, legumes and whole grains. As a supplement, magnesium is considered very safe, with a tolerable upper limit for supplementation without side effects at 250 mg/d set in the EU[4] and a higher level of 350 mg/d in the United States.[31] Side effects over 350 mg/d include mild diarrhea, which is reversible, and doses should be divided to minimize this. Toxic hypermagnesemia, which may present as hypotension or muscular weakness, is only seen at oral doses >2500 mg/d,[4] although caution is advised where amounts absorbed are unclear – as in magnesium enemas or high doses of magnesium-based laxatives or antacids.

ZINC

Zinc is required for the activity of over 300 enzymes and is essential for life, growth, and development.[154] Zinc-dependent enzymes and zinc-finger transcription factors play a critical role in deoxyribonucleic acid replication, cell proliferation, and gene transcription. Zinc deficiency can impair child growth and development, increasing risk of retardation or SGA and influencing the phenotype such that many features of fetal alcohol syndrome can be related to the impaired zinc metabolism caused by alcohol.[155] Zinc deficiency in neonates may increase risk for infection and cause dermatitis. Early neonatal brain development is especially sensitive to zinc deficiency.[156]

Intervention studies with zinc supplementation have shown mixed outcomes, with the most marked results evident with growth, including lean-tissue and bone growth, and survival in zinc-deficient populations or low-income populations.[157–160] Zinc supplementation has also been shown, in small randomized controlled trials, to improve glucose metabolism and reduce C-reactive protein in women with GDM when supplementing with 30 mg elemental zinc.[161,162] Zinc has been proposed as a safe alternative to oral antibiotics, retinoids, and corticosteroids for the treatment of acne in pregnancy.[163]

Zinc absorption is markedly affected by the phytate content of the diet. The recommended intake has therefore been designated a range in the EU from 9.1 mg in a very low phytate diet (high meat, low grains or cereals, low legume intake) to 14.3 mg in a high phytate diet such as vegetarian, vegan, or low meat diet.[7] The US level is set at 11 mg/d, although it is noted that the requirements may be 50% higher in vegans.[6] It is also important to note that low meat diets may exist in low-income populations. The tolerable upper limit is set at 25 mg/d in the EU and 40 mg/d in the United States, although no studies have shown adverse reproductive effects up to 90 mg/d.[4,6] Zinc exposure has not been found to be teratogenic; on the contrary, adequate zinc intake may prevent teratogenesis.[164]

OMEGA-3

Omega-3 fatty acids are essential in many aspects of health and play an important structural role in cell membranes. A large number of studies have linked optimal omega-3 intake with positive fetal and maternal outcomes. Docosahexaenoic acid (DHA), in particular, is a critical component of cell membranes in the brain and retina and is essential for fetal development; fetal DHA accretion is markedly increased in the third trimester.[165] Maternal omega-3 supplementation has been shown to improve short- and long-term neurodevelopment and visual acuity.[166] In several reviews and meta-analyses, supplementation has also been shown to increase birth weight and length of gestation and reduce risk of early or preterm delivery.[32,167,168]

Low maternal omega-3 levels have also been associated with higher risk of postpartum depression and negatively correlate with the Edinburgh Postnatal Depression Scale score, although clearly this is only one of many factors in the etiology.[10,169] A 2013 Cochrane review showed that there was no benefit to omega-3 or DHA supplementation in pregnancy in reducing risk of postpartum depression.[170] A more recent and comprehensive meta-analysis identified mixed results that may depend on baseline status and predisposition or preexisting maternal depression.[169] A small randomized control trial in a low-income population showed reduced stress hormone output and stress responses in pregnant women after supplementation with DHA.[171]

Owing to its critical immunomodulatory role, maternal omega-3 supplementation has also been shown to improve the immunological health of offspring. The risk of atopic eczema and likelihood of having a positive skin prick test to any allergen tested or to any food extract was markedly reduced.[172] In another trial, incidence of asthma, persistent wheeze, and lower respiratory tract infections was also markedly reduced.[173]

The best sources of omega-3 fatty acids, including DHA, are oily fish such as salmon, mackerel, herring, anchovies, and sardines. Pregnant women should be counseled to increase fish intake during pregnancy. However, caution is advised owing to levels of contaminants in high-fat fish, such as dioxins and dioxin-like compounds, which may have detrimental effects on the developing fetus.[174] Wild Pacific salmon is lower in these compounds than farmed European or wild Atlantic salmon, but intake should still be limited to 1 portion per month. To achieve the benefits of omega-3 in pregnancy, a supplement of at least 200 mg of DHA

per day could be used, but a good-quality supplement that has been tested for contaminants and dioxins should always be selected.[175,176]

The recommended intake for DHA has not been officially established in the United States, but recommendations put forward are similar to the EU value of 250 mg/d with an added 200 mg of DHA in pregnancy.[7,33] This would equate to 1 portion of wild Pacific salmon or other oily fish plus 200 mg daily DHA supplementation. One meta-analysis suggested that studies demonstrating the greatest efficacy on birth outcomes have used doses in the range of 1–2 g of omega-3 per day,[177] and this may be required in individuals with chronic low intake of fish. In clinical trials, no harmful effect on the mother or the neonate has been observed with doses up to 2.7 g/d.[32] Potential adverse effects include mild gastrointestinal disturbances such as unpleasant breath or bad taste and mild reflux.[178]

CONCLUSION

This review sets out recommendations for safe and effective supplementation in pregnancy. Pregnant women should be counseled to focus on a well-balanced diet and important sources of particular nutrients. Supplementation may benefit certain individuals who avoid certain food groups such as meat or animal products, or who are at greater risk of deficiencies. In addition, incidence of negative maternal and fetal outcomes may be reduced in high-risk pregnancies. Given the high burden of pregnancy complications, nutritional supplementation is a safe and cost-effective way to reduce risk of outcomes such as preeclampsia, GDM, and SGA, amongst others.

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REFERENCES

1. Gomez MF, Field CJ, Olstad DL, et al. Use of micronutrient supplements among pregnant women in Alberta: results from the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort. *Matern Child Nutr.* 2015;11:497–510.
2. Sullivan KM, Ford ES, Azrak MF, et al. Multivitamin use in pregnant and nonpregnant women: results from the Behavioral Risk Factor Surveillance System. *Public Health Rep.* 2009;124:384–390.
3. Shand AW, Walls M, Chatterjee R, et al. Dietary vitamin, mineral and herbal supplement use: a cross-sectional survey of before and during pregnancy use in Sydney, Australia. *Aust N Z J Obstet Gynaecol.* 2016;56:154–161.
4. European Food Safety Authority (EFSA). Scientific Committee on Food Scientific Panel on Dietetic Products, Nutrition and Allergies. Tolerable Upper Intake Levels for Vitamins and Minerals; 2016. Available at: https://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf. Accessed on May 7, 2019.
5. Blumberg J, Heaney RP, Huncharek M, et al. Evidence-based criteria in the nutritional context. *Nutr Rev.* 2010;68:478–484.
6. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academy Press; 2001.
7. European Food Safety Authority (EFSA). *Dietary Reference Values for Nutrients: Summary Report*. EFSA Supporting Publication; 2017:e15121. Available at: https://www.efsa.europa.eu/sites/default/files/2017_09_DRVs_summary_report.pdf. Accessed May 5, 2019.
8. Dror DK, Allen LH. Interventions with vitamins B6, B12 and C in pregnancy. *Paediatr Perinat Epidemiol*. 2012;26(suppl 1):55–74.
9. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. Washington DC: National Academy Press; 1998.
10. Markhus MW, Skotheim S, Graff IE, et al. Low omega-3 index in pregnancy is a possible biological risk factor for postpartum depression. *PLoS One*. 2013;8:e67617.
11. Schleicher RL, Carroll MD, Ford ES, et al. Serum vitamin C and the prevalence of vitamin C deficiency in the United States: 2003-2004 National Health and Nutrition Examination Survey (NHANES). *Am J Clin Nutr*. 2009;90:1252–1263.
12. Madruga de Oliveira A, Rondo PH, Barros SB. Concentrations of ascorbic acid in the plasma of pregnant smokers and nonsmokers and their newborns. *Int J Vitam Nutr Res.* 2004;74:193–198.
13. Wrieden WL, Hannah MK, Bolton-Smith C, et al. Plasma vitamin C and food choice in the third Glasgow MONICA population survey. *J Epidemiol Community Health*. 2000;54:355–360.
14. Juhl B, Lauszus FF, Lykkesfeldt J. Is diabetes associated with lower vitamin C status in pregnant women? A prospective study. *Int J Vitam Nutr Res.* 2016;86:184–189.
15. Panel on Dietary Antioxidants and Related Compounds. *Institute of Medicine. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington DC: National Academy Press; 2000.
16. Casanueva E, Ripoll C, Tolentino M, et al. Vitamin C supplementation to prevent premature rupture of the chorioamniotic membranes: a randomized trial. *Am J Clin Nutr.* 2005;81:859–863.
17. O'Callaghan KM, Kiely ME. Ethnic disparities in the dietary requirement for vitamin D during pregnancy: considerations for nutrition policy and research. *Proc Nutr Soc.* 2018;77:164–173.
18. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academy Press; 2010.
19. Wagner CL, McNeil RB, Johnson DD, et al. Health characteristics and outcomes of two randomized vitamin D supplementation trials during pregnancy: a combined analysis. *J Steroid Biochem Mol Biol.* 2013;136:313–320.
20. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96:1911–1930.
21. Greene ND, Leung KY, Copp AJ. Inositol, neural tube closure and the prevention of neural tube defects. *Birth Defects Res*. 2017;109:68–80.
22. Crawford TJ, Crowther CA, Alsweiler J, et al. Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes. *Cochrane Database Syst Rev.* 2015;CD011507. doi:10.1002/14651858.CD011507.pub2.
23. Carlomagno G, Unfer V. Inositol safety: clinical evidences. *Eur Rev Med Pharmacol Sci*. 2011;15:931–936.
24. Ganz AB, Klatt KC, Caudill MA. Common genetic variants alter metabolism and influence dietary choline requirements. *Nutrients*. 2017;9:837–848.
25. WHO. *Guideline: Calcium Supplementation in Pregnant Women*. Geneva: World Health Organization; 2013.
26. Buppasiri P, Lumbiganon P, Thinkhamrop J, et al. Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. *Cochrane Database Syst Rev*. 2015;CD007079. doi:10.1002/14651858.CD007079.pub3.
27. Dewey KG, Oaks BM. U-shaped curve for risk associated with maternal hemoglobin, iron status, or iron supplementation. *Am J Clin Nutr.* 2017;106(suppl 6):1694S–1702S.
28. Brannon PM, Taylor CL. Iron supplementation during pregnancy and infancy: uncertainties and implications for research and policy. *Nutrients*. 2017;9:1327–1343.

29. Moshfegh A, Goldman J, Ahuja J, et al. What we eat in America NHANES 2005-2006: usual nutrient intakes from food and water compared to 1997 Dietary Reference Intakes for vitamin D, calcium, phosphorus and magnesium. US Department of Agriculture, Agricultural Research Service. 2009. Available at: http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/0506/usual_nutrient_intake_vitD_ca_phos_mg_2005-06.pdf. Accessed February 9, 2019.
30. National Diet and Nutrition Survey (NDNS) 2000/2001. The National Diet & Nutrition Survey: adults aged 19 to 64 years Volume 3. 2003. Available at: http://www.ons.gov.uk/ons/rel/lifestyles/the-national-diet-and-nutrition-survey/2001-edition/index.html. Accessed February 9, 2019.
31. Food and Nutrition Board, Institute of Medicine (IOM). *Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride*. Washington, DC: National Academy Press; 1997.
32. Larque E, Gil-Sanchez A, Prieto-Sanchez MT, et al. Omega 3 fatty acids, gestation and pregnancy outcomes. *Br J Nutr*. 2012;107(suppl 2):S77–S84.
33. Harris WS, Mozaffarian D, Lefevre M, et al. Towards establishing dietary reference intakes for eicosapentaenoic and docosahexaenoic acids. *J Nutr*. 2009;139:804S–819S.
34. Finnell RH, Shaw GM, Lammer EJ, et al. Gene-nutrient interactions: importance of folates and retinoids during early embryogenesis. *Toxicol Appl Pharmacol*. 2004;198:75–85.
35. Checkley W, West KP Jr, Wise RA, et al. Maternal vitamin A supplementation and lung function in offspring. *N Engl J Med*. 2010;362:1784–1794.
36. Azais-Braesco V, Pascal G. Vitamin A in pregnancy: requirements and safety limits. *Am J Clin Nutr*. 2000;71(suppl 5):1325S–1333S.
37. McCauley ME, van den Broek N, Dou L, et al. Vitamin A supplementation during pregnancy for maternal and newborn outcomes. *Cochrane Database Syst Rev*. 2015;CD008666. doi:10.1002/14651858.CD008666.pub3.
38. Palmer AC, Schulze KJ, Khatry SK, et al. Maternal vitamin A supplementation increases natural antibody concentrations of preadolescent offspring in rural Nepal. *Nutrition*. 2015;31:813–819.
39. WHO. *Global Prevalence of Vitamin A Deficiency in Populations at Risk 1995–2005. WHO Global Database on Vitamin A Deficiency*. Geneva: World Health Organization; 2009.
40. Rothman KJ, Moore LL, Singer MR, et al. Teratogenicity of high vitamin A intake. *N Engl J Med*. 1995;333:1369–1373.
41. Bowling FG. Pyridoxine supply in human development. *Semin in Cell Dev Biol*. 2011;22:611–618.
42. Ronnenberg AG, Venners SA, Xu X, et al. Preconception B-vitamin and homocysteine status, conception, and early pregnancy loss. *Am J Epidemiol*. 2007;166:304–312.
43. Salam RA, Zuberi NF, Bhutta ZA. Pyridoxine (vitamin B6) supplementation during pregnancy or labour for maternal and neonatal outcomes. *Cochrane Database Syst Rev*. 2015;CD000179. doi:10.1002/14651858.CD000179.pub3.
44. Matthews A, Haas DM, O'Mathuna DP, et al. Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst Rev*. 2015;CD007575. doi:10.1002/14651858.CD007575.pub4.
45. Hisano M, Suzuki R, Sago H, et al. Vitamin B6 deficiency and anemia in pregnancy. *Eur J Clin Nutr*. 2010;64:221–223.
46. Ghavanini AA, Kimpinski K. Revisiting the evidence for neuropathy caused by pyridoxine deficiency and excess. *J Clin Neuromuscular Dis*. 2014;16:25–31.
47. Vrolijk MF, Opperhuizen A, Jansen E, et al. The vitamin B6 paradox: supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function. *Toxicol In Vitro*. 2017;44:206–212.
48. De-Regil LM, Pena-Rosas JP, Fernandez-Gaxiola AC, et al. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. *Cochrane Database Syst Rev*. 2015;CD007950. doi:10.1002/14651858.CD007950.pub3.
49. Zaganjor I, Sekkarie A, Tsang BL, et al. Describing the prevalence of neural tube defects worldwide: a systematic literature review. *PLoS One*. 2016;11:e0151586.
50. Bulloch RE, Lovell AL, Jordan VMB, et al. Maternal folic acid supplementation for the prevention of preeclampsia: a systematic review and meta-analysis. *Paediatr Perinat Epidemiol*. 2018;32:346–357.
51. Zhang Q, Wang Y, Xin X, et al. Effect of folic acid supplementation on preterm delivery and small for gestational age births: a systematic review and meta-analysis. *Reprod Toxicol*. 2017;67:35–41.
52. Field MS, Stover PJ. Safety of folic acid. *Ann N Y Acad Sci*. 2018;1414:59–71.
53. Murray LK, Smith MJ, Jadavji NM. Maternal oversupplementation with folic acid and its impact on neurodevelopment of offspring. *Nutr Rev*. 2018;76:708–721.
54. Dolin CD, Deierlein AL, Evans MI. Folic acid supplementation to prevent recurrent neural tube defects: 4 milligrams is too much. *Fetal Diagn Ther*. 2018;44:161–165.
55. Obeid R, Holzgreve W, Pietrzik K. Is 5-methyltetrahydrofolate an alternative to folic acid for the prevention of neural tube defects? *J Perinat Med*. 2013;41:469–483.
56. Obeid R, Schon C, Wilhelm M, et al. The effectiveness of daily supplementation with 400 or 800 μg/day folate in reaching protective red blood folate concentrations in non-pregnant women: a randomized trial. *Eur J Nutr*. 2018;57:1771–1780.
57. Finkelstein JL, Layden AJ, Stover PJ. Vitamin B-12 and perinatal health. *Adv Nutr*. 2015;6:552–563.
58. Paul L, Selhub J. Interaction between excess folate and low vitamin B12 status. *Mol Aspects Med*. 2017;53:43–47.
59. Shipton MJ, Thachil J. Vitamin B12 deficiency – a 21st century perspective. *Clin Med*. 2015;15:145–150.
60. Katre P, Bhat D, Lubree H, et al. Vitamin B12 and folic acid supplementation and plasma total homocysteine concentrations in pregnant Indian women with low B12 and high folate status. *Asia Pacific J Clin Nutr*. 2010;19:335–343.
61. Stabler SP. Clinical practice. Vitamin B12 deficiency. *N Engl J Med*. 2013;368:149–160.
62. Sharabi A, Cohen E, Sulkes J, et al. Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route. *Br J Clin Pharmacol*. 2003;56:635–638.
63. Rumbold A, Ota E, Nagata C, et al. Vitamin C supplementation in pregnancy. *Cochrane Database Syst Rev*. 2015;CD004072. doi:10.1002/14651858.CD004072.pub3.
64. Sharma R, Mehta S. Ascorbic Acid concentration and preterm premature rupture of membranes. *J Obstet Gynaecol India*. 2014;64:417–420.
65. Stuart EL, Evans GS, Lin YS, et al. Reduced collagen and ascorbic acid concentrations and increased proteolytic susceptibility with prelabor fetal membrane rupture in women. *Biol Reprod*. 2005;72:230–235.
66. Ochoa-Brust GJ, Fernandez AR, Villanueva-Ruiz GJ, et al. Daily intake of 100 mg ascorbic acid as urinary tract infection prophylactic agent during pregnancy. *Acta Obstet Gynecol Scand*. 2007;86:783–787.
67. Frei B, Birlouez-Aragon I, Lykkesfeldt J. Authors' perspective: what is the optimum intake of vitamin C in humans? *Crit Rev Food Sci Nutr*. 2012;52:815–829.
68. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? *J Steroid Biochem Mol Biol*. 2014;144(pt A):138–145.
69. van der Pligt P, Willcox J, Szymlek-Gay EA, et al. Associations of maternal vitamin D deficiency with pregnancy and neonatal complications in developing countries: a systematic review. *Nutrients*. 2018;10:640–661.
70. Wang J, Liu N, Sun W, et al. Association between vitamin D deficiency and antepartum and postpartum depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gynecol Obstet*. 2018;298:1045–1059.
71. Sharif K, Sharif Y, Watad A, et al. Vitamin D, autoimmunity and recurrent pregnancy loss: more than an association. *Am J Reprod Immunol*. 2018;80:e12991.
72. Goncalves DR, Braga A, Braga J, et al. Recurrent pregnancy loss and vitamin D: a review of the literature. *Am J Reprod Immunol*. 2018;80:e13022.
73. Wolsk HM, Harshfield BJ, Laranjo N, et al. Vitamin D supplementation in pregnancy, prenatal 25(OH)D levels, race, and subsequent asthma or recurrent wheeze in offspring: secondary analyses from the Vitamin D Antenatal Asthma Reduction Trial. *J Allergy Clin Immunol*. 2017;140:1423–1429. e1425.
74. Perez-Lopez FR, Pasupuleti V, Mezones-Holguin E, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril*. 2015;103:1278–1288. e1274.
75. Rumbold A, Ota E, Hori H, et al. Vitamin E supplementation in pregnancy. *Cochrane Database Syst Rev*. 2015;CD004069. doi:10.1002/14651858.CD004069.pub3.
76. Wang YP, Walsh SW, Guo JD, et al. Maternal levels of prostacyclin, thromboxane, vitamin E, and lipid peroxides throughout normal pregnancy. *Am J Obstetr Gynecol*. 1991;165:1690–1694.
77. Scholl TO, Chen X, Sims M, et al. Vitamin E: maternal concentrations are associated with fetal growth. *Am J Clin Nutr*. 2006;84:1442–1448.
78. Fares S, Sethom MM, Khouaja-Mokrani C, et al. Vitamin A, E, and D deficiencies in tunisian very low birth weight neonates: prevalence and risk factors. *Pediatr Neonatol*. 2014;55:196–201.
79. Shamim AA, Schulze K, Merrill RD, et al. First-trimester plasma tocopherols are associated with risk of miscarriage in rural Bangladesh. *Am J Clin Nutr*. 2015;101:294–301.
80. Shahraki AD. Effects of vitamin E, calcium carbonate and milk of magnesium on muscular cramps in pregnant women. *J Med Sci*. 2006;6:979–983.
81. Wu H, Zhang C, Wang Y, et al. Does vitamin E prevent asthma or wheeze in children: a systematic review and meta-analysis. *Paediatr Respir Rev*. 2018;27:60–68.
82. Traber MG. Vitamin E inadequacy in humans: causes and consequences. *Adv Nutr*. 2014;5:503–514.
83. Shahrook S, Ota E, Hanada N, et al. Vitamin K supplementation during pregnancy for improving outcomes: a systematic review and meta-analysis. *Sci Rep*. 2018;8:11459–11469.
84. Phillippi JC, Holley SL, Morad A, et al. Prevention of vitamin K deficiency bleeding. *J Midwifery Women's Health*. 2016;61:632–636.
85. Fusaro M, Mereu MC, Aghi A, et al. Vitamin K and bone. *Clin Cases Miner Bone Metab*. 2017;14:200–206.
86. Tsuchie H, Miyakoshi N, Hongo M, et al. Amelioration of pregnancy-associated osteoporosis after treatment with vitamin K(2): a report of four patients. *Ups J Med Sci*. 2012;117:336–341.

87. Walther B, Karl JP, Booth SL, et al. Menaquinones, bacteria, and the food supply: the relevance of dairy and fermented food products to vitamin K requirements. *Adv Nutr*. 2013;4:463–473.
88. Zeng L, Yang K. Effectiveness of myoinositol for polycystic ovary syndrome: a systematic review and meta-analysis. *Endocrine*. 2018;59:30–38.
89. Zheng X, Lin D, Zhang Y, et al. Inositol supplement improves clinical pregnancy rate in infertile women undergoing ovulation induction for ICSI or IVF-ET. *Medicine*. 2017;96:e8842–8849.
90. Beemster P, Groenen P, Steegers-Theunissen R. Involvement of inositol in reproduction. *Nutr Rev.* 2002;60:80–87.
91. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. *Curr Diabetes Rep*. 2016;16:7.
92. Brown J, Crawford TJ, Alsweiler J, et al. Dietary supplementation with myo-inositol in women during pregnancy for treating gestational diabetes. *Cochrane Database Syst Rev*. 2016;9:CD012048. doi:10.1002/14651858.CD012048.pub2.
93. Dinicola S, Minini M, Unfer V, et al. Nutritional and acquired deficiencies in inositol bioavailability. Correlations with metabolic disorders. *Int J Mol Sci*. 2017;18:2187–2204.
94. Noventa M, Vitagliano A, Quaranta M, et al. Preventive and therapeutic role of dietary inositol supplementation in periconceptional period and during pregnancy: a summary of evidences and future applications. *Reprod Sci*. 2016;23:278–288.
95. Zeisel SH. The supply of choline is important for fetal progenitor cells. *Semin Cell Dev Biol*. 2011;22:624–628.
96. Shaw GM, Carmichael SL, Yang W, et al. Periconceptional dietary intake of choline and betaine and neural tube defects in offspring. *Am J Epidemiol*. 2004;160:102–109.
97. Shaw GM, Finnell RH, Blom HJ, et al. Choline and risk of neural tube defects in a folate-fortified population. *Epidemiology*. 2009;20:714–719.
98. Jiang X, Yan J, West AA, et al. Maternal choline intake alters the epigenetic state of fetal cortisol-regulating genes in humans. *FASEB J*. 2012;26:3563–3574.
99. Ross RG, Hunter SK, McCarthy L, et al. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. *Am J Psychiatry*. 2013;170:290–298.
100. United States Department of Agriculture. *National Database for Standard Reference*. Maryland, United States: United States Department of Agriculture National Agricultural Library; 2014.
101. Yan J, Jiang X, West AA, et al. Maternal choline intake modulates maternal and fetal biomarkers of choline metabolism in humans. *Am J Clin Nutr*. 2012;95:1060–1071.
102. Meyer KA, Shea JW. Dietary choline and betaine and risk of CVD: a systematic review and meta-analysis of prospective studies. *Nutrients*. 2017;9:711–723.
103. Ettinger AS, Lamadrid-Figueroa H, Mercado-Garcia A, et al. Effect of calcium supplementation on bone resorption in pregnancy and the early postpartum: a randomized controlled trial in Mexican women. *Nutr J*. 2014;13:116.
104. Koo WW, Walters JC, Esterlitz J, et al. Maternal calcium supplementation and fetal bone mineralization. *Obstet Gynecol*. 1999;94:577–582.
105. Bergel E, Gibbons L, Rasines MG, et al. Maternal calcium supplementation during pregnancy and dental caries of children at 12 years of age: follow-up of a randomized controlled trial. *Acta Obstet Gynecol Scand*. 2010;89:1396–1402.
106. Resnick LM. The role of dietary calcium in hypertension: a hierarchical overview. *Am J Hypertens*. 1999;12:99–112.
107. Balk EM, Adam GP, Langberg VN, et al. Global dietary calcium intake among adults: a systematic review. *Osteoporos Int*. 2017;28:3315–3324.
108. Fleet JC, Schoch RD. Molecular mechanisms for regulation of intestinal calcium absorption by vitamin D and other factors. *Crit Rev Clin Lab Sci*. 2010;47:181–195.
109. Hacker AN, Fung EB, King JC. Role of calcium during pregnancy: maternal and fetal needs. *Nutr Rev*. 2012;70:397–409.
110. Lewis JR, Radavelli-Bagatini S, Rejnmark L, et al. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. *J Bone Miner Res*. 2015;30:165–175.
111. Chung M, Tang AM, Fu Z, et al. Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis. *Ann Intern Med*. 2016;165:856–866.
112. Chan SY, Vasilopoulou E, Kilby MD. The role of the placenta in thyroid hormone delivery to the fetus. *Nat Rev Endocrinol*. 2009;5:45–54.
113. Zhang Y, Wang H, Pan X, et al. Patients with subclinical hypothyroidism before 20 weeks of pregnancy have a higher risk of miscarriage: a systematic review and meta-analysis. *PLoS One*. 2017;12:e0175708–e0175720.
114. Maraka S, Ospina NM, O'Keeffe DT, et al. Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. *Thyroid*. 2016;26:580–590.
115. Abel MH, Caspersen IH, Meltzer HM, et al. Suboptimal maternal iodine intake is associated with impaired child neurodevelopment at 3 years of age in the Norwegian mother and child cohort study. *J Nutr*. 2017;147:1314–1324.
116. Bath SC, Steer CD, Golding J, et al. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet*. 2013;382:331–337.
117. Markhus MW, Dahl L, Moe V, et al. Maternal iodine status is associated with offspring language skills in infancy and toddlerhood. *Nutrients*. 2018;10:1270–1282.
118. Abel MH, Ystrom E, Caspersen IH, et al. Maternal iodine intake and offspring attention-deficit/hyperactivity disorder: results from a large prospective cohort study. *Nutrients*. 2017;9:1239–1257.
119. National Health and Medical Research Council (NHMRC). *Iodine Supplementation for Pregnant and Breastfeeding Women*. NHMRC Public Statement. Canberra: Commonwealth of Australia; 2010.
120. Andersen SL, Laurberg P. Iodine supplementation in pregnancy and the dilemma of ambiguous recommendations. *Eur Thyroid J*. 2016;5:35–43.
121. Rebagliato M, Murcia M, Alvarez-Pedrerol M, et al. Iodine supplementation during pregnancy and infant neuropsychological development. INMA Mother and Child Cohort Study. *Am J Epidemiol*. 2013;177:944–953.
122. World Health Organization, United Nations Children's Fund, International Council for the Control of Iodine Deficiency Disorders. *Assessment of the Iodine Deficiency Disorders and Monitoring Their Elimination*. Geneva: WHO; 2006.
123. Wright C, Leeson H. Assessing iodine status in frontline healthcare. *J Nutri Med Diet Care*. 2018;4:028.
124. Gowachirapant S, Jaiswal N, Melse-Boonstra A, et al. Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2017;5:853–863.
125. Vandevijvere S, Amsalkhir S, Mourri AB, et al. Iodine deficiency among Belgian pregnant women not fully corrected by iodine-containing multivitamins: a national cross-sectional survey. *Br J Nutr*. 2013;109:2276–2284.
126. Lindorfer H, Krebs M, Kautzky-Willer A, et al. Iodine deficiency in pregnant women in Austria. *Eur J Clin Nutr*. 2015;69:349–354.
127. Stoutjesdijk E, Schaafsma A, Dijck-Brouwer DAJ, et al. Iodine status during pregnancy and lactation: a pilot study in the Netherlands. *Netherlands J Med*. 2018;76:210–217.
128. WHO, UNICEF. *Reaching Optimal Iodine Nutrition in Pregnant and Lactating Women and Young Children: A Joint Statement by WHO and UNICEF*. Geneva: World Health Organization; 2007.
129. Lazarus J, Brown RS, Daumerie C, et al. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J*. 2014;3:76–94.
130. Garmendia Madariaga A, Santos Palacios S, Guillen-Grima F, et al. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J Clin Endocrinol Metab*. 2014;99:923–931.
131. Lopez A, Cacoub P, Macdougall IC, et al. Iron deficiency anaemia. *Lancet*. 2016;387:907–916.
132. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet*. 2007;370:511–520.
133. Figueiredo A, Gomes-Filho IS, Silva RB, et al. Maternal anemia and low birth weight: a systematic review and meta-analysis. *Nutrients*. 2018;10:601–617.
134. Rahman MM, Abe SK, Rahman MS, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. *Am J Clin Nutr*. 2016;103:495–504.
135. Pena-Rosas JP, De-Regil LM, Garcia-Casal MN, et al. Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev*. 2015;CD004736. doi:10.1002/14651858.CD004736.pub5.
136. Worwood M. Inherited iron loading: genetic testing in diagnosis and management. *Blood Rev*. 2005;19:69–88.
137. Cook JD, Reddy MB. Effect of ascorbic acid intake on nonheme-iron absorption from a complete diet. *Am J Clin Nutr*. 2001;73:93–98.
138. WHO. *Guideline: Daily Iron and Folic Acid Supplementation in Pregnant Women*. Geneva: World Health Organization; 2012.
139. Pavord S, Myers B, Robinson S, et al. UK guidelines on the management of iron deficiency in pregnancy. *Br J Haematol*. 2012;156:588–600.
140. Pena-Rosas JP, De-Regil LM, Gomez Malave H, et al. Intermittent oral iron supplementation during pregnancy. *Cochrane Database Syst Rev*. 2015;CD009997. doi:10.1002/14651858.CD009997.pub2.
141. Szarfarc SC, de Cassana LM, Fujimori E, et al. Relative effectiveness of iron bisglycinate chelate (Ferrochel) and ferrous sulfate in the control of iron deficiency in pregnant women. *Arch Latinoam Nutr*. 2001;51(1, suppl 1):42–47.
142. Abbas AM, Abdelbadee SA, Alanwar A, et al. Efficacy of ferrous bis-glycinate versus ferrous glycine sulfate in the treatment of iron deficiency anemia with pregnancy: a randomized double-blind clinical trial. *J Matern Fetal Neonatal Med*. 2018;1–7.
143. Milman N, Jonsson L, Dyre P, et al. Ferrous bisglycinate 25 mg iron is as effective as ferrous sulfate 50 mg iron in the prophylaxis of iron deficiency and anemia during pregnancy in a randomized trial. *J Perinat Med*. 2014;42:197–206.
144. Dalton LM, Ni Fhloinn DM, Gaydadzhieva GT, et al. Magnesium in pregnancy. *Nutr Rev*. 2016;74:549–557.
145. Dahle LO, Berg G, Hammar M, et al. The effect of oral magnesium substitution on pregnancy-induced leg cramps. *Am J Obstet Gynecol*. 1995;173:175–180.
146. Schoenaker DA, Soedamah-Muthu SS, Mishra GD. The association between dietary factors and gestational hypertension and pre-eclampsia: a systematic review and meta-analysis of observational studies. *BMC Med*. 2014;12:157.

147. Bullarbo M, Odman N, Nestler A, et al. Magnesium supplementation to prevent high blood pressure in pregnancy: a randomised placebo control trial. *Arch Gynecol Obstet.* 2013;288:1269–1274.
148. Zarean E, Tarjan A. Effect of magnesium supplement on pregnancy outcomes: a randomized control trial. *Adv Biomed Res.* 2017;6:109–109.
149. Nair AV, Hocher B, Verkaart S, et al. Loss of insulin-induced activation of TRPM6 magnesium channels results in impaired glucose tolerance during pregnancy. *Proc Natl Acad Sci USA*. 2012;109:11324–11329.
150. Asemi Z, Karamali M, Jamilian M, et al. Magnesium supplementation affects metabolic status and pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*. 2015;102:222–229.
151. Maktabi M, Jamilian M, Amirani E, et al. The effects of magnesium and vitamin E co-supplementation on parameters of glucose homeostasis and lipid profiles in patients with gestational diabetes. *Lipids Health Dis.* 2018;17:163.
152. Makrides M, Crosby DD, Bain E, et al. Magnesium supplementation in pregnancy. *Cochrane Database Syst Rev*. 2014;CD000937. doi:10.1002/14651858.CD000937.pub2.
153. Rylander R. Treatment with magnesium in pregnancy. *AIMS Public Health*. 2015;2:804–809.
154. McCall KA, Huang C, Fierke CA. Function and mechanism of zinc metalloenzymes. *J Nutr*. 2000; 130(suppl 5S):1437S–1446S.
155. Terrin G, Berni Canani R, Di Chiara M, et al. Zinc in early life: a key element in the fetus and preterm neonate. *Nutrients*. 2015;7:10427–10446.
156. Levenson CW, Morris D. Zinc and neurogenesis: making new neurons from development to adulthood. *Adv Nutr*. 2011;2:96–100.
157. Ota E, Mori R, Middleton P, et al. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database Syst Rev.* 2015;CD000230. doi:10.1002/14651858.CD000230.pub5.
158. Nossier SA, Naeim NE, El-Sayed NA, et al. The effect of zinc supplementation on pregnancy outcomes: a double-blind, randomised controlled trial, Egypt. *Br J Nutr.* 2015;114:274–285.
159. Iannotti LL, Zavaleta N, Leon Z, et al. Maternal zinc supplementation and growth in Peruvian infants. *Am J Clin Nutr*. 2008;88:154–160.
160. Merialdi M, Caulfield LE, Zavaleta N, et al. Randomized controlled trial of prenatal zinc supplementation and fetal bone growth. *Am J Clin Nutr.* 2004;79:826–830.
161. Karamali M, Heidarzadeh Z, Seifati SM, et al. Zinc supplementation and the effects on metabolic status in gestational diabetes: a randomized, double-blind, placebo-controlled trial. *J Diabetes Complicat*. 2015;29:1314–1319.
162. Karamali M, Heidarzadeh Z, Seifati SM, et al. Zinc supplementation and the effects on pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial. *Exp Clin Endocrinol Diabetes.* 2016;124:28–33.
163. Chien AL, Qi J, Rainer B, et al. Treatment of acne in pregnancy. *J Am Board Fam Med*. 2016;29:254–262.
164. Uriu-Adams JY, Keen CL. Zinc and reproduction: effects of zinc deficiency on prenatal and early postnatal development. *Birth Defects Res B Dev Reprod Toxicol*. 2010;89:313–325.
165. Swanson D, Block R, Mousa SA. Omega-3 fatty acids EPA and DHA: health benefits throughout life. *Adv Nutr*. 2012;3:1–7.
166. Shulkin M, Pimpin L, Bellinger D, et al. n-3 fatty acid supplementation in mothers, preterm infants, and term infants and childhood psychomotor and visual development: a systematic review and meta-analysis. *J Nutr.* 2018;148:409–418.
167. Imhoff-Kunsch B, Briggs V, Goldenberg T, et al. Effect of n-3 long-chain polyunsaturated fatty acid intake during pregnancy on maternal, infant, and child health outcomes: a systematic review. *Paediatr Perinat Epidemiol*. Jul 2012; 26(suppl 1):91–107.
168. Kar S, Wong M, Rogozinska E, et al. Effects of omega-3 fatty acids in prevention of early preterm delivery: a systematic review and meta-analysis of randomized studies. *Eur J Obstetr Gynecol Reproduct Biol*. 2016;198:40–46.
169. Hsu MC, Tung CY, Chen HE. Omega-3 polyunsaturated fatty acid supplementation in prevention and treatment of maternal depression: putative mechanism and recommendation. *J Affect Disord*. 2018;238:47–61.
170. Miller BJ, Murray L, Beckmann MM, et al. Dietary supplements for preventing postnatal depression. *Cochrane Database Syst Rev.* 2013;CD009104.
171. Keenan K, Hipwell AE, Bortner J, et al. Association between fatty acid supplementation and prenatal stress in African Americans: a randomized controlled trial. *Obstetr Gynecol*. 2014;124:1080–1087.
172. Best KP, Gold M, Kennedy D, et al. Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. *Am J Clin Nutr*. 2016;103:128–143.
173. Bisgaard H, Stokholm J, Chawes BL, et al. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med*. 2016;375:2530–2539.
174. Foran JA, Carpenter DO, Hamilton MC, et al. Risk-based consumption advice for farmed Atlantic and wild Pacific salmon contaminated with dioxins and dioxin-like compounds. *Environ Health Perspect*. 2005;113:552–556.
175. Hajeb P, Jinap S, Shakibazadeh S, et al. Optimisation of the supercritical extraction of toxic elements in fish oil. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. 2014;31:1712–1722.
176. Fernandes AR, Rose M, White S, et al. Dioxins and polychlorinated biphenyls (PCBs) in fish oil dietary supplements: occurrence and human exposure in the UK. *Food Addit Contam*. 2006;23:939–947.
177. Salvig JD, Lamont RF. Evidence regarding an effect of marine n-3 fatty acids on preterm birth: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2011;90:825–838.
178. Freeman MP, Sinha P. Tolerability of omega-3 fatty acid supplements in perinatal women. *Prostaglandins Leukot Essent Fatty Acids*. 2007;77:203–208.